Cuffed endotracheal tubes in neonates

Dr Rebecca E. Thomas
MBBS, FRACP, MRCPCH

This thesis is presented for the degree of

Master of Philosophy

of the University of Western Australia

School of Paediatrics and Child Health
2018
I, Rebecca Thomas, certify that:

This thesis has been substantially accomplished during enrolment in the degree.

This thesis does not contain material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution.

No part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of The University of Western Australia and where applicable, any partner institution responsible for the joint-award of this degree.

This thesis does not contain any material previously published or written by another person, except where due reference has been made in the text and, where relevant, in the Authorship Declaration that follows.

This thesis does not violate or infringe any copyright, trademark, patent, or other rights whatsoever of any person.

The research involving human intervention and data reported in this thesis was assessed and approved by The University of Western Australia Human Research Ethics Committee, approval #: RA/4/1/7608 and Princess Margaret Hospital HREC, approval #: 2014111EP. Written patient consent has been received and archived for the research involving patient data reported in this thesis.

For other retrospective studies and the survey, approval was obtained through CAHS/ WNHS GEKO (Governance Evidence Knowledge Outcomes).

This thesis contains published work and work prepared for publication, some of which has been co-authored.

Signature:

Date: 11th December, 2018
ABSTRACT

**Background and rationale:** Traditionally, uncuffed endotracheal tubes (ETTs) have been used for artificial ventilation of infants and children. More recently, newer designed high volume low pressure (HVLP) cuffed ETTs are being used with increasing frequency in infants from birth with very limited evidence.

**Research objective and aims:** The main objective was to perform a pilot randomised control trial (RCT) of cuffed versus uncuffed ETTs in neonates and small infants to start to bring together scientific evidence for cuffed ETT use in this age group. Four other parallel projects were undertaken by way of: a comprehensive review of the literature; a survey of current practice in Australia and New Zealand; a review of incidence and risk factors for the development of severe subglottic stenosis (SGS) in our institution; and a study of the use of cuffed ETTs in infants <3kg.

**Summary of methods:** For the main RCT, neonates >35 weeks gestation and infants up to 3 months of age who were >3kg were randomised to receive either a cuffed (Microcuff®) ETT or uncuffed (Portex® siliconised) ETT for the period of ventilation. The primary outcome was to show an increase in the ability to sustain the ETT leak within the desirable range of 10-20%. Secondary outcomes included comparable or improved safety and improvement in the ability to ventilate with cuffed ETTs. The literature review included a full search strategy and reporting of any study comparing cuffed and uncuffed ETTs in infants/ small children. The review of local incidence and risk factors for SGS was by way of a retrospective case-control study. The survey of current practice comprised an emailed computerised questionnaire to all of the 28 tertiary neonatal and 7 paediatric ICUs in Australia and New Zealand. The study of the use of cuffed ETT versus uncuffed ETTs in infants <3kg was by way of a retrospective cohort study.

**Interpretation of key results:** From literature review, there is extremely limited evidence for the use of cuffed ETTs in neonates and young infants, with no studies done solely in the neonates. Despite this lack of evidence, our survey showed that
cuffed ETTs are being used in neonates in 33% of neonatal and 100% of paediatric ICUs in Australia and New Zealand. The review of SGS in our institution found that SGS is very rare in intubated infants >34 weeks gestation and that minimising trauma during intubations, avoiding recurrent extubation/reintubations and using appropriate sized ETTs may help prevent this serious complication. The main RCT showed that there were a higher percentage of patients in the cuffed group with a mean leak being in the range 10-20%, however, this did not reach significance. This study did show a statistical difference in the percentage time the patients spent in the leak range 10-20%. In the cuffed group, re-intubation rates and complications during ventilation were significantly lower. There were no differences in complications post-extubation. The study of cuffed ETT use in infants <3kg with a small sample size found that Microcuff® cuffed endotracheal tubes may be safe to use in neonates <3kg.

**Principal conclusions:** This thesis showed that the use of modern Microcuff® ETTs may be advantageous and safe to use in neonates and young infants. These results need to be confirmed in a large multicentre study.
# TABLE OF CONTENTS

Thesis declaration .................................................................................................................. iii
Abstract .................................................................................................................................. v
Table of contents .................................................................................................................... vii
List of Tables ........................................................................................................................ xi
List of Figures ........................................................................................................................ xiii
List of Appendices .................................................................................................................. xv
Glossary of Abbreviations ..................................................................................................... xvii
Acknowledgements ............................................................................................................... xix
Publications and presentations arising from this project ....................................................... xxi
Authorship declaration: Statement of contribution .............................................................. xiii

## CHAPTER 1: Introduction: Thesis overview ........................................................................ 1
1.1 Rationale/ relevance of this research ............................................................................ 3
1.2 Aims and objectives of this research ............................................................................ 4
1.3 Structure of this thesis .................................................................................................... 4

## CHAPTER 2: Literature review .......................................................................................... 7
2.1 Preface .............................................................................................................................. 9
2.2 Introduction ...................................................................................................................... 9
   2.2.1 Search strategy ......................................................................................................... 10
2.3 Traditional use of uncuffed ETTs ............................................................................... 10
   2.3.1 Problems with uncuffed ETTs ............................................................................. 11
2.4 Cuffed ETTs for neonates and infants ......................................................................... 12
   2.4.1 Shortcomings of older HVLP cuffed ETTs ............................................................ 12
   2.4.2 The Microcuff® ETT ............................................................................................. 13
   2.4.3 Advantages of using cuffed ETTs ......................................................................... 14
   2.4.4 Potential disadvantages of using cuffed ETTs ....................................................... 15
   2.4.5 The use of cuffed ETTs ......................................................................................... 19
2.5 Studies comparing cuffed vs uncuffed ETTs ................................................................. 20
   2.5.1 Studies comparing cuffed v uncuffed ETT use in neonates .................................. 20
2.5.2 Studies of short-term cuffed v uncuffed ETT use in anaesthesia......20
2.5.3 Studies of the use of cuffed v uncuffed ETT for longer-term ventilation in PICU.................................................................20

2.6 Conclusions..................................................................................23
2.7 Additional comments.....................................................................23
2.7 Acknowledgements........................................................................24

CHAPTER 3: Subglottic stenosis, the size of the problem.........................25
3.1 Preface..........................................................................................27
3.2 Introduction....................................................................................27
3.3 Methods.......................................................................................28
3.4 Results..........................................................................................30
  3.4.1 Incidence of SGS in neonates in WA (2006-2012).......................32
  3.4.2 Grading of SASGS based on Myer-Cotton Classification............34
  3.4.3 Age at presentation in NICU graduates ......................................34
  3.4.4 Mode of presentation in NICU graduates ....................................34
  3.4.5 Type of surgical airway intervention for NICU graduates ..........34
  3.4.6 Comparison of 35 cases with 70 matched controls......................35
3.5 Discussion....................................................................................37
3.6 Conclusions..................................................................................40
3.7 Acknowledgements.........................................................................41

CHAPTER 4: Current use of cuffed endotracheal tubes in neonates in Australia and New Zealand.................................................................43
4.1 Preface..........................................................................................45
4.2 Introduction....................................................................................45
4.3 Methods.......................................................................................46
  4.3.1 Study population..........................................................................46
  4.3.2 Data collection...............................................................................46
  4.3.3 Survey instrument..........................................................................46
  4.3.4 Outcome measures.........................................................................46
  4.3.5 Statistical analysis..........................................................................47
CHAPTER 5: Cuffed versus uncuffed endotracheal tubes for ventilation of neonates and infants in the neonatal and paediatric intensive care unit: a pilot RCT

5.1 Preface.............................................................................................................57
5.2 Introduction......................................................................................................57
5.3 Methods...........................................................................................................57
  5.3.1 Eligibility and recruitment...........................................................................57
  5.3.2 Consent........................................................................................................58
  5.3.3 Randomisation and masking.......................................................................58
  5.3.4 Intervention................................................................................................58
  5.3.5 Outcomes....................................................................................................60
  5.3.6 Sample size and statistical analysis............................................................60
  5.3.7 Ethics..........................................................................................................61
5.4 Results.............................................................................................................61
  5.4.1 Primary outcome: Leak..............................................................................64
  5.4.2 Process of intubation................................................................................64
  5.4.3 Cuffed ETTs.............................................................................................65
# LIST OF TABLES

## CHAPTER 2

<table>
<thead>
<tr>
<th>Table 2.1</th>
<th>Summary of the advantages and disadvantages of cuffed ETTs in the NICU/ PICU setting</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 2.2</td>
<td>Studies comparing cuffed ETTs versus uncuffed ETTs for short-term use in anaesthesia</td>
<td>21</td>
</tr>
<tr>
<td>Table 2.3</td>
<td>Studies comparing cuffed versus uncuffed ETTs for longer-term ventilation in PICU</td>
<td>22</td>
</tr>
</tbody>
</table>

## CHAPTER 3

| Table 3.1 | Incidence of severe acquired SGS based on gestational age at birth (2006-2012) | 33 |
| Table 3.2 | Incidence of severe acquired SGS based on birth weight (2006-2012) | 33 |
| Table 3.3 | Baseline characteristics of cases and controls | 35 |
| Table 3.4 | Potential contributing factors in the development of SASGS by cases and controls | 36 |
| Table 3.5 | Risk factors assessed for their influence on SASGS showing unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) | 37 |

## CHAPTER 4

| Table 4.1 | The incidence of use of cuffed ETTs in neonates and Infants <3 months of age in neonatal and paediatric intensive care units in Australia and New Zealand | 48 |
| Table 4.2 | The use of cuffed ETTs in infants <3kg in units which use cuffed ETTs | 48 |
| Table 4.3 | The technique of cuff inflation in those units who use cuffed ETTs | 49 |
| Table 4.4 | Which physicians use cuffed ETTs to intubate | 50 |
Table 4.5 If there was evidence for the use of cuffed ETTs, which units would use them.................................................................51

CHAPTER 5
Table 5.1 Patient characteristics, cuffed v. uncuffed ETTs..........................63
Table 5.2 Percentage time spent at different leak ranges, cuffed v. uncuffed ETTs.............................................................64
Table 5.3 Process of intubation, cuffed v. uncuffed ETTs...........................65
Table 5.4 Comparison secondary outcomes, cuffed v uncuffed ETTs..........68
Table 5.5 Follow-up of patients, cuffed v. uncuffed ETTs........................70

CHAPTER 6
Table 6.1 Demographics of patients who received cuffed ETT v uncuffed endotracheal tube (ETT).............................................82
Table 6.2 Outcomes of patients who received cuffed v uncuffed endotracheal tube (ETT)............................................................83
LIST OF FIGURES

CHAPTER 2

Figure 2.1  The Microcuff® endotracheal tube.........................................................13
Figure 2.2  A suggested set-up of manometer to measure cuff pressure..............20

CHAPTER 3

Figure 3.1  Patients who underwent surgery for severe subglottic stenosis (SGS) 2006-2014...........................................................................................................31

CHAPTER 5

Figure 5.1  Patient allocation.....................................................................................61
LIST OF APPENDICES

Appendices..................................................................................................................................................105


# GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>aOR</td>
<td>Adjusted odds ratio</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>CA</td>
<td>Corrected age</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CPAP</td>
<td>Continuous positive airway pressure</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography.</td>
</tr>
<tr>
<td>ENT</td>
<td>Ear, nose, throat</td>
</tr>
<tr>
<td>ETT</td>
<td>Endotracheal tube</td>
</tr>
<tr>
<td>FiO₂</td>
<td>Fraction of inspired oxygen</td>
</tr>
<tr>
<td>HFJ</td>
<td>High frequency jet</td>
</tr>
<tr>
<td>HFO</td>
<td>High frequency oscillation</td>
</tr>
<tr>
<td>HIE</td>
<td>Hypoxic ischaemic encephalopathy</td>
</tr>
<tr>
<td>HVLP</td>
<td>High volume low pressure</td>
</tr>
<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>IUGR</td>
<td>Intrauterine growth retardation</td>
</tr>
<tr>
<td>LTR</td>
<td>Laryngotracheal reconstruction</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean airway pressure</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>N</td>
<td>Number</td>
</tr>
<tr>
<td>N/A</td>
<td>Not applicable</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal intensive care unit</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>N₂O</td>
<td>Nitrous oxide</td>
</tr>
<tr>
<td>OD</td>
<td>Outer diameter</td>
</tr>
<tr>
<td>OI</td>
<td>Oxygenation index</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
</tbody>
</table>

xvii
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCO₂</td>
<td>Partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>PICU</td>
<td>Paediatric intensive care unit</td>
</tr>
<tr>
<td>PEEP</td>
<td>Peak expiratory pressure</td>
</tr>
<tr>
<td>PIP</td>
<td>Peak inspiratory pressure</td>
</tr>
<tr>
<td>PMA</td>
<td>Post-menstrual age</td>
</tr>
<tr>
<td>PVC</td>
<td>Polyvinyl chloride</td>
</tr>
<tr>
<td>R</td>
<td>Range</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised control trial</td>
</tr>
<tr>
<td>RDS</td>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>SASGS</td>
<td>Severe acquired subglottic stenosis</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SGS</td>
<td>Subglottic stenosis</td>
</tr>
<tr>
<td>UE</td>
<td>Unplanned extubation</td>
</tr>
<tr>
<td>VAP</td>
<td>Ventilator associated pneumonia</td>
</tr>
<tr>
<td>Vₜ</td>
<td>Tidal volume</td>
</tr>
<tr>
<td>WA</td>
<td>Western Australia</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

This research was supported by an Australian Government Research Training Program (RTP) Scholarship.

This research was supported by a Telethon Research Fellowship 2015 at Princess Margaret Hospital, Perth.

I would firstly like to thank the parents who at the worst point of their lives, with their newborn baby being so sick, are selfless enough to agree to their child being enrolled in a study to benefit future babies.

Thank you to all my wonderful nursing and medical colleagues, who supported the study through enrolment and recording of data.

Thank you to all my supervisors for their ongoing support and encouragement, in particular Karen Simmer and Shripada Rao. Karen for strongly encouraging me to get involved in research and to apply for the Telethon Research Fellowship. I have learnt so much through this journey and have now ‘caught the bug’ for research. Shripad for the incredible day-to-day support, encouragement and knowledge he has given, as he does for so many others. This whole project would not have happened without him.

Lastly, I would like to thank all my family for being the constant support in my life across jobs and continents.

Elliot and Jake, you are the lights in my life that give me the reason and motivation to do everything I do.
PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS PROJECT

Publications:

The candidate has submitted and published the following manuscripts in the following international peer-reviewed journals. Relevant chapter details can be found after each publication, with the published manuscripts appended.

Statements of candidate contribution and authorship details can be found on the following pages.

1. **Thomas R**, Rao S, Minutillo C. Cuffed endotracheal tubes for neonates and young infants: a comprehensive review. *Arch Dis Child Fetal Neonatal Ed.* 2016;101(2):F168-74 (Chapter 2; Appendix A)


   Corresponding editorial:

Manuscripts not yet published:

Presentations:

1. ‘Cuffed versus uncuffed endotracheal tubes for ventilation of neonates: a pilot RCT’
   Accepted as oral presentation, PSANZ, Gold Coast, March 2018

2. ‘Acquired severe subglottic stenosis in neonatal intensive care graduates’ – poster
   PAS, San Francisco, May 2017

3. ‘Acquired severe subglottic stenosis in neonatal intensive care graduates’ – poster (presented by S. Athikarisamy as unable to attend)
   PSANZ, Canberra, April 2017

4. ‘Cuffed endotracheal tubes in neonates’ – oral poster (presented by S. Rao as unable to attend)
   PSANZ, Townsville, April 2016

5. ‘Cuffed endotracheal tubes in neonates and infants’ – oral
   RACP Advanced Trainee Research Awards (Finalist), CAHS Research Symposium, PMH, Perth, October 2015
This thesis contains work that has been published and work prepared for publication.

<table>
<thead>
<tr>
<th>Details of the work:</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Location in thesis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Student contribution to work:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rebecca Thomas was the primary author of this paper. RT and SR searched for relevant articles. RT drafted the manuscript. SR and CM critically reviewed the manuscript.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-author signatures and dates:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shripada Rao, 10\textsuperscript{th} December 2018</td>
</tr>
<tr>
<td>Corrado Minutillo, 5\textsuperscript{th} December 2018</td>
</tr>
</tbody>
</table>
Details of the work:


Location in thesis:

Chapter 3

Student contribution to work:

Rebecca Thomas was the primary author of this paper. RT, SR, CM and SV all contributed to study design and concept. RT and SR had full access to all the data in the study and take responsibility for the integrity of the data. EN performed statistical methods and analysis. RT led study and drafted manuscript. All authors critically reviewed the manuscript.

Co-author signatures and dates:

Shripada Rao, 10th December 2018

Corrado Minutillo, 5th December 2018

Shyan Vijayasekaran, 10th December 2018

Liz Nathan, 4th December 2018
Details of the work:


Location in thesis:

Chapter 4

Student contribution to work:

Rebecca Thomas was the primary author of this paper. All authors contributed to the study concept and design. RT was responsible for the acquisition, analysis and interpretation of data. The manuscript was drafted by RT and critically reviewed by SR and CM.

Co-author signatures and dates:

[Signature]

Shripada Rao, 10\textsuperscript{th} December 2018

[Signature]

Corrado Minutillo, 5\textsuperscript{th} December 2018
Details of the work:


Location in thesis:
Chapter 5

Student contribution to work:

Rebecca Thomas was the principal investigator for this project, designed the study, designed the data collection instruments, collected and entered data, drafted the initial manuscript, reviewed and revised the manuscript.

SR conceptualized and designed the study, and reviewed and revised the manuscript.

SE, BH, ML, CM and SV designed the study and critically reviewed the manuscript for important intellectual content.

SA co-ordinated the later part of the trial, collected data and reviewed the manuscript for important intellectual content.

MB performed the statistical analyses and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Co-author signatures and dates:

Shripada Rao, 10<sup>th</sup> December 2018

Bruce Hullet, 7<sup>th</sup> December 2018
Simon Erickson, 10th December 2018

Corrado Minutillo, 5th December 2018

Martyn Lethbridge, 6th December 2018

Shyan Vijayasekaran

Sachin Agrawal, 4th December 2018

Prof Max Bulsara, 4th December 2018
Details of the work:


Location in thesis:

Chapter 6

Student contribution to work:

Rebecca Thomas was the primary author of this paper. All authors contributed to the study concept and design. RT was responsible for the acquisition of data. MB provided the statistical analysis. The manuscript was drafted by RT and critically reviewed by SR, CM, BH and MB.

Co-author signatures and dates:

- Shripada Rao, 10\(^{th}\) December 2018
- Corrado Minutillo, 5\(^{th}\) December 2018
- Bruce Hullet, 7\(^{th}\) December 2018
- Prof Max Bulsara, 4\(^{th}\) December 2018
Student signature:

[Redacted]

Rebecca Thomas, 11th December 2018

I, Karen Simmer, certify that the student’s statements regarding their contribution to each of the works listed above are correct.

Coordinating supervisor signature:

[Redacted]

Date: 11th December 2018
1.1 RATIONALE/ RELEVANCE OF THIS RESEARCH

In order to adequately artificially ventilate a patient, the endotracheal tube (ETT) needs to provide a reliable connection between the patient’s lungs and the ventilator. Ideally this connection should have minimal leak without causing undue pressure to laryngeal or tracheal structures.

Minimising the circuit leak produces improved efficacy of ventilation, maintenance of PEEP, constant minute ventilation, more reliable respiratory monitoring and end-tidal carbon dioxide monitoring and decreased risk of pulmonary aspiration. A good seal is particularly important in those with poor lung compliance in order to achieve adequate ventilation. On the other hand, an ETT which is too tight may cause laryngeal/ tracheal damage resulting in subglottic stenosis (SGS).

Complications with regard to inadequate ventilation contribute to prolonged hospital stay and inappropriate ETT selection and multiple ETT changes contribute to airway trauma potentially requiring airway reconstruction inferring a high cost to the patient and health care system.

There has been much debate in recent years over the use of cuffed versus uncuffed ETTs for the ventilation of neonates, infants and children. Traditionally, uncuffed ETTs have been used due to concerns over the safety of using cuffed ETTs in small children. However, over the last few years with the advent of the newer high-volume low-pressure cuffed tubes (HVLP), there has been an increase in the use of cuffed ETTs in children from birth (>3kg) particularly during anaesthesia for surgical procedures. Cuffed ETTs potentially offer the advantage of less or a more manageable air leak and therefore improved ventilation.

Prior to this project, we noted that in our institution, cuffed ETTs were being increasingly used by anaesthetists in neonates undergoing surgery. Due to neonatologists’ unfamiliarity with cuffed ETTs and concerns over safety due to lack of literature, when the patient came back from surgery with a cuffed ETT in place, the cuff would be deflated or the ETT changed to an uncuffed ETT, both with the potential for significant morbidity.
There is only a small amount of literature on the use of the newer HVLP cuffed ETTs in this age group. The available evidence is almost exclusively for short-term ventilation during anaesthesia, looking at the outcomes of post-extubation stridor and the need for re-intubation to change to an appropriate tube size. Hence, we are left with a question as to whether cuffed ETTs are a safe and effective and perhaps advantageous for longer term ventilation in neonates and small infants in the intensive care setting.

1.2 AIMS AND OBJECTIVES OF THIS RESEARCH

Since there is no real experience of cuffed ETT use in neonates in the NICU, the main aim of this project is to carry out a pilot RCT evaluating the usefulness and safety of cuffed ETTs in comparison to uncuffed ETTs in this setting prior to the potential of embarking upon a costly large RCT.

A number of parallel projects were run to:

a) Systematically review the literature to determine previous studies of cuffed ETTs in this age group.

b) Evaluate the incidence and risk factors for the development of severe SGS requiring surgical intervention in the local paediatric population.

c) Determine the current rate of use and management of cuffed ETTs in neonates and small infants in the intensive care setting in Australia and New Zealand.

d) Study the use of cuffed ETTs in infants <3kg.

1.3 STRUCTURE OF THIS THESIS

This thesis is organised in a series of chapters, as a thesis by publication. Each of these chapters is presented in a format that either has, or could be published following peer review.

Chapter 1 begins with an overview of the background and aims of the research presented.
Chapter 2 provides an overview of the literature related to this research. This manuscript has been peer-reviewed and was published in the journal *Archives of Disease in Childhood, Fetal and Neonatal Edition* (appendix A).

Chapter 3 presents the results of a case-control study defining the local incidence and risk factors for the development of severe subglottic stenosis (SGS) requiring surgery in NICU graduates. This manuscript has been peer-reviewed and was published in the journal *Archives of Disease in Childhood, Fetal and Neonatal Edition* (appendix B).

Chapter 4 presents the results of a survey of the rate of use and management of cuffed ETTs in neonates and small infants in NICUs/ PICUs in Australia and New Zealand. A truncated form of this manuscript has been peer-reviewed and was published in the journal *Archives of Disease in Childhood, Fetal and Neonatal Edition* (appendix C).

Chapter 5 presents the results of the main study of this thesis, a pilot RCT comparing cuffed versus uncuffed ETTs for ventilation of neonates and young infants in the intensive care setting. This manuscript is in the process of being prepared for submission for peer-reviewed publication.

Chapter 6 presents the results of a retrospective cohort study comparing cuffed versus uncuffed ETTs in neonates <3kg. This manuscript has been peer-reviewed and was published in the journal *Pediatric Anesthesia* (appendix D).

Chapter 7 provides a general discussion bringing together the research presented in this thesis. In addition, the scope for further research is addressed.
CHAPTER 2 – Literature Review

CONTENTS OF CHAPTER

CHAPTER 2 .................................................................................................................................................. 7

2.1 Preface .................................................................................................................................................. 9

2.2 Introduction ......................................................................................................................................... 9

2.2.1 Search strategy .............................................................................................................................. 10

2.3 Traditional use of uncuffed ETTs .................................................................................................. 10

2.3.1 Problems with uncuffed ETTs .................................................................................................... 11

2.4 Cuffed ETTs for neonates and infants ............................................................................................ 12

2.4.1 Shortcomings of older HVLP cuffed ETTs .................................................................................. 12

2.4.2 The Microcuff® ETT ....................................................................................................................... 13

2.4.3 Advantages of using cuffed ETTs ................................................................................................. 14

2.4.4 Potential disadvantages of using cuffed ETTs ............................................................................. 15

2.4.5 The use of cuffed ETTs ................................................................................................................ 19

2.5 Studies comparing cuffed vs uncuffed ETTs ................................................................................ 20

2.5.1 Studies comparing cuffed v uncuffed ETT use in neonates ....................................................... 20

2.5.2 Studies of short-term cuffed v uncuffed ETT use in anaesthesia .............................................. 20

2.5.3 Studies of the use of cuffed v uncuffed ETT for longer-term ventilation in PICU .................. 20

2.6 Conclusions ....................................................................................................................................... 23

2.7 Additional comments ....................................................................................................................... 23

2.8 Acknowledgements ......................................................................................................................... 24
2.1 PREFACE

Traditionally, uncuffed endotracheal tubes (ETTs) have been used for artificial ventilation of infants and children. More recently, newer designed high volume low pressure (HVLP) cuffed ETTs are being used with increasing frequency in infants from birth.

This review examines the reasons behind the traditional use of uncuffed ETTs and the problems associated with their use; newer HVLP cuffed ETTs and what they can potentially offer neonates; and reviews evidence from studies comparing the use of cuffed and uncuffed ETTs in neonates and small infants.

The findings from this literature review have been peer reviewed and were published in the journal Archives of Disease in Childhood, Fetal and Neonatal Edition. A copy of the published manuscript is presented in Appendix A.

2.2 INTRODUCTION

Traditional teaching has been that cuffed ETTs should not be used in children under 8-10 years of age because of the fear that they are associated with mucosal injury leading to subglottic stenosis. This teaching has also extended to neonates.

However, since the late 1990s, with the advent of the newer PVC high-volume low-pressure (HVLP) cuffed ETTs, and then the introduction of the ultrathin polyurethane Microcuff® pediatric ETT in 2004, there has been an increase in the use of cuffed ETTs in children from birth, particularly during anaesthesia and for ventilation in paediatric intensive care units (PICUs).

The use of uncuffed ETTs remains the standard practice in neonatal intensive care units (NICUs). However, in surgical NICUs, infants are now sometimes being admitted from theatre with cuffed ETTs in place. The cuff is often deflated, causing problems with ventilation, or the tube is replaced for an uncuffed one, resulting in an unnecessary further intubation. Considering that many paediatric anaesthetists and intensivists are already using cuffed ETTs in infants >3kg from birth, should neonatologists be doing the same?
2.2.1 Search strategy:

The databases PubMed (www-ncbi.nlm.nih.gov, 1966-2015), EMBASE (Excerpta Medica database) via Ovid (http://ovidsp.tx.ovid.com, 1980-2015), Cochrane Central Register of Controlled Trials (www.thecochranelibrary.com, through August 2015), CINAHL (Cumulative Index of Nursing and Allied Health Literature) via OVID (http://ovidsp.tx.ovid.com, 1980-August 2015), were searched in May 2015 and repeated in August 2015. The reference lists of eligible studies and review articles were searched to identify additional studies. Reviewers RT and SR conducted the literature search independently. Medline was searched using the following terminologies: [(tube OR tracheal OR endotracheal) AND (cuff OR cuffed)] OR (microcuff)) AND (infant/ OR infant, newborn/ OR child/ OR paediatrics). The other databases were searched using similar terminologies.

The literature searches retrieved 262 potential relevant citations after removing duplicates. Following careful review of the abstracts, 29 reports were selected for inclusion based upon their relevance with regards to: potential advantages and disadvantages of cuffed endotracheal tubes; and studies comparing the use of cuffed and uncuffed endotracheal tubes in neonates and small infants (n=7). A further 9 relevant reports were found from checking references from the included studies.

2.3 TRADITIONAL USE OF UNCUFFED ETTs

The traditional teaching of using an uncuffed ETT in infants is based upon studies of cadaveric specimens of children (4mo-14yrs), which showed that the airway of an infant/child is funnel shaped, and that the narrowest part is the circumferential, non-distensible cricoid cartilage which is a circular in shape. Therefore, an uncuffed ETT which fits snugly through the cricoid, leaving some space to allow an air leak at a peak inspiratory pressure (PIP) of 20-25cmH₂O should provide a sufficient seal, making a cuff unnecessary.
2.3.1 Problems with uncuffed ETTs:

An uncuffed ETT must be precisely the right size for the individual infant to fulfil both requirements of leak and seal. There are high ETT exchange and leak rates when using uncuffed ETTs.

(i) The shape of the paediatric airway is not as traditionally taught:

Recent research on the paediatric airway refutes traditional teachings. Litman et al performed MRIs on 99 sedated unparalysed children (2mo-13yrs), Dalal et al carried out video-bronchoscopic images on 135 paralysed children (6mo-13yrs) and Wani et al carried out CT images on 135 spontaneously breathing children (1mo-114mo). All 3 studies came to similar conclusions: the cricoid is not round, but an elliptical structure with the transverse dimensions being narrower than the antero-posterior dimensions; the narrowest part of the larynx is not the cricoid but the glottis/subglottic region; and the paediatric airway is more cylindrical, like adults, rather than funnel shaped.

The cricoid being elliptical means that when an uncuffed tube is inserted into the noncircular lumen of the cricoid to give a reasonable seal, the pressure exerted on the lateral walls of the cricoid are unknown and could be considerable.

(ii) ETTs which are too tight:

Upon insertion of an ETT, standard anaesthetic practice is to demonstrate a leak at a PIP of 20-25cmH₂O to ensure the ETT is not too tight. However, this is rarely done in neonatal practice. It is also quite a common conception in neonates to be happy with no leak as this improves ventilation. It has been shown that ETTs which are too tight can cause airway damage in infants and children.

(iii) ETTs with a large leak:

Minimising the ETT leak provides: more efficient ventilation; maintenance of positive end expiratory pressure; maintenance of constant minute ventilation, stabilising gas parameters; more reliable respiratory monitoring; and decreases risk of pulmonary aspiration.
Brinsmead et al studied uncuffed ETT leaks in their NICU and found that there was a large leak of >25% on 19% of occasions and in 27% of patients at some point. Dorsey et al found a clinically significant ETT leak in 19.4% of infants (0-2 years) with burns who had uncuffed ETTs in their study. Mahmoud et al showed that 42.3% of all neonates studied with an uncuffed ETT experienced a leak of >40% at some point. Leak varies with time, position, level of sedation/muscle relaxation, and with change in compliance of the lungs.

Tidal volume ($V_T$)-targeted ventilation is commonly used in neonates. $V_T$ measurement and control become inaccurate in the presence of substantial airway leak. Although newer ventilators now offer leak compensation, Keszler claims that this is an imperfect solution given the large fluctuation in the ETT leak over time and that auto-triggering and failure to breath-terminate in flow-cycled modes are likely to occur with substantial ETT leaks.

### 2.4 CUFFED ETTs FOR NEONATES AND INFANTS

Over 15 years ago, several authors suggested using the newer high-volume low-pressure (HVLP) PVC cuffed ETTs in infants and children <8 years of age. The use of a cuffed ETT allows adjustment of the cuff to enable adequate sealing of the airway with an estimation of the pressure exerted on the tracheal mucosa.

#### 2.4.1 Shortcomings of older HVLP cuffed ETTs

When the adequacy of the design of readily available PVC cuffed ETTs was investigated by Weiss et al in 2004, they found that there was a marked variation between ETTs from different manufacturers in regards to: outer diameter; cuff diameter; position of the cuff in regards to the ETT tip; presence of a depth marking; and distance from the depth marking to the tube tip. They concluded that most cuffed ETTs were poorly designed and that a better designed cuffed ETT was required.
2.4.2 The Microcuff® ETT

In 2004, to address the above issues with older HVLP cuffed ETTs, the Microcuff® Pediatric ETT was introduced. The Microcuff® ETT is a HVLP cuff made of ultrathin polyurethane, which is thought to improve sealing characteristics, allowing shorter cuffs. There is no Murphy eye which allows a more distal placement of the cuff (figure 2.1). It has an appropriate intubation depth mark which has been shown to allow adequate placement of the ETT with a cuff-free subglottic zone and without the risk of endobronchial intubation. The polyurethane cuff also avoids the formation of longitudinal folds and channels which prevents fluid leakage and potentially avoids irritation of the mucosa.

Figure 2.1 - The Microcuff® endotracheal tube.

Note the absence of a Murphy eye, enabling a distally placed short cuff and an adequate depth marking.

The Microcuff® ETT has been shown to require significantly lower cuff sealing pressures in children than other tracheal tube brands. Dullenkopf et al reported on tracheal sealing with the Microcuff® ETT in 500 infants and children (birth-16yrs) and showed that in 95% of patients, the trachea was sealed with a cuff pressure of <15cmH₂O (mean 9.7cmH₂O).
2.4.3 Advantages of using cuffed ETTs

Cuffed ETTs potentially offer the advantages of: lower rate of ETT leak; improved ventilation; less re-intubations to find the correct ETT size; a smaller ETT through the delicate cricoid; less ventilator-associated pneumonia/aspirations; and the use of less anaesthetic and other gases.

(i) **Decreased re-intubation rates:**

A number of studies have reported significantly reduced re-intubation rates to find the correct ETT size when using cuffed ETTs. Khine et al 1997 showed re-intubation rates of 0% with cuffed ETT use compared with 30% with uncuffed ETT use in infants (0-2yrs) \( p<0.0001 \). Dullenkopf et al 2005 showed that the tube exchange rate with cuffed ETTs was only 1.6% in 500 children (birth-16yrs). Salgo et al 2006 showed a re-intubation rate of 2.6% with cuffed ETT use in 150 children (birth-5yrs). Weiss et al 2009 showed re-intubation rates of 2.1% with cuffed ETTs and 30.8% with uncuffed ETTs in 2246 children (birth-5yrs) \( p<0.0001 \). Dorsey et al 2010 showed re-intubation rates of 7.2% with cuffed ETTs and 37.6% with uncuffed ETTs in burns patients aged 0-10yrs.

Although these studies show impressively reduced rates of re-intubation with cuffed ETTs in infants and children, there is no data exclusively for the neonatal population.

(ii) **Lower clinically significant air leak/improved ventilation:**

This has not been studied in great detail. Dorsey et al 2010 reported clinically significant air leaks at a rate of 1.8% with cuffed ETTs and 27% with uncuffed ETTs in 228 intubation events in 145 burns patients (0-10yrs) \( p=0.003 \).

(iii) **Decreased rates of aspiration and ventilator-associated pneumonia:**

Gopalareddy et al sampled ETT aspirates in 27 patients (4mo-19yrs) undergoing ventilation in a PICU. The group with cuffed tubes had a lower incidence of aspirates positive for pepsin than the uncuffed group (53%v100%, \( p<0.05 \)). Dullenkopf et al found in vitro that the Microcuff® ETT was significantly better than other brands in preventing fluid leakage past the cuff.
Miller et al found that in adults (n=3207), the polyurethane cuffed ETT is associated with significantly decreased rates of ventilator-associated pneumonia (p=0.032).23

(iv) **Decreased fresh and volatile gas use:**

A number of studies have shown significantly reduced rates of fresh and volatile gas consumption with cuffed ETT use, which decreases patient cost and pollution of the atmosphere8,19 (see section on studies cuffed v uncuffed ETTs below). This could be particularly relevant with nitric oxide (NO) use in neonates.

Murat et al reported a dramatic decrease in pollution due to volatile agents since cuffed ETTs were introduced to their paediatric anaesthetic department. The concentrations of sevoflurane and N₂O decreased from 48.1ppm and 192ppm in June 1997 to 0.3ppm and 29.4ppm in December 1999 respectively.9

(v) **Theoretically, may cause less airway damage:**

For cuffed ETTs, a smaller diameter tube (0.5mm less than uncuffed ETT) is selected which does not wedge within the delicate cricoid and could make intubation less traumatic. The cuff makes its seal in the trachea where there are U-shaped cartilages and a muscular dorsal wall which allow for some distension, in contrast with the rigid cricoid ring where the uncuffed ETT makes its seal.

Inflating the cuff may ease the tube tip away from the anterior wall reducing tube tip damage1 and cause less movement of the ETT in the airway. There is also less exposure to repeated intubations to find the right sized ETT.

2.4.4 Potential disadvantages of using cuffed ETTs

(i) **Smaller internal diameter causing increased resistance and potential for ETT blockage:**

One of the main concerns of cuffed ETTs is the requirement to use an ETT smaller than the uncuffed equivalent. This increases the tube resistance, particularly in the smaller sizes, which could lead to higher ventilator pressure requirements and harder work of breathing on weaning from the ventilator. The smaller diameter ETT could also lead to increased episodes of tube blockage and more difficult
suctioning. To date, there are no studies looking at cuffed versus uncuffed ETTs in these respects.

(ii) **Increased airway damage:**

For some, there remains a concern that the use of cuffed ETTs in infants and children could be causing damage.

Murat reported on their use of cuffed ETTs for anaesthesia in 904 patients <1 year old and had no respiratory complications which could be attributed to the ETT. No studies comparing cuffed and uncuffed ETTs in infants and children have found a difference in post-extubation stridor (see section below, studies comparing cuffed v uncuffed ETTs), however, airway problems have not been studied well in the longer-term.

Holzki (1997) warns of the risks of using cuffed ETTs in children <8 yrs. He presented a case series of laryngoscopically documented injuries from uncuffed and cuffed ETTs in infants and children. He comments that the most common injury is from a too-large uncuffed ETT, causing the injury in 92% patients. However, Holzki et al (2009) show trauma secondary to over-inflated cuffs causing circular necrosis leading to cicatricial subglottic stenosis. They also show documentation of trauma seen from the cuff being inflated in the larynx and from the sharp shoulder of certain cuffed ETTs where the cuff joins the ETT shaft. They criticise studies of cuffed versus uncuffed ETTs in children for not having any endoscopic evidence to substantiate their recommendations.

Holzki et al (2009) also claim that stridor is not a validated measure in screening for airway injuries. They suggest that in many instances, significant airway damage may only present sometime later as scar tissue forms and is not always associated with post-extubation stridor. They provide documentary evidence of cases of severe airway damage in children who did not have post-extubation stridor.

Sathyamoorthy et al reported on 3 neonates who were intubated with Microcuff® ETTs for surgical procedures and had significant post-extubation stridor. The first neonate was an ex-28 week preterm infant who at 8 weeks age (36 weeks corrected) and 2.6kg was intubated with a 3.0mm Microcuff® ETT. The second
infant was an ex-30 week preterm infant who at 6 weeks of age (36 weeks corrected) and 2.8kg was intubated with a 3.0mm Microcuff® ETT. The third infant was a term infant weighing 4kg who at 3 weeks of age was intubated with a 3.5mm Microcuff® ETT. None of the 3 patients underwent a leak check or had cuff pressure monitoring. In all 3 patients, the most likely explanation for the post-extubation stridor was that the cuffed ETT size was inappropriately large. The manufacturer does not recommend the Microcuff® ETT for infants below 3kg. The manufacturer recommends the 3.0mm Microcuff® ETT for infants 3kg- ≤8 months of age and the 3.5mm Microcuff® ETT only for infants ≥8 months of age.

(iii) Price:

The cost of the Microcuff® ETT is around three times as much as the uncuffed equivalent for a patient. However, this is thought to be compensated by the decreased need to re-intubate and the decreased use of anaesthetic and fresh gases. (Table 2.1)
Table 2.1- Summary of the advantages and disadvantages of cuffed ETTs in the NICU/ PICU setting:

<table>
<thead>
<tr>
<th>Advantages (with some body of evidence):</th>
<th>Potential disadvantages (with no evidence):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased re-intubation rate to find correct sized ETT.</td>
<td>Increased airway damage if the cuffed ETTs are not used correctly.</td>
</tr>
<tr>
<td>Decreased clinically significant ETT leak.</td>
<td>Smaller diameter ETT:</td>
</tr>
<tr>
<td>Decreased aspiration and ventilator associated pneumonia.</td>
<td>- Increased ETT blockage/ decreased successful suctioning of secretions.</td>
</tr>
<tr>
<td>Decreased fresh and volatile gas use and less air pollution.</td>
<td>- Increased ventilator/ pressure requirements (due to increased ETT resistance).</td>
</tr>
<tr>
<td>✅ Potential advantages (with no evidence):</td>
<td>- Increased work of breathing on being weaned from ventilator.</td>
</tr>
<tr>
<td>Due to decreased ETT leak:</td>
<td></td>
</tr>
<tr>
<td>- Improved ventilation.</td>
<td></td>
</tr>
<tr>
<td>- Maintenance of PEEP.</td>
<td></td>
</tr>
<tr>
<td>- Less incidence ventilator associated atelectasis.</td>
<td></td>
</tr>
<tr>
<td>- More likely to be able to successfully use set volume guarantee/ control ventilation.</td>
<td></td>
</tr>
<tr>
<td>- More likely to successfully record capnography trace.</td>
<td></td>
</tr>
<tr>
<td>Cause less airway damage due to:</td>
<td></td>
</tr>
<tr>
<td>- Smaller ETT sitting through cricoid.</td>
<td></td>
</tr>
<tr>
<td>- Less traumatic intubation as ETT smaller.</td>
<td></td>
</tr>
<tr>
<td>- Inflated cuff lifting ETT tip of anterior wall trachea.</td>
<td></td>
</tr>
<tr>
<td>Fewer total intubations.</td>
<td></td>
</tr>
<tr>
<td>Less accidental extubations.</td>
<td></td>
</tr>
</tbody>
</table>
2.4.5 The use of cuffed ETTs

The smallest manufactured Microcuff® ETT is 3.0mm internal diameter and is recommended for infants ≥3kg. There is no generally accepted guideline as to how to manage the cuff and practice varies enormously. There are differing methods used to decide whether and how much to inflate the cuff, the maximum cuff pressure to be used and how often to check cuff pressures.

The most common method used to inflate the cuff is until the leak just disappears at a PIP of 20-25cmH₂O. It is generally accepted that a cuff pressure of >20cmH₂O should not be used as though not known, 20cmH₂O is thought to be the capillary perfusion pressure in the trachea of small children (it is known to be 25-30cmH₂O in adults). Dullenkopf et al concluded that if the cuff pressure was held <20cmH₂O there was no increased airway morbidity with a rate of post-extubation croup requiring therapy of 0.4%.

It is clear that cuff pressures should be checked. Bernet et al showed that small amounts of inflated air led to a rapid increase in cuff pressure and volume. Cuff pressure has been shown to change with head position, N₂O use, and altitude on transport. How often the cuff pressure is checked varies greatly. Cuff pressure inflation and monitoring are generally done with a handheld manometer with a syringe setup (figure 2.2). There have been suggestions of setups for continuous pressure monitoring.

Many neonates in NICU are ventilated with alternative modes of ventilation such as high frequency oscillation or high frequency jet ventilation. There are no reports on the use of cuffed ETTs with these modes, in particular, what ETT leak to aim for and how to determine the cuff pressure required.
2.5 STUDIES COMPARING CUFFED Vs UNCUFFED ETTs

2.5.1 Studies comparing cuffed v uncuffed ETT use in neonates

There are no studies which compared the use of cuffed versus uncuffed ETTs solely in neonates and/or small infants.

2.5.2 Studies of short-term cuffed v uncuffed ETT use in anaesthesia

There are 3 randomised controlled trials (RCTs)\textsuperscript{8,18,19} and 1 retrospective review\textsuperscript{17} which compared the short-term use of cuffed versus uncuffed ETTs during anaesthesia for surgical procedures in children. These studies included some neonates and infants, but breakdown of data was limited (table 2.2).

2.5.3 Studies of the use of cuffed v uncuffed ETT for longer-term ventilation in PICU

There are 2 published non-randomised studies\textsuperscript{13,14} and one unpublished RCT (conference proceedings of which the full peer reviewed publication is awaited)\textsuperscript{20} which compared cuffed versus uncuffed ETTs in the PICU setting in children. These studies included neonates and infants, but data breakdown was limited (table 2.3).
<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Study</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Main Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khine et al²</td>
<td>RCT</td>
<td>488 children from birth to 8 yrs of age (251 cuffed: 237 uncuffed) requiring anaesthesia for surgery.</td>
<td>(a) Number of intubations required to achieve appropriately sized ETT, (b) the need to use &gt;2L/min fresh gas flow, (c) concentration of nitrous oxide (N₂O) in the operating room, and (d) incidence of croup were compared.</td>
<td>(i) In patients &lt;2 years age, the ETT exchange rate was 0% cuffed ETT: 30% uncuffed ETT. (ii) Requirement for &gt;2L/min fresh gas flow was significantly less with cuffed ETTs (1.2%) v those with uncuffed ETTs (11%) (p&lt;0.001). (iii) Ambient N₂O concentration exceeded 25 ppm in 0% cuffed ETT: 37% uncuffed ETT (p&lt;0.001). (iv) No difference in treatment for stridor between 2 groups (1.2% cuffed: 1.3% uncuffed).</td>
<td>Mallinkrodt lo-pro or Sheriden low-pressure cuffed ETTs were used.</td>
</tr>
<tr>
<td>Weiss et al¹⁸</td>
<td>Multicentre RCT (24 centres across Europe)</td>
<td>2246 children birth – 5 yrs age requiring anaesthesia for surgery (1119 cuffed: 1127 uncuffed). 624 patients aged 0-8 months (28% of the patient sample).</td>
<td>(a) Incidence of post-extubation stridor and (b) ETT exchange rates.</td>
<td>(i) No difference in post-extubation stridor was noted (4.4% cuffed: 4.7% uncuffed (p=0.543). (ii) ETT exchange rate 2.1% cuffed: 30.8% uncuffed groups (p &lt;0.001). (iii) Minimal cuff pressure required to seal the trachea was 10.6 (4.3) cmH₂O with the cuffed ETTs.</td>
<td>Standardised Microcuff cuffed ETT v non-standardised uncuffed ETT.</td>
</tr>
<tr>
<td>Eschertzhuber et al¹⁹</td>
<td>RCT</td>
<td>70 children aged 0-5 years (35 cuffed: 35 uncuffed) undergoing surgery.</td>
<td>Anaesthetic gas consumption using cuffed v uncuffed ETTs.</td>
<td>With use cuffed ETTs there was significantly less: (i) Fresh gas flow requirement (cuffed 1.0 (0.5-1.0) L/min: uncuffed 2.0 (0.5-4.3) L/min, p&lt;0.001), (ii) sevoflurane use (cuffed 6.2 (1.1-14.9) mL: uncuffed16.1 (6.4-82.8) mL, p=0.003), and (iii) medical gas use (cuffed 46 (9/149) L: uncuffed129 (53-552), p&lt;0.001).</td>
<td>(iv) Total costs for sevoflurane and medical gases significantly less in the cuffed ETT group (cuffed 5.2 (1.0-12.5) €: uncuffed 13.4 (6.0-67.3) €, p&lt;0.001). (v) Concluded that increased cost cuffed ETTs is compensated by reduction in gas consumption.</td>
</tr>
<tr>
<td>Dorsey et al²⁰</td>
<td>Retrospective cohort study</td>
<td>327 burns patient aged 0-10 years undergoing anaesthetic (228 intubation events where the type of ETT used was clear, 111 cuffed: 117 uncuffed), over 10 year period 1998-2007.</td>
<td>Review of adverse events.</td>
<td>(i) They showed clinically significant loss of tidal volume with uncuffed ETTs (OR 10.62, 95% CI 2.2-50.5 p&lt;0.003) and (ii) clinically significant higher requirement for immediate reintubation to change ETT size/type with uncuffed ETTs (cuffed 7.2%: uncuffed 37.6%, OR 5.54, 95% CI 1.1-13.6). (iii) No significant differences rates of post-extubation stridor (7.2% cuffed: 4.3% uncuffed), self-extubation (0.9% both groups), aspiration (0 patients both groups) and failed exubation (1.8% cuffed: 3.4% uncuffed). (iv) When the sample was restricted to aged 0-2 years, (a) reintubations were significantly higher in the uncuffed group (OR 10.0, 95% CI 2.1-48.5, p=0.004). (b) There were no clinically significant air leaks in the cuffed ETT group, whereas there were significant air leaks in 19.4% of the uncuffed ETT group.</td>
<td>Not randomised. Rate of cuffed ETT use increased over the studied years.</td>
</tr>
</tbody>
</table>
**Table 2.3 - Studies comparing cuffed versus uncuffed ETTs for longer-term ventilation in PICU**

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Study</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Main Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deakers et al <em>(1994)</em></td>
<td>Prospective cohort</td>
<td>282 consecutive tracheal intubations (243 patients, which included 83 patients &lt;1 year age) in a PICU over 7 month period (1988-1989). 49% patients cuffed ETTs. 188 intubation episodes analysed once patients who had died or who had an upper airway abnormality had been excluded (123 cuffed: 120 uncuffed). &lt;1 year age 21 cuffed: 62 uncuffed)</td>
<td>(a) Post-extubation stridor and (b) significant long-term sequelae.</td>
<td>(i) No difference in overall rates of post-extubation stridor (15.1% cuffed: 14.7% uncuffed). (ii) In the group &lt;1 year of age, 1/16 (6.1%) of patients with cuffed ETTs and 14/95 (14.7%) of patients with uncuffed ETTs developed stridor but due to small numbers, this did not reach significance (p=0.43). (iii) 33/188 (17%) patients re-admitted over following 18 months, and none showed problems with upper airway. (iv) They concluded that cuffed ETTs in paediatric patients are not associated with an increased risk of laryngeal injury</td>
<td>Not randomised, no standardised criteria for ETT selection. Decision for type of tube up to treating physician. Cuffed ETTs of older low volume high pressure type.</td>
</tr>
<tr>
<td>Newth et al <em>(2004)</em></td>
<td>Prospective cohort</td>
<td>860 critically ill children in a PICU over 1 year period. 597 patients in the first 5 years of life with 210 patients (35%) having a cuffed ETT. 79 patients were &lt;1 month age (27 cuffed: 115 uncuffed intubations) and 310 patients 1 month – 1 year age (126 cuffed: 208 uncuffed intubations).</td>
<td>Incidence of post-extubation stridor.</td>
<td>(i) No difference in number requiring adrenaline for post-extubation stridor in the &lt;1 month age group (7.4% cuffed: 6.1% uncuffed) or the 1 month-1 year age group (9.5% cuffed: 6.7% uncuffed). (ii) They concluded no significant differences in use of racemic epinephrine for post-extubation stridor, the rate of successful extubation or the need for tracheotomy between those with cuffed and uncuffed ETT in any age group.</td>
<td>Not randomised, choice of ETT up to treating physician.</td>
</tr>
<tr>
<td>Fernandes et al <em>(2014)</em></td>
<td>RCT</td>
<td>Children under 8 years age in PICU setting. 136 cuffed:118 uncuffed.</td>
<td>(a) Post-intubation laryngitis and (b) failed extubation.</td>
<td>Incidence of post-intubation laryngitis 58.8% in cuffed group v 62.7% in the uncuffed group (p=0.52). Extubation failure occurred 8.8% of children in cuffed group v 9.3% in the uncuffed group (p=0.89).</td>
<td>Conference proceedings presented at 7th World Congress on Pediatric Intensive and Critical Care (PICC) in 2014. No further details available.</td>
</tr>
</tbody>
</table>
2.6 CONCLUSIONS

Since the advent of new HVLP cuffed ETTs, they are being used with increasing frequency from birth. Cuffed ETTs offer the advantages of a more controllable leak improving ventilation, a decreased need to re-intubate to find the correct size tube, decreased fresh and anaesthetic gas use and potentially decreased airway damage. There is mounting evidence for the safety of the use of cuffed ETTs in infants and small children for short-term ventilation during anaesthesia with regards to short-term outcomes. However, the use of cuffed ETTs for longer-term ventilation in the intensive care setting, efficiency of ventilation, use with high frequency ventilation and longer-term outcomes is poorly studied.

2.7 ADDITIONAL COMMENTS

Since this literature review and publication, there have been further papers published in this field:

Sathyamoorthy et al retrospectively review 324 intubated neonates over a one year period (May 2011-June 2012) comparing uncuffed and cuffed (Microcuff®) ETTs with regards to the outcome of post-extubation stridor. 29 patients received a cuffed ETT during surgery and the other 295 patients received uncuffed ETTs. However, they do not report on the weight or gestational age at the time of intubation, only birth weight and gestational age at birth. They reported an incidence of post-extubation stridor in 17.2% of those receiving cuffed ETT and 7.5% receiving uncuffed ETT. After multi-regression analysis, they report that the use of Microcuff® ETT was associated with an increased odds of stridor (AOR= 9.27, CI 1.88-45.67). However, they state that 26/29 patients with cuffed ETTs had a larger than recommended size and that cuff pressures were not checked.54

DeMichele et al reported upon their experience of the use of using cuffed ETTs in 196 infants <5kg undergoing major cardiac surgery (2008-2013). The mean weight of the study infants was 3.6kg (SD 0.6). Nearly 26% of the infants were preterm (<37 weeks gestation) and <3kg. The average period of intubation was 7-9 days. They described that their practice was to remove all air from the cuff and then
inflate the cuff until a minimal air leak was observed with a goal cuff pressure of 10-12 mmHg. If the infant could be adequately ventilated with the cuff down, after discussion with the intensivist, the cuff could be deflated. They concluded that the use of cuffed ETTs was not associated with airway complications.55

Chambers et al performed an RCT in children (0-16yrs) comparing tidal volume and leakage around cuffed and uncuffed tracheal tubes in children who required standardised mechanical ventilation of their lungs in the operating theatre. During volume-controlled ventilation, leakage was significantly less with cuffed ETTs than with uncuffed ETTs; in ml.kg⁻¹, median (IQR [range]) 0.20 (0.13-0.39 [0.04-0.60]) vs. 0.82 (0.58-1.38 [0.24-4.85]), respectively, p < 0.001. There were more short-term complications with uncuffed tracheal tubes, but no major complications were recorded in either group at long-term follow-up.56

2.8 ACKNOWLEDGEMENTS

Full authorship list

The published manuscript included the following authors: Shripada Rao and Corrado Minutillo.

Author Contributions

Rebecca Thomas was the primary author of this paper. RT and SR searched for relevant articles. RT drafted the manuscript. SR and CM critically reviewed the manuscript.

Prior Publication

The data and scientific discussion presented in this chapter has been peer reviewed and published in Archives of Disease in Childhood, Fetal and Neonatal Edition, which has been incorporated into this thesis.

3.1 PREFACE

The most serious of long-term complications occurring from the use of endotracheal tubes is subglottic stenosis (SGS). SGS is a narrowing of the airway in the subglottic area which rarely is congenital, and most commonly is acquired from scarring secondary to airway instrumentation. SGS is graded according to the Myer-Cotton system. The Myer-Cotton classification of SGS is as follows: Grade 1 (0-50% stenosis); Grade 2 (51-70% stenosis); Grade 3 (71-99% stenosis); and Grade 4 (100% stenosis). Depending upon the degree of stenosis, SGS causes varying symptoms of airway obstruction. In the severest of cases (grades 3 and 4), patients require a tracheostomy and/ or laryngotracheal reconstructive (LTR) surgery.

Historically there have been concerns that the use of cuffed ETTs in neonates and infants increases the risk of SGS. This chapter describes a retrospective study aiming to analyse the current incidence and risk factors associated with severe SGS in neonates in our institution. This is in order to define the current size of this most important complication of intubation for ventilation which causes high cost to both the healthcare system and the patient and family.

The data presented in this chapter have been peer reviewed and published in Archives of Disease in Childhood, Fetal and Neonatal Edition. Copies of the published manuscript and forward from the editor (by way of ‘Highlights from this issue - Editor’s Choice’) are presented in Appendix B.

3.2 INTRODUCTION

Severe acquired subglottic stenosis (SASGS) in neonatal intensive care unit (NICU) graduates is a serious consequence of endotracheal intubation for mechanical ventilation, which incurs a high cost to the individual patient and family and to the healthcare system.

The reported incidence of subglottic stenosis (SGS) in this group ranges from 0-11%, but is generally believed to be between 0-2%. The main reported risk factors for SASGS are low birth weight, low gestational age, longer duration of intubation, traumatic intubation, multiple numbers of endotracheal tubes (ETTs), a
large diameter ETT, and infant activity level. These reports have varied in their definition of SASGS, the method used for diagnosis and the population studied. In addition, due to the rarity of SASGS, many studies have suffered from low numbers making it difficult to perform any meaningful analyses. The majority of reports are from the 1970s and 1980s when the care of neonates in the intensive care was quite different and the surviving neonates were of higher gestational age and birth weight. Recent advances in neonatal intensive care have resulted in increased survival of extremely low birth weight infants. There have been no published studies on incidence of acquired SGS in neonates since 2007 or on the associated risk factors since 2000.

Therefore, we aimed to analyze the current incidence and risk factors associated with SASGS requiring surgical intervention in NICU graduates.

### 3.3 METHODS

We performed a retrospective case-control study of NICU graduates who developed SASGS requiring surgical intervention over a 9 year period from January 2006 to December 2014. Princess Margaret Hospital for Children (PMH), Perth is the only tertiary children’s hospital in the state of Western Australia (WA) and caters to a total population of nearly 2.5 million people. King Edward Memorial Hospital for Women (KEMH) is the sole tertiary perinatal centre in the entire state of Western Australia. The combined neonatal directorate of KEMH and PMH care for more than 3000 neonates per year, of whom, approximately 500 receive mechanical ventilation. All newborn infants in the state requiring level 3 neonatal care are managed in one of these institutions. Being the sole tertiary paediatric centre in the state, PMH is the only place where advanced surgical airway procedures are performed children.

**Inclusion criteria:** Cases of SASGS were defined as children with SGS who required laryngotracheal reconstruction (LTR), cricoid split or tracheostomy and had previously been intubated in the neonatal period. They were initially identified from the ENT database and confirmed as having received intubation in the neonatal
period by checking the NICU database. The NICU database is a centralised database that has information about all neonates admitted across both sites (KEMH and PMH). The symptoms of SASGS could have appeared while still in the NICU or following discharge home.

**Exclusion criteria:** Children who had surgical intervention for SASGS, but were not previously intubated in the neonatal period, those with genetic syndromes, congenital SGS and those who had their neonatal care outside of our institution were excluded. Congenital SGS was defined as SGS diagnosed on laryngoscopy where the patient had never previously been intubated or where there was other associated airway anomalies.

For each case, two matched controls were selected randomly from the centralised NICU database. The controls were matched for gestation and year of birth. The clinical details of the study participants were obtained by reviewing their medical records. Information was collected on gestational age, birth weight, age at presentation, laryngoscopy findings prior to surgery graded according to Myer-Cotton grading system\(^5^7\) where available, details of surgical airway procedures, and age at surgical intervention. The details of number of intubations, days intubated, unplanned extubations (an extubation which had not been medically ordered, i.e. accidental), size of ETT, number of intubation attempts, traumatic intubations (where fresh blood was reported immediately post-intubation or there was a written comment of ‘traumatic intubation’ in patient records), culture proven sepsis (blood culture positive), and CMV infection. The Sherman Ratio\(^6^4\) (ETT internal diameter (mm)/ gestational age) was calculated for each intubation episode to assess appropriateness of ETT size. A Sherman Ratio of >0.10 indicates that the ETT is disproportionately larger for the gestational age of the infant. Similar information was collected for the controls.

Normal intubation practice during the study period was to use uncuffed Portex\(^\circ\) siliconized ETTs. In general, infants <1000g received 2.5mm ETT; 1000-2000g 3.0mm; 2000-3000g 3.0-3.5mm; and >3000g 3.5mm. The predominant route of intubation was oro-tracheal.
Incident cases of SASGS were calculated for infants born from 2006-2012 inclusive, as some of the neonates born from 2013 onwards may not have yet presented with SASGS. The denominator for population incidence was from the data of registered births from WA Government over that time period. The denominators for NICU admissions and ventilated patients were obtained from the NICU databases.

Statistical analyses were performed using IBM SPSS 20.0 for Windows (Armonk, NY: IBM Corp) and StatXact 8.0, Cytel Inc, 2007. Continuous data were summarised using medians, interquartile ranges (IQR) and ranges (R), and categorical data summarised using frequency distributions. Univariate comparisons of continuous outcomes were conducted using general linear models with matched cases and controls modelled as random effects. Conditional logistic regression was used to test the association between categorical intubation characteristics and SASGS univariately, and multivariately with simultaneous modelling of other candidate risk factors, including assessment of the matched variables. Multivariate modelling was conducted using a forward step-wise method to avoid overfitting of parameters.

Data are presented as unadjusted (OR) and adjusted odds ratios (aOR) with accompanying 95% confidence intervals (CI). All tests were two-sided, and a p-value <0.05 was considered statistically significant.

The study was reviewed and approved by the hospital’s Quality Improvement Committee as having met the ‘Australian National Health and Medical Research Council requirements for quality assurance and audit projects’.

3.4 RESULTS

Over the nine year period, 50 infants and children underwent surgical intervention for SGS: 7/50 (14%) had congenital SGS and 43/50 (86%) had SASGS (aged 2 weeks–13 years). Of the 43 with SASGS, 37 were patients who had previously been intubated in the neonatal period, of which, 35/37 (94.6%) were <30 weeks gestation at birth. Thirty-five neonates were cared for in our NICUs. The other 2 ex-preterm infants were of 28 and 30 weeks gestation and were born and cared for in another country, hence, further details were not available. Of the two infants >30 weeks gestation, one was a 34 week neonate with congenital hydrops (dry weight...
~2300g) intubated for 16 days with 3.5mm ETT; and the other a 38 week neonate of 3220g intubated for seizures for 3 days with 3.5mm ETT. The remaining 6 patients were PICU graduates (see figure 3.1).

*Figure 3.1 – Patients who underwent surgery for severe subglottic stenosis (SGS) 2006-2014*

The non-NICU graduates who developed acquired SGS were: a six week old infant with bronchiolitis who was intubated for 5 days; a three month old infant with trisomy 21 who was intubated for 2 days post-cardiac surgery; a 15 month old with Pierre-Robin Sequence who in had a tracheostomy in the neonatal period which caused SGS; a nine year old with lymphoma who developed SGS secondary to
vincristine toxicity; a nine year old child with trisomy 9p who was intubated for 10 days for sepsis; and a 13 year old child with staphylococcal sepsis who was intubated for 10 days and was assumed to have necrotising tracheitis.

Of the seven patients with congenital SGS, two were diagnosed at birth, three patients between 1-3 months of age, one patient at one year of age and one patient at 12 years. The modes of presentation were: stridor in four patients; dyspnoea in one patient; and difficulties intubating for an unrelated procedure in two patients. Four patients with congenital SGS had associated syndromes/other anomalies (Di George Syndrome, TAR syndrome/ VACTERL association/ anorectal anomaly) whilst it was an isolated finding in the other three patients. All patients underwent a LTR, though two patients had an initial supraglottoplasty, one of which having a temporary tracheostomy prior to LTR.

3.4.1 Incidence of SGS in neonates in WA (2006-2012):

The incidence of congenital SGS requiring surgical intervention in all live born infants was 4/216,748= 0.002%, equating to a population incidence of 1.8/100,000 live births.

The incidence of SASGS in surviving previously intubated neonates was 27/2913 (0.93%). The overall population incidence was 27/216,748= 0.012%, equating to a population incidence of 12.5/100,000 live births (table 3.1). The incidence was higher in preterm infants <28 weeks gestation (24/623 (3.8%)) compared to infants ≥28 weeks (3/2290 (0.13%); p=0.0001). The incidence of acquired SGS was almost exclusively confined to infants <1500g at birth (table 3.2).
### Table 3.1 – Incidence of severe acquired SGS based on gestational age at birth (2006-2012)

<table>
<thead>
<tr>
<th>Gestation at Birth</th>
<th>All neonatal admissions (Actual values, percentage and 95% confidence intervals)</th>
<th>Intubated neonates (Actual values, percentage and 95% confidence intervals)</th>
<th>Neonates intubated and survived to discharge (Actual values, percentage and 95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22/40</td>
<td>0/3 = 0% (0%-56%)</td>
<td>0/3 = 0% (0%-56%)</td>
<td>0/3 = 0% (0%-56%)</td>
</tr>
<tr>
<td>23/40</td>
<td>5/88 = 5.7% (2.4%-12.6%)</td>
<td>5/88 = 5.7% (2.4%-12.6%)</td>
<td>5/55 = 9.1% (3.9%-19.6%)</td>
</tr>
<tr>
<td>24/40</td>
<td>5/120 = 4.2% (1.8%-9.4%)</td>
<td>5/120 = 4.2% (1.8%-9.4%)</td>
<td>5/99 = 5.1% (2.1%-11.3%)</td>
</tr>
<tr>
<td>25/40</td>
<td>5/147 = 3.4% (1.5%-7.7%)</td>
<td>5/147 = 3.4% (1.5%-7.7%)</td>
<td>5/127 = 3.9% (1.7%-8.9%)</td>
</tr>
<tr>
<td>26/40</td>
<td>2/197 = 1.0% (0.2%-3.6%)</td>
<td>2/190 = 1.1% (0.2%-3.75%)</td>
<td>2/171 = 1.2% (0.3%-4.2%)</td>
</tr>
<tr>
<td>27/40</td>
<td>7/199 = 3.5% (1.7%-7.1%)</td>
<td>7/176 = 4.0% (1.9%-7.98%)</td>
<td>7/168 = 4.1% (2.0%-8.35%)</td>
</tr>
<tr>
<td>28/40</td>
<td>1/283 = 0.35% (0.06%-1.97%)</td>
<td>1/238 = 0.42% (0.07%-2.34%)</td>
<td>1/223 = 0.45% (0.08%-2.5%)</td>
</tr>
<tr>
<td>29/40</td>
<td>1/310 = 0.32% (0.06%-1.8%)</td>
<td>1/214 = 0.47% (0.08%-2.6%)</td>
<td>1/203 = 0.49% (0.09%-2.7%)</td>
</tr>
<tr>
<td>30-33/40</td>
<td>0/2536 = 0% (0%-0.15%)</td>
<td>0/705 = 0% (0%-0.54%)</td>
<td>0/676 = 0% (0%-0.56%)</td>
</tr>
<tr>
<td>34-36/40</td>
<td>1/4315 = 0.02% (0%-0.13%)</td>
<td>1/456 = 0.22% (0.04%-1.2%)</td>
<td>1/430 = 0.23% (0.04%-1.3%)</td>
</tr>
<tr>
<td>&gt;37/40</td>
<td>0/7578 = 0% (0%-0.07%)</td>
<td>0/1274 = 0% (0%-0.3%)</td>
<td>0/758 = 0% (0%-0.5%)</td>
</tr>
<tr>
<td>Overall</td>
<td>27/15803 = 0.17% (0.12%-0.25%)</td>
<td>27/3155 = 0.85% (0.59%-1.24%)</td>
<td>27/2913 = 0.93% (0.64%-1.34%)</td>
</tr>
</tbody>
</table>

### Table 3.2 – Incidence of severe acquired SGS based on birth weight (2006-2012)

<table>
<thead>
<tr>
<th>Birth weight</th>
<th>All neonatal admissions (Actual values, percentage and 95% confidence intervals)</th>
<th>Neonates intubated and survived to discharge (Actual values, percentage and 95% confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All infants &lt;1500g</td>
<td>27/1988 = 1.4% (0.93%-1.97%)</td>
<td>27/1847 = 1.5% (1%-2.1%)</td>
</tr>
<tr>
<td>&lt;500g</td>
<td>1/43 = 2.3% (0.41%-12.1%)</td>
<td>1/22 = 4.5% (0.81%-21.8%)</td>
</tr>
<tr>
<td>500-999g</td>
<td>19/747 = 2.5% (1.63%-3.94%)</td>
<td>19/659 = 2.9% (1.85%-4.6%)</td>
</tr>
<tr>
<td>1000-1499g</td>
<td>6/1198 = 0.5% (0.23%-1.1%)</td>
<td>6/1166 = 0.5% (0.23%-1.1%)</td>
</tr>
<tr>
<td>1500-1999g</td>
<td>0/2128 = 0% (0%-0.18%)</td>
<td>0/211 = 0% (0%-1.79%)</td>
</tr>
<tr>
<td>Infants ≥2000g</td>
<td>1/11687 = 0.009% (0%-0.05%)</td>
<td>1/855 = 0.12% (0.02%-0.66%)</td>
</tr>
<tr>
<td>Overall</td>
<td>27/15803 = 0.17% (CI: 0.12%-0.25%)</td>
<td>27/2913 = 0.93% (CI: 0.64%-1.35%)</td>
</tr>
</tbody>
</table>
3.4.2 Grading of SASGS based on Myer-Cotton Classification:\(^{57}\)

Of the thirty-five patients who underwent surgical intervention for SASGS, on laryngoscopy, seven patients had grade 2 stenosis, 23 patients had grade 3, and one patient had grade 4 on the Myer-Cotton Classification.\(^{57}\) For the remaining four patients, information on the grade was not available.

3.4.3 Age at presentation in NICU graduates:

The median chronological age at which symptoms of SASGS appeared was 3.0 months (IQR: 1.9-4.2, R: 0.2-78.6). The median chronological age at which LTR was performed was 12.7 months (IQR: 5.9-38.7, R: 3.3-151.2) and median corrected age (CA) 10.2 months (IQR: 2.0-35.0, R: (-0.5)-147.2).

3.4.4 Mode of presentation in NICU graduates:

The modes of presentation were: stridor in 20/35 (51.7%) of which, nine (45%) of these developed stridor during their NICU stay and eleven (55%) post-discharge; failed extubation in the NICU in 6/35 (17.1%); symptoms during a viral illness in 5/35 (14.3%); inability to be weaned off CPAP in 2/35 (5.7%); and other respiratory symptoms such as dyspnoea/nocturnal symptoms/’wheeze’ in 2/35 (5.7%).

3.4.5 Type of surgical airway intervention for NICU graduates:

Three patients initially underwent a supraglottoplasty at a postmenstrual age (PMA) of 32 weeks, 40 weeks PMA and two months CA respectively, and subsequently all required LTR. Eleven patients underwent an initial tracheostomy at a median PMA of 47 weeks (range 32 weeks PMA - 6 months CA). All but three of these patients subsequently underwent LTR at a median CA of 15.5 months (range 5 - 36 months CA). The median time from tracheostomy to LTR was 15.5 months (range 1 - 35 months). Of the 32/35 that underwent LTR, the procedure occurred at a median CA of 10.5 months (range 0 - 88 months CA).
3.4.6 Comparison of 35 cases with 70 matched controls:

Baseline characteristics were similar between cases and controls (table 3.3).

**Table 3.3 – Baseline characteristics of cases and controls**

<table>
<thead>
<tr>
<th></th>
<th>Cases N=35</th>
<th>Controls N=70</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)*</td>
<td>25.7 (24.0-27.4; 23.0-38.0)</td>
<td>25.4 (24.1-27.2; 23.1-38.9)</td>
<td>0.615</td>
</tr>
<tr>
<td>Birth weight (g)*</td>
<td>730 (645-1040; 410-3220)</td>
<td>718 (596-961; 400-3395)</td>
<td>0.274</td>
</tr>
<tr>
<td>Male gender*</td>
<td>23/35 (65.7%)</td>
<td>42/70 (60.0%)</td>
<td>0.597</td>
</tr>
<tr>
<td>Intrauterine growth restriction* (IUGR)</td>
<td>4/35 (11.4%)</td>
<td>11/70 (15.7%)</td>
<td>0.572</td>
</tr>
<tr>
<td>Antenatal corticosteroids*</td>
<td>29/33 (87.8%)</td>
<td>63/67 (94.0%)</td>
<td>0.434</td>
</tr>
<tr>
<td>Inborn*</td>
<td>28/34 (82.3%)</td>
<td>64/69 (92.7%)</td>
<td>0.172</td>
</tr>
<tr>
<td>Chorioamnionitis*</td>
<td>3/34 (8.8%)</td>
<td>7/69 (10.1%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

*Data represents median (interquartile range; range)* or N (%)* as appropriate unless otherwise specified.

Infants with SASGS were more likely to have had more previous ETTs (median 4 vs median 2; p<0.001), an episode of traumatic intubation [12/35 (34.3%) v 5/70 (7.1%); p=0.003], an episode of unplanned extubation [16/35 (45.7%) vs 14/70 (20.0%), p=0.007]; an oversized ETT (i.e. Sherman Ratio >0.1) [26/35 (74.3%) v 30/70 (42.9%); p=0.001] and ETT for >7 days [28/35 (80%) v 40/70 (57.1%), p=0.009] (table 3.4). Risk factors evident only in infants with SGS were stridor during neonatal admission 20/35 (57.1%), acquired CMV 3/35 (8.8%), and inability to extubate 5/35 (14.3%) (table 3.4).
Table 3.4 – Potential contributing factors in the development of SASGS by cases and controls

<table>
<thead>
<tr>
<th></th>
<th>Cases N=35</th>
<th>Controls N=70</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of previous intubations*</td>
<td>4 (2.9; 1-20)</td>
<td>2 (1-5; 0-8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;5 previous intubations</td>
<td>15 (42.9%)</td>
<td>12 (17.1%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Total days with ETT *</td>
<td>16 (8-49; 1-99)</td>
<td>9.5 (1-37.5; 0-80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of days each ETT was in place*</td>
<td>4.5 (3.0-6.3; 1.0-16.5)</td>
<td>4.3 (n=64) (2.0-7.5; 0.5-26.7)</td>
<td>0.359</td>
</tr>
<tr>
<td>ETT &gt;7 days*</td>
<td>28 (80%)</td>
<td>40 (57.1%)</td>
<td>0.009</td>
</tr>
<tr>
<td>ETT &gt;14 days*</td>
<td>21 (60%)</td>
<td>32 (45.7%)</td>
<td>0.069</td>
</tr>
<tr>
<td>ETT &gt;21 days*</td>
<td>15 (42.9%)</td>
<td>28 (40.0%)</td>
<td>0.695</td>
</tr>
<tr>
<td>Episode of unplanned extubation*</td>
<td>16 (45.7%)</td>
<td>14 (20.0%)</td>
<td>0.007</td>
</tr>
<tr>
<td>&gt;2 unplanned extubations/100 days ventilated*</td>
<td>15 (42.9%)</td>
<td>12 (17.1%)</td>
<td>0.005</td>
</tr>
<tr>
<td>Multiple attempts at intubation*</td>
<td>12 (34.3%)</td>
<td>15 (21.4%)</td>
<td>0.170</td>
</tr>
<tr>
<td>Episode of traumatic intubation*</td>
<td>12 (34.3%)</td>
<td>5 (7.1%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Episode of intubation where Sherman ratio &gt;0.1*</td>
<td>26 (74.3%)</td>
<td>30 (42.9%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Episode of proven sepsis*</td>
<td>19 (55.9%)</td>
<td>47 (67.1%)</td>
<td>0.222</td>
</tr>
</tbody>
</table>

Data represents median* (interquartile range; range) or N (%)* as appropriate unless otherwise specified.

On multivariate analysis, risk factors for SASGS included: intubation with an ETT with a Sherman Ratio >0.1 (aOR: 6.40; 95% CI: 1.65-24.77; p=0.007); >5 previous ETTs (aOR: 3.74; 95% CI: 1.15-12.19; p=0.029) and traumatic intubation (aOR: 3.37; 95% CI: 1.01-11.26; p=0.048) (table 4). SASGS was diagnosed in only 4/35 (11.4%) infants with none of these risk factors, 15/35 (42.9%) with one risk factor and 16/35 (45.7%) with two or three risk factors. 6/35 (17.1%) infants had all three risk factors. Other risk factors assessed in the model included ETT for >7 days, multiple attempts at intubation, unplanned extubations/100 days ventilated, sepsis, and the matched characteristics, all of which were not significant in the adjusted analyses (table 3.5).
Table 3.5 – Risk factors assessed for their influence on SASGS showing unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Unadjusted OR 95% CI</th>
<th>Adjusted OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episode of intubation where Sherman Ratio &gt;0.1</td>
<td>7.92 (2.25-27.92)</td>
<td>6.40 (1.65-24.77)</td>
</tr>
<tr>
<td>&gt;5 previous ETTs</td>
<td>4.13 (1.46-11.71)</td>
<td>3.74 (1.15-12.19)</td>
</tr>
<tr>
<td>Episode of traumatic intubation</td>
<td>4.80 (1.69-13.62)</td>
<td>3.37 (1.01-11.26)</td>
</tr>
<tr>
<td>Duration ETT &gt;7 days</td>
<td>4.65 (1.46-14.76)</td>
<td>1.85 (0.44-7.85)</td>
</tr>
<tr>
<td>Multiple attempts at intubation</td>
<td>1.88 (0.76-4.62)</td>
<td>0.94 (0.33-2.62)</td>
</tr>
<tr>
<td>Episode of sepsis</td>
<td>0.57 (0.23-1.41)</td>
<td>0.37 (0.08-1.64)</td>
</tr>
</tbody>
</table>

**OR-odds ratio; CI-confidence interval; ETT-endotracheal tube**

### 3.5 DISCUSSION

This population-based case-control study reports on the association between SASGS and various neonatal risk factors among a modern cohort of NICU graduates from Western Australia. It also reports on the incidence of SASGS across various gestational age and birth weight categories.

Leung et al\textsuperscript{78} reported on the population incidence of neonatally acquired SGS in a comparable population in the state of Victoria, Australia. The incidence of 4.95/100,000 live births was lower than our incidence of 12.5/100,000 live births. The possible reason for this disparity was the fact that they included infants only up to 12 months of age at surgery, whereas we included all children up to 12 years of age. The other reason could be the fact that there were no patients born <24 weeks gestation in their cohort.

The incidence of SASGS in our study was 0.93% out of a total of 2913 children who had required endotracheal intubation and mechanical ventilation in the neonatal period and survived to discharge. Previously reported incidences of SGS in all intubated neonates was 0% by Walner et al\textsuperscript{69} and Contencin et al,\textsuperscript{65} but their numbers of ventilated patients were very small (281 and 247 respectively). Other authors reported on a selected population only (e.g. patients ventilated for >48hrs,\textsuperscript{67, 70} or >7 days,\textsuperscript{71, 73}) and some reported on a specific groups of
Our incidence of 27/1847 (1.5%) in infants with a birth weight of <1500g is comparable with Suzumura et al.\textsuperscript{73} and Nicklaus et al.\textsuperscript{66} who reported incidences of 3.1% and 2.4% respectively. Gaynor et al.\textsuperscript{72} reported an incidence of 0% in infants<1500 grams, although they only had a denominator of 128 patients. Acquired SGS has not previously been shown to be associated with gestational age.\textsuperscript{63,64,73,74} However, previous numbers were small from an era when extremely preterm infants born at 23 and 24 week gestation infants did not survive. Our figures show that the incidence of SASGS is especially high in surviving extreme premature infants of 23 and 24 weeks gestation. This raises the importance of having a high index of suspicion of SGS in such infants, given that more than 30% of our study infants were asymptomatic in the neonatal period. Downing et al.\textsuperscript{71} carried out laryngoscopy on 117 preterm infants who had been intubated for >7 days or who had an O\textsubscript{2} requirement at 28 days or at 36 weeks CGA and found that 27.3% had moderate or severe abnormalities and 11.1% had SGS.

Commonly reported risk factors in the development of acquired SGS are the number of ETTs\textsuperscript{63,64,66,71,77} and length of time intubated.\textsuperscript{64,66,71,75,80} Like previous studies, we found an increased risk of SASGS in infants intubated for >7 days,\textsuperscript{63} but not for those intubated >14 days\textsuperscript{73,80} or >21 days.

Unplanned extubations (UE) have been suggested as a risk factor for development of SGS.\textsuperscript{81} Da Silva et al showed a link between UE and post-extubation stridor, but the patients did not go on to subsequently present with SGS.\textsuperscript{82} Our study found that UE in the neonatal period was associated with acquired SGS on univariate analyses, but not multivariate analysis.

Our study supports findings of previous studies that have shown an association between the size of ETT and subsequent development of SASGS.\textsuperscript{64,65,71} Lima et al.\textsuperscript{83} showed that the area of the cricoid lumen in extremely preterm infants is smaller than the external diameter of any available ETTs. Sherman et al.\textsuperscript{64,84} proposed the following formula to guide the selection of the appropriate size of that ETT for neonatal intubations: ETT size/ gestational age <0.1 and found this approach to significantly reduce the incidence of SGS in neonates. Based on this formula, infants with gestational age <30 weeks would receive 2.5mm ETT, those at 31-35 weeks
receive 3.0mm ETT and >36 weeks receive 3.5mm ETT. From a cohort of 247 neonates, Contencin et al\textsuperscript{65} showed that intubation with 2.5mm ETT for infants <2.5kg and 3.0mm ETT for those 2.5-4kg, resulted in zero incidence of SGS. However, the patients were of higher birth weight and had a shorter duration of intubation than in other studies. The use of such small sized ETTs could cause problems with ventilation due to large leaks around the ETT. Hence, using the Sherman Ratio when selecting the size of ETT and ensuring an appropriate ‘leak around the ETT’ upon intubation, has the potential to achieve adequate ventilation, whilst avoiding the side effects of unduly large ETTs.

A theoretically attractive option to reduce the incidence of SASGS is to use cuffed ETTs for neonatal intubations.\textsuperscript{85} This is due to the fact that the outer diameter of the ETT used is 0.5mm smaller for a cuffed ETT than for an uncuffed ETT. This means that there is a smaller ETT through the delicate elliptically shaped\textsuperscript{83} non-distensible cricoid and instead the cuff makes its seal in the trachea where there are U-shaped cartilages and a muscular dorsal wall which allows for some distension. However, since the smallest available cuffed ETT is 3.0mm (Microcuff\textsuperscript{®} ETT), they are not of use in extremely preterm infants.

In our cohort of infants with SASGS, nearly 44% did not have stridor in the neonatal period. Holzki et al\textsuperscript{43} cautioned that airway injury is not always accompanied by post-extubation stridor, and that it may develop months after extubation as scar tissue forms. Fan et al\textsuperscript{86} showed that in 73 consecutively intubated neonates, 38% with moderate to severe injury on laryngoscopy did not have stridor. On the other hand, all patients with stridor had moderate or major injury. None of our patients without SASGS had stridor during their neonatal stay, suggesting that as demonstrated by Fan et al,\textsuperscript{86} presence of stridor should alert to the possibility of significant injury.

Suzumura et al\textsuperscript{73} showed a relationship between infection and development of SGS, however, in our study, there was no correlation with sepsis on multivariate analysis. Of interest, there have been case reports of CMV causing SGS and laryngotracheitis in infants and immunocompromised patients.\textsuperscript{87-90} In our cohort, three patients with
SASGS had acquired CMV infection with none in the control group. Though this was an interesting finding, multivariate analysis did not confirm an association.

The main study limitation is that this is a retrospective study, and hence relied upon the reporting of procedures and incidents in the medical records, which was suboptimal at times. This is particularly relevant for events such as unplanned extubation and traumatic intubation. It is possible that some of the cases and controls might have moved interstate/overseas and hence were not identified in our ENT database. Although the cohort is large for this type of study, associations do not always equate to cause and effect. Conversely, the associations that did not reach statistical significance cannot be totally dismissed; the lack of apparent significance may simply be due to the fact that the sample size was insufficient to detect a statistically significant difference. Another limitation was that since it was a retrospective study, information on the severity of SGS based on accepted system of Myer-Cotton grading was not available from the medical records of all the study infants. A third limitation was that even though we labelled all our cases as having SASGS, there is a possibility that some of them may have had an element of congenital SGS which became symptomatic subsequently. The fourth limitation is that the incidence of SASGS that we have reported may not be generalizable, given that prenatal care of high-risk women and postnatal care of preterm infants differ from one country to another and one region in a country to another. The main strengths of this study are the reasonably large size and the inclusion of all SASGS from a state-wide population which included all ventilated neonates in the state. The other strength is the use of multivariate analysis to adjust for potential confounders and the fact that the study population is from the recent decade.

3.6 CONCLUSION

SASGS is a serious consequence of intubation for mechanical ventilation in NICU graduates, especially in extremely preterm infants. Minimising trauma during intubation, avoiding recurrent extubation/ intubations and using appropriate sized ETTs may be potential strategies to prevent this serious complication. Similar
studies from other centres will enhance further understanding of the causative factors of this serious condition and also enable benchmarking.

3.7 ACKNOWLEDGEMENTS

**Full authorship list**

This chapter included the following authors: Shripada Rao, Corrado Minutillo, Shyan Vijayasekaran, Elizabeth Nathan.

**Author contributions**

Rebecca Thomas was the primary author of this paper. RT, SR, CM and SV all contributed to study design and concept. RT and SR had full access to all the data in the study and take responsibility for the integrity of the data. EN performed statistical methods and analysis. RT led study and drafted manuscript. All authors critically reviewed the manuscript.

**Additional contributions**

Thank you to Dr Jagdev Singh who assisted in data collection and Damber Surestha for providing local neonatal unit statistics.

**Prior Publication**

The data and scientific discussion presented in this chapter has been peer reviewed and published in *Archives of Disease in Childhood, Fetal and Neonatal Edition*, which has been incorporated into this thesis.


This paper was ‘Editor’s choice’ and was forwarded in ‘highlights in this issue’.
CHAPTER 4 – Current use of cuffed endotracheal tubes in neonates in Australia and New Zealand

CONTENTS OF CHAPTER

CHAPTER 4 .......................................................................................................................... 43
4.1 Preface.......................................................................................................................... 45
4.2 Introduction.................................................................................................................... 45
4.3 Methods......................................................................................................................... 46
  4.3.1 Study population.................................................................................................... 46
  4.3.2 Data collection....................................................................................................... 46
  4.3.3 Survey instrument................................................................................................. 46
  4.3.4 Outcome measures............................................................................................... 46
  4.3.5 Statistical analysis................................................................................................. 47
  4.3.6 Ethics..................................................................................................................... 47
4.4 Results.......................................................................................................................... 47
  4.4.1 Sample characteristics.......................................................................................... 47
  4.4.2 Rates of cuffed ETT use....................................................................................... 47
  4.4.3 Use of cuffed ETTs in infants <3kg.................................................................... 48
  4.4.4 Type of cuffed ETTs used.................................................................................... 49
  4.4.5 Technique for cuff inflation.................................................................................. 49
  4.4.6 Regularity of cuff pressure checks...................................................................... 49
  4.4.7 Maximum cuff pressure used.............................................................................. 49
  4.4.8 Which physicians intubate with cuffed ETTs...................................................... 50
  4.4.9 Reported problems with the use of cuffed ETTs............................................... 50
  4.4.10 Future use of cuffed ETTs if evidence for use provided.................................... 51
4.5 Discussion...................................................................................................................... 51
4.6 Additional comments................................................................................................... 53
4.7 Acknowledgements...................................................................................................... 53
4.1 PREFACE

We have been aware that over the last few years, cuffed ETTs have been increasingly used in neonates by anaesthetists in surgical patients at our institution. We are anecdotally aware that this is also happening in other institutions, however, there is no literature to say how often cuffed ETTs are being used in neonates and small infants.

To answer this question, we surveyed all level 3 NICUs and PICUs in Australia and New Zealand to find out how many units are using cuffed ETTs and how they are managing them.

A truncated version of these data presented in this chapter has been peer reviewed and published in *Archives of Disease in Childhood, Fetal and Neonatal Edition*. A copy of the published manuscript is presented in Appendix C.

4.2 INTRODUCTION

Orliaguet et al in 2001 surveyed the practice of 200 paediatric anaesthetists across France. The response rate was 65% and they found that 25% paediatric anaesthetists used cuffed ETTs in children routinely and 38% used them frequently.10

Flynn et al in 2008 surveyed 30 PICUs and paediatric anaesthetic departments across the United Kingdom. The response rate was 67% for PICUs and 50% for anaesthetic departments. Overall, 60% PICU consultants described themselves as frequent or routine cuffed ETT users compared with only 27% of anaesthetists. Only 5% PICU and 7% anaesthetic respondents routinely used cuffed ETTs in neonates and infants.91

The only other published data on the use of cuffed ETTs in infants and children is by Nishisaki et al in 2013. They reported that 90% of tracheal intubations across 15 PICUs in North America were with cuffed ETTs, but there was no breakdown of the data for different age-groups.92
Little is known about the current incidence of the use of cuffed ETTs in neonates and small infants, particularly in neonatal intensive care units (NICUs). Therefore, we carried out a survey to evaluate the use of cuffed ETTs in neonates and infants <3 months of age, along with the type of cuffed ETT chosen and management of the cuff.

4.3 METHODS

4.3.1 Study population

The heads of department of all of the 28 tertiary NICUs and 7 exclusively paediatric ICUs across Australia and New Zealand were surveyed regarding their units’ practice.

4.3.2 Data collection

All heads of department of each unit were emailed explaining the study and their participation was requested. A link to the confidential survey was provided. The survey was conducted using web-based survey software (SurveyMonkey.com). A follow-up email was sent to non-respondents after 1 week and then once again 2 weeks following that. There were no incentives for participating in the survey. Data was collected in March-April 2015.

4.3.3 Survey instrument

The survey consisted of 10 questions. Most questions were close-ended with categorical answers to choose from. Some questions had boxes for free text.

4.3.4 Outcome measures

The questionnaire asked about: how often cuffed ETTs are used; use of cuffed ETTs in infants <3kg; the type of cuffed ETT used; the technique used to inflate the cuff; how often cuff pressure is checked; the maximum cuff pressure used; which physicians use cuffed ETTs; if there was evidence in favour of using cuffed ETTs whether they would use them more frequently; and if a neonatal unit, what type of unit they are (perinatal versus surgical).
4.3.5 Statistical analysis

Actual numbers are presented, and percentages calculated where appropriate.

4.3.6 Ethics

The survey was reviewed and approved by the hospital’s Quality Improvement Committee as having met the ‘Australian National Health and Medical Research Council requirements for quality assurance and audit projects’.79

4.4 RESULTS

4.4.1 Sample characteristics

The response rate was 27/28 (96.4%) for NICUs and 7/7 (100%) for PICUs surveyed. 24/27 of the NICU survey responses and 7/7 of the PICU responses were complete.

Of the neonatal units, 12/26 (46.1%) described themselves as a perinatal unit, 2/26 as a mainly surgical unit and 12/26 (46.1%) as a mix of surgical and perinatal (1 respondent did not answer this question).

4.4.2 Rates of cuffed ETT use

**NICUs:**

When NICUs were asked about cuffed ETT use in neonates >3kg, overall, 18/27 (66.7%) of units ‘never’ use, 6/27 (22.2%) ‘rarely’ use and 3/27 (11.1%) ‘sometimes’ use cuffed ETTs. No units use them ‘often’ or ‘always’. This means that 9/27 (33.3%) of neonatal units either ‘rarely’ or ‘sometimes’ use cuffed ETTs (*table 4.1*).

When the neonatal units were subdivided into type: 12/12 (100%) of perinatal NICUs ‘never’ use cuffed ETTs and 2/2 (100%) of mainly surgical NICUs ‘sometimes’ use cuffed ETTs. In the mixed perinatal and surgical NICU group, there was a variety of responses (*table 4.1*).

**PICUs:**

When PICUs were asked about their use of cuffed ETTs for neonates and infants up to 3 months of age, 1/7 (14.3%) ‘sometimes’ use and 6/7 (85.7%) ‘often’ use cuffed
ETTs. This means that 7/7 (100%) of PICUs are either ‘sometimes’ or ‘often’ using cuffed ETTs in infants under 3 months of age (table 4.1).

**Table 4.1 – The incidence of use of cuffed ETTs in neonates and Infants <3 months of age in neonatal and paediatric intensive care units in Australia and New Zealand**

<table>
<thead>
<tr>
<th>Use of Cuffed ETTs?</th>
<th>Overall NICU</th>
<th>Perinatal Units</th>
<th>Mainly Surgical Units</th>
<th>Mix of Perinatal and Surgical Units</th>
<th>Type of Unit Unknown</th>
<th>PICU</th>
<th>Overall NICU and PICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>18/27 (66.7%)</td>
<td>12/12 (100%)</td>
<td>6/12 (50%)</td>
<td>18/34 (54.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely</td>
<td>6/27 (22.2%)</td>
<td></td>
<td>5/12 (41.7%)</td>
<td>6/34 (18.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sometimes</td>
<td>3/27 (11.1%)</td>
<td>2/2 (100%)</td>
<td>1/12 (8.3%)</td>
<td>4/34 (12.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Often</td>
<td></td>
<td></td>
<td></td>
<td>6/7 (85.7%)</td>
<td>5/34 (15.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td></td>
<td></td>
<td></td>
<td>0/0 (0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**4.4.3 Use of cuffed ETTs in infants <3kg:**

When NICUs who use cuffed ETTs were asked about the use of cuffed ETTs in infants <3kg, 5/9 (55.6%) ‘never’ use and 4/9 (44.4%) are ‘rarely’ or ‘sometimes’ using cuffed ETTs. Of interest, the 2 units who ‘sometimes’ use cuffed ETTs in infants <3kg, were both the mainly surgical NICUs. For PICUs, 7/7 (100%) are ‘rarely’ or ‘sometimes’ using cuffed ETTs in infants <3kg (table 4.2).

**Table 4.2 – The use of cuffed ETTs in infants <3kg in units which use cuffed ETTs**

<table>
<thead>
<tr>
<th>Use of Cuffed ETTs in Infants &lt;3kg?</th>
<th>NICU</th>
<th>PICU</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never</td>
<td>5/9  (55.6%)</td>
<td>5/16 (31.2%)</td>
<td></td>
</tr>
<tr>
<td>Rarely</td>
<td>2/9  (22.2%)</td>
<td>1/7  (14.3%)</td>
<td>3/16 (18.8%)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>2/9  (22.2%)</td>
<td>6/7  (85.7%)</td>
<td>8/16 (50%)</td>
</tr>
<tr>
<td>Often</td>
<td></td>
<td></td>
<td>0/16 (0%)</td>
</tr>
<tr>
<td>Always</td>
<td></td>
<td></td>
<td>0/16 (0%)</td>
</tr>
</tbody>
</table>
4.4.4 Type of cuffed ETTs used:

When the NICUs which use cuffed ETTs were asked about the type of cuffed ETTs used, 7/9 (77.8%) used Microcuff® ETTs and for 2/9 (22.2%), there was no response to this question. When PICUs were asked, 5/7 (71.4%) use Microcuff® ETTs, 1/7 (14.3%) use Mallinckrodt® ETTs and 1/7 (14.3%) use Microcuff® or Mallinckrodt® ETTs.

4.4.5 Technique for cuff inflation:

When asked about the technique used for cuff inflation, there was a wide variety of management strategies and interestingly, of the NICUs which use cuffed ETTs, 3/9 (33.3%) never inflate the cuff (table 4.3).

<table>
<thead>
<tr>
<th>Technique to Determine Cuff Inflation?</th>
<th>NICU</th>
<th>PICU</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cuff Never Inflated</td>
<td>3/9  (33.3%)</td>
<td></td>
<td>3/15 (20%)</td>
</tr>
<tr>
<td>Cuff Inflated Until Audible Leak Disappears</td>
<td>2/9  (22.2%)</td>
<td>3/7  (42.9%)</td>
<td>4/15 (26.7%)</td>
</tr>
<tr>
<td>Leak Targeted from ventilator Readings</td>
<td>2/9  (22.2%)</td>
<td>1/7  (14.3%)</td>
<td>3/15 (20%)</td>
</tr>
<tr>
<td>Target a Pressure</td>
<td></td>
<td>2/7  (28.6%)</td>
<td>2/15 (13.3%)</td>
</tr>
<tr>
<td>Clinicians Discretion</td>
<td>1/7  (14.3%)</td>
<td></td>
<td>1/15 (6.7%)</td>
</tr>
<tr>
<td>No Protocol</td>
<td>1/9  (11.1%)</td>
<td></td>
<td>1/15 (6.7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1/9  (11.1%)</td>
<td></td>
<td>1/15 (6.7%)</td>
</tr>
</tbody>
</table>

4.4.6 Regularity of cuff pressure checks:

When the NICUs who use cuffed ETTs and inflate the cuffs were asked how often they check the cuff pressure, 3/5 (60%) responded never, 1/5 (20%) check 4-6 hourly and 1/5 (20%) have no protocol. For PICUs, 1/7 (14.3%) check the cuff pressure 1-2 hourly, 3/7 (42.9%) it 4-6 hourly and 3/7 (42.9%) check it 8-12 hourly.

4.4.7 Maximum cuff pressure used:

When the neonatal units who use cuffed ETTs and inflate the cuff were asked about the maximum cuff pressure used, 2/5 (40%) use a maximum of 20cmH₂O (this was
the 2 mainly surgical neonatal units), 2/5 (40%) do not measure cuff pressure and 1/5 (20%) have no protocol. For the PICUs, 5/7 (71.4%) use a maximum cuff pressure of 20cmH₂O, 1/7 (14.3%) use 30cmH₂O as a maximum and 1/7 (14.3%) it is at the clinicians discretion.

4.4.8 Which physicians intubate with cuffed ETTs:

When asked who uses cuffed ETTs to intubate infants, of the NICUs who use cuffed ETTs, more anaesthetists than neonatologists use cuffed ETTs and for PICUs, more intensivists than anaesthetists intubate with cuffed ETTs (table 4.4).

<table>
<thead>
<tr>
<th>Table 4.4 – Which physicians use cuffed ETTs to intubate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which Physicians Use Cuffed ETTs to Intubate?</td>
</tr>
<tr>
<td>All neonatologists/ intensivists</td>
</tr>
<tr>
<td>Some neonatologists/ intensivists</td>
</tr>
<tr>
<td>All anaesthetists</td>
</tr>
<tr>
<td>Some anaesthetists</td>
</tr>
</tbody>
</table>

4.4.9 Reported problems with the use of cuffed ETTs:

When the units who use cuffed ETTs were asked if they have ever had problems with the use of cuffed ETTs, of the NICUs, 5/9 (55.6%) said no, 2/9 (22.2%) said no more than with uncuffed ETTs, 1/9 (11.1%) said yes and 1/9 (11.1%) did not respond.

The unit which responded that they had had problems with cuffed ETTs commented: ‘We had a problem with a sick baby having a cuffed tube that was deflated and thus ventilation was difficult. It is hard to change the ETT in an unstable patient. We are not used to using cuffed ETTs and thus they can be problematic. We prefer to stick to uncuffed ETTs.’

Of the PICUs, 1/7 (14.3%) said no and 6/7 (85.7%) said no more than with uncuffed ETTs.
4.4.10 Future use of cuffed ETTs if evidence for use provided:

When asked if there was evidence for the use of cuffed ETTs in neonates and infants if their units would use them in the future, there was a strong interest within NICUs surveyed, with 20/24 (83.3%) reporting that their unit would consider using them in the future. The majority, 6/7 (85.7%) of PICUs are already happy using cuffed ETTs in this age group (table 4.5).

Table 4.5 – If there was evidence for the use of cuffed ETTs, which units would use them

<table>
<thead>
<tr>
<th>If there was evidence for use of cuffed ETTs would you use them?</th>
<th>NICU Overall</th>
<th>Perinatal Units</th>
<th>Mainly Surgical Unit</th>
<th>Mix of Perinatal and Surgical</th>
<th>PICU</th>
<th>Overall NICU and PICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>3/24 (12.5%)</td>
<td>3/12 (25%)</td>
<td></td>
<td></td>
<td>3/31 (9.7%)</td>
<td></td>
</tr>
<tr>
<td>Possibly depending upon how good the evidence was</td>
<td>17/24 (70.8%)</td>
<td>7/12 (58.3%)</td>
<td>1/2 (50%)</td>
<td>9/10 (90%)</td>
<td>1/7 (14.3%)</td>
<td>18/31 (58.1%)</td>
</tr>
<tr>
<td>Yes</td>
<td>3/24 (12.5%)</td>
<td>2/12 (16.7%)</td>
<td>1/10 (10%)</td>
<td>1/7 (14.3%)</td>
<td>4/31 (12.9%)</td>
<td></td>
</tr>
<tr>
<td>We are already happily using cuffed ETTs</td>
<td>1/24 (4.2%)</td>
<td></td>
<td></td>
<td>5/7 (71.4%)</td>
<td>6/31 (19.4%)</td>
<td></td>
</tr>
</tbody>
</table>

4.5 DISCUSSION

We surveyed all the tertiary NICUs and PICUs in Australia and New Zealand and found that 33.3% of NICUs and 100% PICUs are, to a lesser or greater extent, using cuffed ETTs in neonates >3kg and infants under 3 months of age despite the lack of good evidence in favour of their use for longer term ventilation in the intensive care setting.

The most commonly used cuffed ETT is the Microcuff® ETT with a couple of units using Mallinckrodt® cuffed ETTs. The smallest size that both these manufacturers make is 3.0mm which is recommended for infants >3kg both by the manufacturers and in the literature. Despite this, 10/15 (66.7%) of NICUs and PICUs who use cuffed ETTs are ‘rarely’ or ‘sometimes’ using cuffed ETTs in infants <3kg. There are no reports of studies of the use of cuffed ETTs in infants <3kg.
In the literature, there is no clear guide or general consensus as to how to use the cuff in regards to technique for inflation and how often to check cuff pressure. This is reflected in the range of responses we had as to how units are managing cuffs.

There was only one unit who reported problems with the use of cuffed ETTs and this was not in relation to the cuffed ETT itself, but the cuffed ETT not being used in the way in which they were designed to be used. It is common practice in neonatal units (33.3%) to deflate the cuff, in cuffed ETTs placed by an anaesthetist, as neonatologists are not generally accustomed to looking after cuffed ETTs. This practice can lead to large ETT leaks, making ventilation challenging, potentially destabilising the patient and necessitating an unnecessary ETT change to a larger uncuffed ETT.

There is apparent interest in the use of cuffed ETTs in neonates and small infants with the majority of units reporting that they would consider using them if there was good evidence for their use.

Although we had an extremely high response rate, there are some limitations to our study. Firstly, the closed-ended questions with descriptive words for incidence of use were open for individual interpretation. We tried to compensate for this by adding in free text boxes for comment. Secondly, the survey took place in Australia and New Zealand and the results may not reflect the practice in other countries.

Evidence from randomised controlled trials (RCTs) is required before general use of cuffed ETTs in this age group should be advocated for longer term ventilation in the intensive care setting. In the meantime, there are certain patients chosen on an individual basis, who may benefit from their use. Also, it would seem essential that neonatologists who look after surgical infants become familiar with the use of cuffed ETTs so that if a patient returns from theatre with one in place, it can be used correctly to avoid causing the patient to deteriorate and avoid unnecessary ETT changes.
4.6 ADDITIONAL COMMENTS

Since publication of this paper, an additional survey has been published. Sathyamoorthy et al surveyed members of the Society of Pediatric Anaesthesia in the US electronically between December 2013 and February 2014. There was a 28% response rate. They reported that 60% of respondents used cuffed ETTs in full-term neonates >50% of the time, with 29% always using them and 5% never using them.93

4.7 ACKNOWLEDGEMENTS

Full authorship list

The published manuscript included the following authors: Shripada Rao and Corrado Minutillo.

Author Contributions

Rebecca Thomas was the primary author of this paper. All authors contributed to the study concept and design. RT was responsible for the acquisition, analysis and interpretation of data. The manuscript was drafted by RT and critically reviewed by SR and CM.

Prior Publication

A truncated version of the data and scientific discussion presented in this chapter has been peer reviewed and published in *Archives of Disease in Childhood, Fetal and Neonatal Edition*, which has been incorporated into this thesis.

CHAPTER 5 – Cuffed versus uncuffed endotracheal tubes for ventilation of neonates and infants in the neonatal and paediatric intensive care unit: a pilot RCT

CONTENTS OF CHAPTER

<table>
<thead>
<tr>
<th>CHAPTER 5</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.1 Preface</td>
<td>57</td>
</tr>
<tr>
<td>5.2 Introduction</td>
<td>57</td>
</tr>
<tr>
<td>5.3 Methods</td>
<td>57</td>
</tr>
<tr>
<td>5.3.1 Eligibility and recruitment</td>
<td>57</td>
</tr>
<tr>
<td>5.3.2 Consent</td>
<td>58</td>
</tr>
<tr>
<td>5.3.3 Randomisation and masking</td>
<td>58</td>
</tr>
<tr>
<td>5.3.4 Intervention</td>
<td>58</td>
</tr>
<tr>
<td>5.3.5 Outcomes</td>
<td>60</td>
</tr>
<tr>
<td>5.3.6 Sample size and statistical analysis</td>
<td>60</td>
</tr>
<tr>
<td>5.3.7 Ethics</td>
<td>61</td>
</tr>
<tr>
<td>5.4 Results</td>
<td>61</td>
</tr>
<tr>
<td>5.4.1 Primary outcome: Leak</td>
<td>64</td>
</tr>
<tr>
<td>5.4.2 Process of intubation</td>
<td>64</td>
</tr>
<tr>
<td>5.4.3 Cuffed ETTs</td>
<td>65</td>
</tr>
<tr>
<td>5.4.4 Uncuffed ETTs</td>
<td>66</td>
</tr>
<tr>
<td>5.4.5 Secondary outcomes</td>
<td>67</td>
</tr>
<tr>
<td>5.4.6 Video laryngoscopy</td>
<td>67</td>
</tr>
<tr>
<td>5.4.7 Follow-up</td>
<td>69</td>
</tr>
<tr>
<td>5.5 Discussion</td>
<td>70</td>
</tr>
<tr>
<td>5.6 Conclusions</td>
<td>73</td>
</tr>
<tr>
<td>5.7 Acknowledgements</td>
<td>73</td>
</tr>
</tbody>
</table>
5.1 PREFACE

This chapter presents the main RCT of this thesis. It is a pilot study comparing cuffed and uncuffed ETTs in neonates and small infants ventilated in the ICU setting. The aim is to commence the process of bringing together more scientific evidence on the use of cuffed ETTs in this age group.

5.2 INTRODUCTION

There remains a lack of scientific evidence for the use of cuffed ETTs in neonates and young infants in the neonatal intensive care unit (NICU) and paediatric intensive care unit (PICU) setting. Therefore, the aim of this pilot trial was to study the feasibility, effectiveness and safety of cuffed versus uncuffed ETTs in a group of near-term neonates and young infants in the intensive care setting.

We hypothesised that the Microcuff® high volume low pressure (HVLP) cuffed ETT increases the ability to successfully ventilate neonates and infants by enabling a manageable airway leak, and so improving ventilation, without increasing the incidence of adverse clinical outcomes when compared with the use of traditional uncuffed ETTs.

5.3 METHODS

We conducted a single-centre, two-group pilot randomised controlled trial (RCT) of cuffed versus uncuffed ETTs for ventilation of near-term neonates and young infants in the NICU and PICU setting. The study took place at Princess Margaret Hospital for Children, Perth (now Perth Children’s Hospital), the sole tertiary children’s hospital in the State of Western Australia.

5.3.1 Eligibility and recruitment

Patients were enrolled between 2nd February 2015 and 26th August 2016. All consecutive infants admitted or being admitted to the NICU or PICU requiring an ETT for mechanical ventilation were assessed for eligibility. Eligibility criteria for study inclusion were all medical and surgical neonates ≥35 weeks corrected
gestational age and up to 3 months of age who were ≥3kg in weight at the time of intubation and expected to require ventilation for >12 hours. Exclusion criteria were: ex-preterm infants <32 weeks gestation at birth who had previously received an ETT; those with a known or suspected airway abnormality; intubations happening in neonates being retrieved and travelling by aircraft; or parents declined consent.

5.3.2 Consent

For stable infants, informed parental consent was gained prior to randomisation. However, for emergent intubations, delayed consent was attained once the baby had been stabilised. If at this point, parents declined consent, no data was collected, but the infant continued with the type of ETT inserted, unless a reintubation was medically indicated. Delayed consent was granted ethical approval as both NICU and PICU at our institution already use both types of ETTs.

5.3.3 Randomisation and masking

Computer-generated randomisation sequences were generated. Patients were stratified as [NICU or PICU] and [medical or surgical]. Infants were randomised immediately prior to intubation via sealed, opaque, sequentially numbered envelopes. Due to the nature of the intervention, blinding of clinicians to the type of intervention was not possible.

5.3.4 Intervention

Patients were prospectively randomised to receiving a cuffed (Halyard Microcuff®) ETT or an uncuffed (Smiths Medical Portex®) ETT for the duration of the ventilation period.

*Cuffed ETTs:*

All patients randomised to the cuffed ETT group were to receive a 3.0mm Microcuff® ETT (outer diameter (OD) 4.3mm), which the manufacturer recommends for infants ≥3kg up to 8 months of age. Length of insertion was determined by using the vocal cord guide. Upon intubation, the cuff was inflated with a 1mL syringe attached via a 3-way tap to a manometer (see chapter 2, page
26, *figure 2.2*) until the ventilator leak measurement read 10-20% or until the audible leak had just disappeared on transport or in theatre. The maximum cuff pressure allowed was 20cmH\(_2\)O. All patients in NICU or PICU were ventilated with Draeger VN500 ventilators with breath-to-breath percentage leak readings. This ventilator displays leak as full number from 10-100%, but if <10% it displays ‘0%’.

The cuff was readjusted every 4 hours by attaching to a manometer setup, pressing the pressure relief button so reducing the cuff pressure to 0cmH\(_2\)O, reading the ventilator leak for around 30 seconds and reinflating the cuff if required to bring the ventilator leak reading to 10-20%. If there was a leak <20%, the cuff was not aspirated until the pilot balloon was flat, with the manometer reading a negative pressure, rather the cuff pressure was left at 0cmH\(_2\)O. This inevitably meant that there was some amount of air in the cuff, but there was no pressure being exerted on the tracheal tissue.

*Uncuffed ETTs:*

Uncuffed ETT size selection was at the discretion of the treating physician. Uncuffed ETTs used were Portex® 3.0mm (OD 4.2mm), 3.5mm (OD 4.8mm) or 4.0mm (OD 5.5mm). If there was no/ minimal leak at intubation but the ETT passed easily through the cords, the ETT could be used as per normal unit practice.

All ETTs were assessed for presence of leak at intubation. ETTs were to be x-rayed for tip position and readjusted accordingly. For both types of ETT, induction agents, route of intubation, and decision to re-intubate with a different size or type of ETT was at the discretion of the treating physician. If there was an unplanned extubation or the patient required re-intubation within 12 hours of the trial of extubation, the patient was to receive the same type of ETT used for the study unless felt inappropriate by the treating physician. Trial completion occurred 12 hours after successful extubation.

An extubation flexible video laryngoscopy was planned for each patient. This was to be carried out with a 2.5mm endoscope (Karl Storz 11101SKK2, Rhino-Laryngo-Fiberscope, 2.5 x 270 mm) passed through the ETT at the time of extubation, with video taken as the ETT and scope were withdrawn together. If the treating physician felt a scope was inappropriate due to patient condition, the scope would
unduly delay extubation, or the ENT fellow or scope was unavailable then it was not done. The anonymised videos were analysed and graded at a later date by an ENT surgeon who was blinded to the type of ETT used.

5.3.5 Outcomes

The primary outcome was to show an increase in the ability to maintain the ETT leak between 10-20% when using the Microcuff® ETT compared to the use of uncuffed ETTs. This range was chosen as a 0% leak, could mean there was an unnecessarily high cuff pressure being used/tight uncuffed ETT, and higher leaks can interfere with effective ventilation.

Secondary outcomes were: re-intubation to find correct ETT size; FiO₂, ventilator pressure requirement and blood gases during ventilation period; unplanned extubations (UEs); episodes of atelectasis; ETT blockage; pneumothorax during ventilation; ventilation associated pneumonia (VAP); length of ventilation period; post-extubation stridor; dexamethasone and nebulised adrenaline use; re-intubation for airway symptoms; rates of airway damage on extubation endoscopy; time to discharge; death and airway problems at chart review at >24 months.

5.3.6 Sample size and statistical analysis

Prior data from our unit indicated that the success rate (i.e. ability to achieve a mean ETT leak of 10-20%) among neonates managed with uncuffed ETTs was 0.35. If the true success rate for infants managed with cuffed ETT is 0.7, it was estimated that we would require studying 37 infants in each group to be able to reject the null hypothesis that the success rates for cuffed and uncuffed ETTs are equal with a probability (power) of 0.8. The type one error probability associated with this test of this null hypothesis was set at 0.05.

Statistical analysis was performed using Stata v15 software (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC). For normally distributed continuous data, groups were compared using independent sample t-test. For data with skewed distribution, Wilcoxon rank sum test was planned to be used. For categorical variables, groups were compared using chi-squared with Fishers exact p-value. Results for binary outcomes were presented as odds ratio
(OR) with corresponding 95% confidence intervals. For comparison of continuous outcomes, we used mean difference with accompanying 95% confidence intervals (CI). All tests were two-sided and a P value of <0.05 was considered statistically significant.

5.3.7 Ethics

The Human Ethics Committees of Princess Margaret Hospital for Children and the University of Western Australia approved the study. The study was registered with the Australian and New Zealand Clinical Trials Registry, trial number ACTRN12615000081516. A data safety monitoring committee (DSMC) was set up and provided interim review of the trial’s progress.

5.4 RESULTS

There were 76 patients randomised, 40 to cuffed and 36 to uncuffed ETT. There were 65 NICU patients and 11 PICU patients. 36 patients were assigned as medical patients and 40 as surgical patients (figure 5.1).

*Figure 5.1 – Patient allocation*
Of the patients randomised to a cuffed ETT, 2 patients were extubated in theatre, 1 patient was transferred interstate for specialist surgery whilst still ventilated on the trial and 1 patient with severe hypoxic ischaemic encephalopathy (HIE) and multiorgan failure died following an active decision to cease further intensive care management. All available data for these patients was included in analyses.

Of the patients randomised to uncuffed ETT, two patients were changed to cuffed ETT at the time of intubation in theatre after a trial with an uncuffed ETT was unsatisfactory. One patient was changed to a cuffed ETT after some hours ventilated with an uncuffed ETT during a procedure in theatre. One patient was transferred interstate whilst still ventilated and on the trial. The patients who were changed to cuffed ETT at the time of initial intubation were included with the cuffed ETT group for leak and outcome analyses. The patient who had the type of ETT changed part way through the ventilation period was analysed as per the randomised/first ETT used i.e. uncuffed group. The patient who was transferred interstate had all available data used up until the time of transfer.

The median chronological age at enrolment was 1 day (IQR:1-10 days; R:0-89 days). The median postmenstrual age at enrolment was 39.7 weeks gestation (IQR:37.9-41.1 weeks; R:35.7-52.7 weeks). At the time of enrolment, the median weight was 3445g (IQR:3152-3765g; R:2800-6340g). Patients were ventilated for a median of 65.5 hours (IQR:35-96.5 hours; R:1-238 hours).

The main diagnoses were: respiratory disease (n=26); surgical gastrointestinal (n=19); cardiac (n=15); neurosurgical (n=5); neurological disease/seizures (n=4); surgical urological (n=4); surgical thoracic (n=3); sepsis/infection (n=1); multiorgan (n=1). A total of 32/70 (45.7%) had evidence of respiratory disease at intubation.

The place of intubation was: NICU in 48.7% (n=37); theatre in 43.4% (n=33); on transport in 6.6% (n=5); and PICU in 1.3% (n=1). The reasons for the study intubation were: respiratory support (n=40); surgery (n=32); neurological (n=3); and to facilitate analgesia (n=1).

There were no differences in baseline characteristics (table 5.1).
<table>
<thead>
<tr>
<th></th>
<th>Cuffed ETT (n=40)</th>
<th>Uncuffed ETT (n=36)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gestational age at birth (weeks)</strong>*</td>
<td>38.2 (1.7)</td>
<td>38.6 (2.1)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Birth weight (g)</strong></td>
<td>3341 (524.2)</td>
<td>3343 (558.6)</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>Age at enrolment (days)</strong>*</td>
<td>12 (20.9)</td>
<td>10.7 (20.5)</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>Postmenstrual age at intubation (weeks)</strong>*</td>
<td>39.9 (3.2)</td>
<td>40.1 (3.2)</td>
<td>0.80</td>
</tr>
<tr>
<td><strong>Weight at intubation (g)</strong>*</td>
<td>3495 (471.5)</td>
<td>3592 (625.7)</td>
<td>0.45</td>
</tr>
<tr>
<td><strong>Sex male</strong></td>
<td>28 (70.0%)</td>
<td>26 (72.2%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>NICU patient</strong></td>
<td>34 (85%)</td>
<td>31 (86.1%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Surgical patient</strong></td>
<td>19 (47.5%)</td>
<td>18 (50%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Respiratory disease at intubation</strong></td>
<td>17 (42.5%)</td>
<td>15 (41.7%)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>PRISM score</strong>*</td>
<td>17.1 (7.1)</td>
<td>18.1 (7.2)</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>SNAP II score</strong>*</td>
<td>24.1 (17.1)</td>
<td>16.7 (10.9)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Lowest mean BP (mmHg)</strong>*</td>
<td>38.8 (8.5)</td>
<td>36.9 (6.3)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>Hypotension requiring inotropic support</strong></td>
<td>8 (20.0%)</td>
<td>12 (33.3%)</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Time on inotropic support (hours)</strong>*</td>
<td>11.1(26.1)</td>
<td>15.2 (31.1)</td>
<td>0.53</td>
</tr>
<tr>
<td><strong>Hydrocortisone for hypotension</strong></td>
<td>2 (5.0%)</td>
<td>3 (8.3%)</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Previous ETT</strong></td>
<td>11 (27.5%)</td>
<td>5 (13.9%)</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Use volume targeted ventilation</strong></td>
<td>31 (77.5%)</td>
<td>25 (69.4%)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Pre-extubation steroids</strong></td>
<td>3/38 (7.9%)</td>
<td>4/35 (11.4%)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Any use of steroids during ventilation period</strong></td>
<td>5/38 (13.2%)</td>
<td>7/35 (20.0%)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Data represents *mean (SD) and N (%) for all other variables.

ETT, endotracheal tube; NICU, neonatal intensive care unit
5.4.1 Primary outcome: Leak

The mean leak was in the range 10-20% in 13/42 (30.9%) of those with cuffed ETTs and 6/34 (17.6%) with uncuffed ETTs, P=0.28 [OR=2.09; 95% CI (0.71 – 6.08)]. When the mean percentage time each patient spent at different leak ranges was compared, cuffed ETTs spent a significantly higher percentage of time ventilated in the 10-20% leak range as compared with uncuffed. Uncuffed ETTs, spent a significantly higher percentage time in the <10% leak range. The comparison of leak ranges >20% showed no difference (table 5.2).

Table 5.2 – Percentage time spent at different leak ranges, cuffed v. uncuffed ETTs

<table>
<thead>
<tr>
<th>Leak range</th>
<th>Cuffed ETTs (n=42)</th>
<th>Uncuffed ETTs (n=36)</th>
<th>P value</th>
<th>Mean difference with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
<td>63.1%</td>
<td>76.4%</td>
<td>0.02</td>
<td>13.2% (1.8, 24.5%)</td>
</tr>
<tr>
<td>10-20%</td>
<td>29.0%</td>
<td>17.9%</td>
<td>0.01</td>
<td>-11.1% (-2.2, -20.0%)</td>
</tr>
<tr>
<td>21-30%</td>
<td>5.7%</td>
<td>2.7%</td>
<td>0.16</td>
<td>-3.0% (-7.3, 1.3%)</td>
</tr>
<tr>
<td>31-40%</td>
<td>2.1%</td>
<td>1.0%</td>
<td>0.18</td>
<td>-1.1% (-2.8, 0.5%)</td>
</tr>
<tr>
<td>41-50%</td>
<td>2.1%</td>
<td>1.2%</td>
<td>0.56</td>
<td>-0.8% (-3.8, 2.1%)</td>
</tr>
<tr>
<td>51-60%</td>
<td>0.5%</td>
<td>0.7%</td>
<td>0.73</td>
<td>0.1% (-0.9, 1.2%)</td>
</tr>
<tr>
<td>&gt;60%</td>
<td>0.2%</td>
<td>0.5%</td>
<td>0.45</td>
<td>0.2% (-0.4, 1.0%)</td>
</tr>
</tbody>
</table>

Data represents mean percentage time spent in each leak range. Data significance is presented as p value; mean difference (95% CI)

ETT, endotracheal tube

Volume-targeted ventilation was turned off because of a large leak in 0/31 (0%) of those with cuffed ETTs and 2/26 (7.7%) of those with uncuffed ETTs, P=0.11 [OR cannot determine].

5.4.2 Process of Intubation

There were no differences in premedication use, sedation level, route of intubation, number of attempts at intubation, ease of ETT passage, leak demonstrated at
intubation or depth of insertion. There was a significant difference in the rates of re-intubation required to find the correct ETT size at initial intubation, re-intubation for any reason during study period and re-intubation to change ETT size or ETT type during the study period (table 5.3).

Table 5.3 – Process of intubation, cuffed v. uncuffed ETTs

<table>
<thead>
<tr>
<th>Significance</th>
<th>Cuffed ETTs (n=40)</th>
<th>Uncuffed ETTs (n=36)</th>
<th>P value</th>
<th>Odds ratio or mean difference with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premedication given</td>
<td>39 (97.5%)</td>
<td>35 (97.2%)</td>
<td>1.00</td>
<td>1.1 (0.07, 18.4)</td>
</tr>
<tr>
<td>Sedation level adequate or muscle relaxed</td>
<td>40 (100.0%)</td>
<td>35 (97.2%)</td>
<td>0.28</td>
<td>OR cannot determine</td>
</tr>
<tr>
<td>No of attempts at intubation*</td>
<td>1.24 (0.55)</td>
<td>1.36 (0.59)</td>
<td>0.38</td>
<td>0.11 (-0.14, 0.38)</td>
</tr>
<tr>
<td>Ease ETT passed (tight or somewhat tight)</td>
<td>1/37 (2.7%)</td>
<td>3/35 (8.6%)</td>
<td>0.35</td>
<td>0.30 (0.03, 2.9)</td>
</tr>
<tr>
<td>Route ETT oral</td>
<td>29/39 (74.3%)</td>
<td>24 (66.7%)</td>
<td>0.61</td>
<td>1.4 (0.53, 3.9)</td>
</tr>
<tr>
<td>Leak demonstrated upon intubation</td>
<td>27/38 (71.0%)</td>
<td>18 (50%)</td>
<td>0.09</td>
<td>2.4 (0.94, 6.4)</td>
</tr>
<tr>
<td>Correct depth insertion</td>
<td>30/37 (81.1%)</td>
<td>25/35 (71.4%)</td>
<td>0.41</td>
<td>1.7 (0.56, 5.1)</td>
</tr>
<tr>
<td>ETT too short</td>
<td>3/37 (8.1%)</td>
<td>6/35 (17.1%)</td>
<td>0.30</td>
<td>0.43 (0.10, 1.8)</td>
</tr>
<tr>
<td>ETT too long</td>
<td>4/37 (10.8%)</td>
<td>4/35 (11.4%)</td>
<td>1.00</td>
<td>0.94 (0.22, 4.0)</td>
</tr>
<tr>
<td>Re-intubation for inadequately fitting ETT at time of primary intubation</td>
<td>0/40 (0%)</td>
<td>12/36 (33.3%)</td>
<td>&lt;0.001</td>
<td>OR cannot determine</td>
</tr>
<tr>
<td>Re-intubation for any reason during study period</td>
<td>1 (2.5%)</td>
<td>14 (38.9%)</td>
<td>&lt;0.001</td>
<td>0.04 (0.005, 0.33)</td>
</tr>
<tr>
<td>Re-intubation to change ETT size</td>
<td>0 (0%)</td>
<td>10 (27.8%)</td>
<td>&lt;0.001</td>
<td>OR cannot determine</td>
</tr>
<tr>
<td>Re-intubation to other type of ETT</td>
<td>0 (0%)</td>
<td>3 (8.3%)</td>
<td>0.10</td>
<td>OR cannot determine</td>
</tr>
</tbody>
</table>

Data represents N (%) and *mean (SD) for all other variables.
Data significance is presented as p value; OR (95% CI) or *p value; mean difference (95% CI)

5.4.3 Cuffed ETTs

All but one patient received a 3.0 Microcuff® ETT. The other patient received a 3.5 Microcuff® ETT in error (also the single patient with cuffed ETT where at intubation, ease at passing through cords was described as relatively tight). The cuff pressure
was monitored/ known on average 99.1% of the time ventilated (median 100%, R:89.3-100%).

Cuff pressures were adjusted on average every 5.1 hours. In 37/40 (92.5%) patients, the cuff pressure was set appropriately 100% of the time. In the other 3 patients, at times, the cuff pressure should have been higher to control the leak into the desirable range.

The average median cuff pressure required was 4.1 cmH\textsubscript{2}O (R:0-15 cmH\textsubscript{2}O). The average minimum cuff pressure required was 0.66 cmH\textsubscript{2}O (R:0-12 cmH\textsubscript{2}O). The average maximum cuff pressure required was 10.8 cmH\textsubscript{2}O (R:0-20 cmH\textsubscript{2}O).

40/41 (97.6%) patients required a cuff pressure of 0cmH\textsubscript{2}O at some time during the ventilation period, with 12/41 (29.3%) patients requiring a cuff pressure of 0cmH\textsubscript{2}O for the entire period of ventilation. 11/41 (26.8%) patients required a cuff pressure of 20cmH\textsubscript{2}O at some point in the ventilated period. Three patients had a leak >20% despite a cuff pressure 20cmH\textsubscript{2}O at some point.

5.4.4 Uncuffed ETTs

At initial intubation, 8/36 (22.2%) received 3.0mm, 25/36 (69.4%) of patients received a 3.5mm, and 1/36 (2.8%) received a 4.0mm ETT. 10/36 (27.8%) patients were re-intubated to a different sized ETT: 4 were sized down from 3.5mm to 3.0mm as the ETT was too tight; and 6 were sized up from 3.0mm to 3.5mm as the ETT leak was too large. 2 patients were switched from a 3.5mm uncuffed ETT to a 3.0mm cuffed ETT as the leak was too large. One of the patients who was sized down from a 3.5mm to 3.0mm ETT was subsequently re-intubated in theatre after some hours with a 3.0mm cuffed ETT due to leak. The final sized uncuffed ETTs were: 3.0mm in 7/34 (20.6%), 3.5mm in 26/34 (76.4%) and 4.0mm in 1/34 (2.9%).

Of the complications: the VG was turned off due to large leak in one patient with 3.0mm ETT and one with 3.5mm ETT; all patients with atelectasis had a 3.5mm ETT; ETT blockage happened in 2 patients with 3.0mm ETT and one patient with 3.5mm ETT; both patients with VAP had a 3.5mm ETT; and post-extubation stridor occurred in 1 patient with a 3.0mm ETT and 5 patients with 3.5mm ETTs.
5.4.5 Secondary outcomes

There was no difference found in gaseous exchange, ventilator parameters, post-extubation complications, length of ventilation, length of stay or death. There was a significant difference found in episodes of atelectasis and the combination of ventilatory complications (unplanned extubation (UE), episode atelectasis, ETT blockage, pneumothorax whilst intubated, VAP) both being more common in uncuffed ETT group (table 5.4).

5.4.6 Video laryngoscopy

11 patients underwent video laryngoscopy at extubation: 7 with cuffed ETTs and 4 with uncuffed ETTs. Most other laryngoscopies were not carried out due to either unavailability of equipment or staff. A few were not carried out due to physician concern over peri-extubation stability of the patient. On expert review of the 11 extubation video laryngoscopies, no video was of sufficient quality for which to make firm conclusions.
### Table 5.4 – Comparison secondary outcomes, cuffed vs uncuffed ETTs

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cuffed ETTs (n=42)</th>
<th>Uncuffed ETTs (n=34)</th>
<th>Significance</th>
<th>P value</th>
<th>Odds ratio or mean difference with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total length of intubation (hours)*</td>
<td>77.4 (52.0)</td>
<td>70.1 (56.7)</td>
<td></td>
<td>0.56</td>
<td>-7.3 (-32.4, 17.8)</td>
</tr>
<tr>
<td>Lowest pH*</td>
<td>7.26 (0.11)</td>
<td>7.27 (0.07)</td>
<td></td>
<td>0.59</td>
<td>0.01 (-0.03, 0.05)</td>
</tr>
<tr>
<td>Mean pH*</td>
<td>7.37 (0.04)</td>
<td>7.37 (0.04)</td>
<td></td>
<td>0.59</td>
<td>-0.005 (-0.02, 0.01)</td>
</tr>
<tr>
<td>Highest pCO₂ (mmHg)*</td>
<td>58.4 (16.7)</td>
<td>53.5 (10.7)</td>
<td></td>
<td>0.13</td>
<td>-4.9 (-11.3, 1.5)</td>
</tr>
<tr>
<td>Mean pCO₂ (mmHg)*</td>
<td>44.3 (6.1)</td>
<td>41.9 (5.7)</td>
<td></td>
<td>0.08</td>
<td>-2.4 (-5.1, 0.3)</td>
</tr>
<tr>
<td>Highest OI*</td>
<td>9.6 (8.3)</td>
<td>8.5 (8.3)</td>
<td></td>
<td>0.65</td>
<td>-1.0 (-6.0, 3.8)</td>
</tr>
<tr>
<td>Mean OI*</td>
<td>4.9 (0.5)</td>
<td>4.2 (0.6)</td>
<td></td>
<td>0.32</td>
<td>-0.75 (-2.3, 0.78)</td>
</tr>
<tr>
<td>Mean MAP (cmH₂O)*</td>
<td>9.1 (1.7)</td>
<td>9.2 (1.8)</td>
<td></td>
<td>0.83</td>
<td>0.08 (-0.75, 0.92)</td>
</tr>
<tr>
<td>Mean PIP (cmH₂O)*</td>
<td>18.9 (3.8)</td>
<td>18.3 (3.4)</td>
<td></td>
<td>0.46</td>
<td>-0.60 (-2.2, 1.0)</td>
</tr>
<tr>
<td>Mean FiO₂*</td>
<td>0.29 (7.8)</td>
<td>0.28 (6.5)</td>
<td></td>
<td>0.46</td>
<td>-0.012 (-0.044, 0.020)</td>
</tr>
<tr>
<td>HFOV/ HFJV use</td>
<td>2 (5.0%)</td>
<td>2 (5.6%)</td>
<td></td>
<td>1.00</td>
<td>0.8 (0.11, 6.0)</td>
</tr>
<tr>
<td>NO use</td>
<td>7 (17.5%)</td>
<td>6 (16.7%)</td>
<td></td>
<td>1.00</td>
<td>0.93 (0.28, 3.09)</td>
</tr>
<tr>
<td>Unplanned extubation (UE)</td>
<td>2 (4.8%)</td>
<td>2 (5.9%)</td>
<td></td>
<td>1.00</td>
<td>0.8 (0.11, 6.0)</td>
</tr>
<tr>
<td>Episode atelectasis</td>
<td>0 (0%)</td>
<td>4 (11.8%)</td>
<td></td>
<td><strong>0.03</strong></td>
<td>OR cannot determine</td>
</tr>
<tr>
<td>ETT blockage</td>
<td>0 (0%)</td>
<td>3 (8.8%)</td>
<td></td>
<td>0.08</td>
<td>OR cannot determine</td>
</tr>
<tr>
<td>Pneumothorax whilst intubated</td>
<td>0 (0%)</td>
<td>1 (2.9%)</td>
<td></td>
<td>0.44</td>
<td>OR cannot determine</td>
</tr>
<tr>
<td>Ventilator associated pneumonia (VAP)</td>
<td>0 (0%)</td>
<td>2 (5.9%)</td>
<td></td>
<td>0.19</td>
<td>OR cannot determine</td>
</tr>
<tr>
<td>Any complication of ventilation (atelectasis/ UE/ ETT blockage/ Pneumothorax/ VAP)</td>
<td>2 (4.8%)</td>
<td>9 (26.5%)</td>
<td></td>
<td><strong>0.01</strong></td>
<td>0.14 (0.03, 0.70)</td>
</tr>
<tr>
<td>Re-intubation for any reason during study period*</td>
<td>1 (2.5%)</td>
<td>14 (38.9%)</td>
<td></td>
<td>&lt;0.001</td>
<td>0.04 (0.005, 0.33)</td>
</tr>
<tr>
<td>Total no of intubations during study period*</td>
<td>1.07 (0.26)</td>
<td>1.35 (0.65)</td>
<td></td>
<td><strong>0.02</strong></td>
<td>0.28 (0.04, 0.51)</td>
</tr>
<tr>
<td>Post-extubation stridor</td>
<td>5/40 (12.5%)</td>
<td>5/33 (14.7%)</td>
<td></td>
<td>0.74</td>
<td>0.8 (0.21, 3.04)</td>
</tr>
<tr>
<td>Post-extubation dexamethasone</td>
<td>4/40 (10.0%)</td>
<td>3/33 (8.8%)</td>
<td></td>
<td>1.00</td>
<td>1.1 (0.23, 5.3)</td>
</tr>
<tr>
<td>Post-extubation adrenaline nebuliser</td>
<td>0/40 (0%)</td>
<td>2/33 (5.9%)</td>
<td></td>
<td>0.20</td>
<td>OR cannot determine</td>
</tr>
<tr>
<td>Post-extubation non-invasive support for airway</td>
<td>1/40 (2.5%)</td>
<td>5/33 (15.2%)</td>
<td></td>
<td>0.08</td>
<td>0.14 (0.02, 1.3)</td>
</tr>
<tr>
<td>Post-extubation non-invasive support (any reason)</td>
<td>22/39 (56.4%)</td>
<td>20/33 (60.6%)</td>
<td></td>
<td>0.81</td>
<td>0.84 (0.33, 2.1)</td>
</tr>
<tr>
<td>Re-intubation for airway</td>
<td>0/40 (0%)</td>
<td>1/33 (3.0%)</td>
<td></td>
<td>0.45</td>
<td>OR cannot determine</td>
</tr>
<tr>
<td>Time to discharge following extubation (days)*</td>
<td>13.0 (11.8)</td>
<td>15.5 (20.1)</td>
<td></td>
<td>0.53</td>
<td>2.5 (-5.5, 10.5)</td>
</tr>
<tr>
<td>Total length of stay (days)*</td>
<td>20.6 (17.3)</td>
<td>21.6 (24.2)</td>
<td></td>
<td>0.83</td>
<td>1.0 (-8.8, 10.9)</td>
</tr>
<tr>
<td>Death</td>
<td>1 (2.6%)</td>
<td>0 (0%)</td>
<td></td>
<td>1.00</td>
<td>OR cannot determine</td>
</tr>
</tbody>
</table>

Data represents N (%) and *mean (SD) for all other variables.

Data significance is presented as p value; OR (95% CI) or *p value; mean difference (95% CI)

ETT, endotracheal tube; OI, oxygenation index; MAP, mean airway pressure; PIP peak inspiratory pressure; FiO₂, fraction of inspired oxygen; HFOV, high frequency oscillatory ventilation; HFJV, high frequency jet ventilation; NO, nitric oxide
5.4.7 Follow-up

At notes review in October/November 2018, of the 75 patients who survived to discharge, all but two charts were able to be obtained. One patient in the cuffed ETT group moved interstate directly following discharge. Two patients (one in each group) received hospital follow-up until 5 months of age, but then moved interstate/overseas. One patient from the uncuffed ETT group died at 6 months of age from cardiomyopathy. Seventeen patients (9 cuffed ETT, 8 uncuffed ETT groups) did not attend for any type of hospital follow-up. The diagnosis for all of these 17 patients was straightforward respiratory distress syndrome (RDS), bronchiolitis or infection which did not qualify for hospital follow-up. For the patients who received hospital follow-up, the data is presented in table 5.5. Importantly, no child has been diagnosed with subglottic stenosis (SGS). Six children have been diagnosed with vocal cord palsy. All of these patients had cardiac surgery and thought to be the cause for this.

Table 5.5 – Follow-up of patients, cuffed v. uncuffed ETTs

<table>
<thead>
<tr>
<th></th>
<th>Cuffed ETTs (n=42)</th>
<th>Uncuffed ETTs (n=34)</th>
<th>Significance</th>
<th>P value</th>
<th>Odds ratio or mean difference with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at notes review (months)*</td>
<td>34.9 (5.2)</td>
<td>34.5 (7.6)</td>
<td>0.77</td>
<td>-0.45</td>
<td>(-3.6-2.7)</td>
</tr>
<tr>
<td>Age last seen at hospital (months)*</td>
<td>27.3 (10.1) (n=31)</td>
<td>23.0 (11.0) (n=24)</td>
<td>0.14</td>
<td>-4.2</td>
<td>(-10.0, 1.5)</td>
</tr>
<tr>
<td>No. further ETTs since study*</td>
<td>0.93 (1.3) (n=30)</td>
<td>1.0 (1.7) (n=24)</td>
<td>0.87</td>
<td>0.06</td>
<td>(0.09, 0.93)</td>
</tr>
<tr>
<td>Airway symptoms</td>
<td>1/31 (3.2%)</td>
<td>0/24 (0%)</td>
<td>1.00</td>
<td>OR cannot determine</td>
<td></td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>3/31 (9.7%)</td>
<td>5/24 (20.8%)</td>
<td>0.27</td>
<td>0.41</td>
<td>(0.09, 1.9)</td>
</tr>
<tr>
<td>ENT review post study period</td>
<td>3/31 (9.7%)</td>
<td>2/24 (8.3%)</td>
<td>1.00</td>
<td>1.1</td>
<td>(0.18, 7.6)</td>
</tr>
<tr>
<td>Subglottic stenosis (SGS)</td>
<td>0/31 (0%)</td>
<td>0/24 (0%)</td>
<td>1.00</td>
<td>OR cannot determine</td>
<td></td>
</tr>
<tr>
<td>Vocal cord palsy (VCP)</td>
<td>3/31 (9.7%)</td>
<td>3/24 (12.5%)</td>
<td>1.00</td>
<td>0.75</td>
<td>(0.14, 4.0)</td>
</tr>
<tr>
<td>VCP resolved</td>
<td>3/3 (100%)</td>
<td>2/3 (66.7%)</td>
<td>1.00</td>
<td>OR cannot determine</td>
<td></td>
</tr>
</tbody>
</table>

Data represents N (%) and *mean (SD) for all other variables. Data significance is presented as p value; OR (95% CI) or *p value; mean difference (95% CI) ETT, endotracheal tube
5.5 DISCUSSION

Cuffed ETTs potentially offer the advantage of a more manageable air leak and therefore improved ventilation. There is a growing body of evidence to show that they decrease clinically significant ETT leak.\textsuperscript{17, 56} In this study, although there were a higher percentage of patients in the cuffed group with a mean leak being in the range 10-20%, we did not show a significant difference. This may be because our pre-RCT cohort of patients with uncuffed ETTs on which we calculated the sample size showed a higher rate of being within the desirable range and we had an expectation that cuffed ETTs would make a larger difference than they did. A larger sample size may therefore have shown a difference in this study. A particular limitation of the calculation of mean leak was that the actual values <10% were unknown as they all read ‘0%’. Therefore, when calculating the mean leak, a figure of 5% was picked to replace all readings of <10%. This was to give both groups the same benefit of having a normal range of values between 0-9%. However, this may not have been so and may have favoured one group over the other. This study did show a statistical difference in the percentage time the patients spent in the leak range 10-20%. Patients with uncuffed ETTs were more likely to be in the leak range <10%, meaning that these ETTs were generally tighter and giving the potential to cause damage.

In young children, cuffed ETTs have been shown by a number of studies to reduce re-intubation rates to find the correct sized ETT\textsuperscript{8, 17, 18, 39, 40, 56} which we also found. This is an important finding as re-intubation may cause morbidities including airway trauma.

Potential disadvantages of cuffed ETTs include the requirement for higher pressures during ventilation due to the smaller size of ETT, more difficult weaning from the ventilator and more difficult suctioning of secretions all due to the smaller ETT used.\textsuperscript{85} We showed no significant difference in ventilator pressure requirements or gaseous exchange. Interestingly, there were more episodes of ETT blockage in the uncuffed ETT group, though this did not reach statistical significance.

In adults, cuffed ETTs have been shown to decrease rates of VAP\textsuperscript{23} and this is also a potential benefit in the infant population. We showed less VAP in the cuffed ETT
group, but this didn’t reach significance with this sample size. In theory, cuffed ETTs could cause less episodes of atelectasis if used appropriately by causing less leak around the ETT, and we showed significantly less atelectasis in the cuffed group. The combination of the ventilator complications of atelectasis, UE, VAP, pneumothorax, and ETT blockage were also significantly less in the cuffed ETT group which is an exciting potential use for cuffed ETTs. One would hope that fewer complications of ventilation may cause reduced hours of ventilation and length of stay, which we did not show with this small pilot RCT.

Theoretically, cuffed ETTs may cause less airway damage. Recent research on the paediatric airway refutes traditional teachings. A smaller sized cuffed ETT is used (0.5mm less than uncuffed ETT) which may not wedge within the delicate cricoid and may cause less airway trauma. The cuff makes its seal in the trachea where there are U-shaped cartilages and a muscular dorsal wall which allow for some distension, in contrast with the rigid cricoid ring where the uncuffed ETT makes its seal. However, there remains the concern that cuffs could cause tracheal mucosal damage. Like previous studies\textsuperscript{13 14 17 18 20 56 95}, we saw no difference in post-extubation complications.

Unfortunately, we did not achieve sufficient quality extubation endoscope videos to report on signs of trauma to the airway. This was in part due to the quality of picture with the smallest (2.5mm) scope on the market which would fit through such small ETTs. To get good pictures was technically very difficult. When the scope was through the ETT, the patient was not being ventilated and so there was very limited time to carry out the procedure. As the scope and ETT were withdrawn, together over around a second, there was only one chance and we often found that if the scope moved even a small amount the picture would be of the posterior wall of the subglottis or of the ETT itself. As soon as the scope and ETT were withdrawn through the vocal cords, there was no view of the subglottis. The only way to get good views would be to do an immediate post-extubation rigid endoscope, but this is neither feasible nor ethical.

As the only centre in the State of Western Australia to perform paediatric airway surgery, all patients are seen here if they have SGS or significant airway issues.
Therefore, follow-up should be complete. Though we know we lost 3 patients interstate or overseas, and 2 patients’ notes were unavailable, notes review of the other patients showed no patients with subglottic stenosis in either study group.

It would be extremely hard to carry out a trial to show that there is a difference in rates of SGS with cuffed and uncuffed ETTs. We published a study which included the incidence of subglottic stenosis in neonates and using these same figures, the number of SGS requiring surgical intervention over a 9 year period in ventilated neonates ≥3kg in NICU is 1/1220, an incidence of 0.8/1000 (0.08%). In PICU patients <3months of age for the same period, there was 1/363, an incidence of 2.7/1000 (0.27%). This gives an overall incidence of SGS in this population of 1.75/1000 (0.17%). Therefore, to show a difference would require tens of thousands of participants, which is not feasible.

Therefore, we must take all current data we have, none of which is concerning, along with the scientific theory which says cuffed ETTs may cause less damage along with the shown benefits of less intubations and the potential of less ventilatory complications and make an educated decision about using cuffed ETTs in this age group. Neonates are returning from surgery more commonly with cuffed ETTs in place, and neonatologists must become comfortable with their use. To care for a cuffed ETT is more labour intensive than with an uncuffed ETT and must be done properly to avoid potential complications. Any future studies need to be on a larger scale as a multicentre RCT and look at the outcomes of improving ventilatory complications and so reducing number of hours ventilated and length of ICU stay without causing post-extubation complications. A subgroup analysis should also look at cuffed ETT use with different modes of ventilation ie. high frequency oscillation and jet ventilation.
5.6 CONCLUSIONS

Cuffed ETTs in neonates and small infants offer a feasible alternative to the traditional uncuffed ETT. They are being used more commonly and neonatologists, particularly in surgical centres, must become comfortable with their use. Cuffed ETTs may reduce complications during ventilation, with the potential to decrease ventilation hours and length of intensive care stay. This needs to be confirmed in a large multi-centre trial.

5.7 ACKNOWLEDGEMENTS

Full authorship list

This chapter included the following authors: Shripada Rao, Simon Erickson, Bruce Hullet, Martyn Lethbridge, Corrado Minutillo, Shyan Vijayasekaran, Sachin Agrawal, Max Bulsara.

Author contributions

Rebecca Thomas was the principal investigator for this project, designed the study, designed the data collection instruments, collected and entered data, drafted the initial manuscript, reviewed and revised the manuscript.

SR conceptualized and designed the study, and reviewed and revised the manuscript. SE, BH, ML, CM and SV designed the study and critically reviewed the manuscript for important intellectual content. SV designed the study and critically reviewed the manuscript for important intellectual content and reviewed the laryngoscopes. SA co-ordinated the later part of the trial, collected data and reviewed the manuscript for important intellectual content. MB performed the statistical analyses and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Additional contributions

Thank you to Guicheng Zhang (statistician, sample size calculation), Matt Cooper (statistician, randomisation process), Jaslyn Ong (data collection), Hannah North (ENT fellow, extubation endoscopy), Hayley Herbert (ENT fellow, extubation endoscopy), Tobias Strunk (DSMC), Mairead Heaney (DSMC), and Eva Malacova (DSMC).
CHAPTER 6 – The use of cuffed endotracheal tubes in infants less than 3kg

CONTENTS OF CHAPTER

CHAPTER 6 .......................................................................................................................... 75

6.1 Preface.......................................................................................................................... 77

6.2 Introduction................................................................................................................... 77

6.3 Methods....................................................................................................................... 78

6.4 Results........................................................................................................................ 80
  6.4.1 Subjects who received cuffed ETTs................................................................. 80
  6.4.2 Controls who received uncuffed ETTs............................................................. 81
  6.4.3 Cuffed versus uncuffed...................................................................................... 81

6.5 Discussion................................................................................................................. 83

6.6 Conclusions............................................................................................................... 86

6.7 Acknowledgements................................................................................................... 87
6.1 PREFACE

Since cuffed ETTs have been increasingly used over the last few years in our unit, we have noted that smaller infants <3kg are receiving them also. From our survey, presented in Chapter 4 we found that other units in Australasia are also sometimes using cuffed ETTs in infants <3kg.

There have been no research reports previously published exploring the use of cuffed ETTs in this group of infants. Presented in this chapter is a retrospective study of cuffed versus uncuffed ETTs in neonates 2-3kg to start to bring together some evidence in the use of cuffed ETTs in this patient population.

The data presented in this chapter have been peer reviewed and published in *Pediatric Anesthesia*. Copies of the published manuscript and an editorial written on the subject from the same journal edition are presented in Appendix D.

6.2 INTRODUCTION

The smallest Microcuff® ETT has an internal diameter of 3.0mm and the manufacturer recommends its use in term infants ≥3kg. All studies using cuffed ETTs in infants reported in the literature thus far only include infants ≥3kg.\(^8\,^{13}\,^{14}\,^{17}\,^{19}\)

Our group recently surveyed all of the neonatal intensive care units (NICU) and PICUs in Australia and New Zealand on their use of cuffed ETTs in neonates and small infants. We found that 7/7 (100%) of PICUs and 4/9 (44.4%) NICUs who use cuffed ETTs were ‘sometimes’ or ‘rarely’ using cuffed ETTs in infants <3kg.\(^16\)

Though uncuffed ETTs remain the predominant device used for artificial ventilation in our NICU, Microcuff® cuffed ETTs have become more commonly used by anaesthetists in surgical infants >3kg over about the last 5 years. Of late, we noted an increasing number of infants <3kg returning from the operating room with a Microcuff® cuffed ETT in place. We therefore conducted a study to compare the use of Microcuff® cuffed ETTs and uncuffed ETTs in infants 2-3kg in our NICU.
6.3 METHODS

We undertook a retrospective cohort study comparing the use of cuffed versus uncuffed ETTs in infants of 2-3kg in weight at the time of intubation. The study took place in the NICU of Princess Margaret Hospital for Children, the sole tertiary children’s hospital in Perth, Western Australia.

The subjects included were all infants <3kg intubated with a cuffed ETT over the period January 2015-January 2016. These were compared with the same number of controls who were all infants of 2000-2999g, intubated with uncuffed ETTs from September 2015-January 2016. Our aims were to present our experience in the use of cuffed ETTs in the described group and compare with the use of uncuffed ETTs with regards to the demographics and outcomes of: weight at intubation; gestational age at intubation; age at intubation; hours ventilated; change of ETT to find correct size; median ventilator leak reading; highest ventilator leak reading; unplanned extubations; episodes of atelectasis; ETT blockage; pneumonia; post-extubation stridor; post-extubation dexamethasone; post-extubation adrenaline; post-extubation supplemental oxygen or CPAP; and re-intubation for stridor.

Patients intubated with cuffed ETTs received a 3.0mm Microcuff® Tracheal Tube. Patients with an uncuffed ETT received a Portex® siliconized ETT, of which the size was decided upon by the physician intubating the infant. On insertion of the ETT, to determine fit of the ETT, along with ease of passage, anaesthetists carry out a ‘leak test’ to check that there is an audible leak at an inspiratory pressure of 20cmH2O or by using the leak measurement generated by the Draeger iPrimus® anaesthetic machines. The ‘leak test’ is not carried out on those intubated by NICU physicians as this is not normal unit policy. Rather, if the ETT fits through the cords with ease and there is no large leak, it is deemed suitable to use.

For infants with cuffed ETTs, cuff inflation during surgery was decided by the attending anaesthetist. Once admitted to the NICU, according to local unit consensus protocol, the cuff is only inflated if the ventilator leak reading is consistently >20% as this may interfere with efficient volume-targeted ventilation. In this case the cuff is inflated until the ventilator leak reading just drops to <10% to a maximum cuff pressure of 20cmH2O. If the cuff is inflated, the ventilator leak and
cuff pressure is checked and readjusted every 4 hours. It is encouraged in our unit that if cuff inflation is not required to leave the cuff at 0cmH₂O, which will inevitably mean some air in the cuff, rather than emptying the cuff fully causing a negative pressure and the potential for wrinkles or ridges. This was a policy decided upon by consensus opinion between local anesthetists and neonatologists.

Data collected included: gestation at birth; birth weight; any previous intubations; age at intubation; corrected gestational age at intubation; weight at intubation; reason for intubation; size of ETT; leak test; any reintubations and reasons for; whether the cuff was inflated; maximum cuff pressure; ventilator leak readings; episodes of atelectasis or pneumonia; episodes of ETT blockage; unplanned extubations; days ventilated; post-extubation stridor; use of dexamethasone/adrenaline; need for non-invasive support post-extubation; and re-intubation for airway problems.

Statistical analysis was done using the STATA 14.0 software (Stata Corp. 2015 Stata Statistical Software: Release 14. College Station, TX; Stata Corp LP). The summary statistics for normally distributed continuous variables were expressed as mean and standard deviations; those with skewed distribution were expressed as median, interquartile range (IQR) and range. Categorical variables were expressed as frequency and percentage. For comparison of infants with cuffed ETT versus uncuffed ETT, two tailed student-t test was used for comparing continuous variables with normal distribution; Mann-Whitney U test was used for comparing data with skewed distribution and Fisher’s exact test using 2x2 tables was used to compare the categorical outcomes. Differences in medians along with the 95% confidence intervals were calculated where appropriate. Odds ratio and confidence intervals were calculated for categorical variables. For all analyses, a p-value of <0.05 was considered statistically significant. Multivariate analysis was not attempted given the small sample size.

The study was reviewed and approved by the hospital’s Quality Improvement Committee as having met the ‘Australian National Health and Medical Research Council requirements for quality assurance and audit projects.’
6.4 RESULTS

6.4.1 Subjects who received cuffed ETTs

Twenty-three patients <3kg received a cuffed ETT during the study period. All of the infants were intubated for surgical procedures by anaesthetists in the operating room and all received a 3.0mm Microcuff® ETT. The route of intubation was oral in 14/23 (60.9%) and nasal in 9/23 (39.1%).

On initial insertion of the ETT, 19/23 (82.6%) patients passed the ‘leak test’ and in the other 4/23 (17.4%), this was not documented. 14/23 (60.9%) patients had the cuff inflated in the operating room, for 2/23 (8.7%) it was not documented and 7/23 (30.4%) did not have the cuff inflated in the operating room. Of the 17 patients that had a cuff pressure recorded, the median was 15cmH₂O (range 0-20cmH₂O). None of the patients had their cuff inflated in NICU. 6/23 (26.1%) patients should have had their cuff inflated in NICU if unit protocol had been followed as they had a sustained leak of >20% at times. It is important to note that leak was very variable in most patients. The patients who had leaks of >20% also all had leaks of 0% at times.

On X-ray, the ETT position was correct in 16/23 (69.6%), long (close to the carina) in 4/23 (17.4%), short in 2/23 (8.7%) and there was one patient who had no X-ray taken. In 4/23 (17.4%) patients there was radiological evidence of atelectasis on chest radiograph done subsequently to the initial one taken for ETT placement. Of note, one of these patients had a large ETT leak and did not have the ETT cuff inflated as per unit protocol. There were no episodes of ETT blockage or pneumonia.

2/23 (8.7%) patients received pre-extubation steroids as prophylaxis for the length of time they had been intubated (8 and 17 days respectively). 1/23 (4.3%) patients had post-extubation stridor which settled over a couple of hours after a single dose of dexamethasone and did not require nebulised adrenaline, supplemental oxygen, non-invasive ventilation or re-intubation. This patient had been intubated for 45 hours, had passed the 'leak test' upon ETT insertion, had a leak of >10% for 80% of his intubated time and had never required the cuff to be inflated. One other patient
was re-intubated 6 hours post-extubation for respiratory distress due to de-recruitment of the lungs.

6.4.2 Controls who received uncuffed ETTs

Of the 23 control patients who received uncuffed ETTs, only 3/23 (13.0%) were intubated for surgery by anaesthetists and the rest, 20/23 (87.0%) were intubated by neonatologists for the following medical reasons: 12/23 (52.2%) respiratory disease; 7/23 (30.4%) neurological disease; and 1/23 (4.3%) cardiovascular collapse. 10/23 (43.5%) were initially intubated with a 3.0mm uncuffed ETT, but 3/10 (30.0%) of these patients required re-intubation with a 3.5mm uncuffed ETT for a large leak interfering with ventilation. 13/23 (56.5%) patients were initially intubated with a 3.5mm ETT. One of these patients was re-intubated with a 3.0mm in the operating room following sizing by an ENT specialist. So finally, 8/23 (34.8%) had a 3.0mm ETT and 15/23 (65.2%) had a 3.5mm ETT. The route of intubation was oral for 22/23 (95.7%) and nasal for 1/23 (4.3%) patients.

6.4.3 Cuffed versus uncuffed ETTs

When comparing the demographics of the 23 patients who received cuffed ETTs with the 23 control patients who received uncuffed ETTs, there was no significant difference in weight at intubation or the number of hours ventilated, but there was a significant difference in age at intubation median and gestational age at intubation (table 6.1).
Table 6.1 – Demographics of patients who received cuffed ETT v uncuffed endotracheal tube (ETT)

<table>
<thead>
<tr>
<th></th>
<th>Cuffed (n=23)</th>
<th>Uncuffed (n=23)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight at intubation (g)</td>
<td>2620g (IQR: 2540-2690g; R: 2050-2850g)</td>
<td>2590g (IQR: 2430-2770g; R: 2260-2960g)</td>
<td>diff in median = 10 95% CI (-120, 130)</td>
</tr>
<tr>
<td>Gestational age at intubation</td>
<td>37 weeks (IQR: 36-37; R: 35-39)</td>
<td>35 weeks (IQR: 35-37; R: 32-39)</td>
<td>diff in median = -1 95% CI (-2, 0)</td>
</tr>
<tr>
<td>Age at intubation</td>
<td>6 days (IQR: 1-16; R: 0-97)</td>
<td>0 days (IQR: 0-2; R: 0-51)</td>
<td>diff in median = -4 95% CI (-10, -1)</td>
</tr>
<tr>
<td>Hours ventilated</td>
<td>27 hours (IQR: 11-52; R: 3-414h)</td>
<td>44 hours (IQR: 26-107h; R: 3-217h)</td>
<td>diff in median = 17 95% CI (-5, 46)</td>
</tr>
</tbody>
</table>

Median (Interquartile range (IQR); Range (R))

When comparing the outcomes of those who received cuffed v uncuffed ETTs, there was no statistical difference in: number requiring a change of ETT to find correct size; the median ventilator leak reading; the highest ventilator leak reading; number of unplanned extubations; number of episodes of atelectasis; rate of ETT blockage; episodes of pneumonia; use of pre-extubation steroids; rate of post-extubation stridor; requirement for post-extubation dexamethasone; rate of post-extubation adrenaline; need for post-extubation supplemental oxygen, CPAP or re-intubation for stridor (table 6.2).
### Table 6.2 – Outcomes of patients who received cuffed vs uncuffed endotracheal tube (ETT)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cuffed (n=23)</th>
<th>Uncuffed (n=23)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change of ETT to find correct size</td>
<td>0/23 (0%)</td>
<td>4/23 (17.4%)</td>
<td>p=0.109 OR = 0.13 95% CI (0.01, 1.41)</td>
</tr>
<tr>
<td>Median ventilator leak reading (%)</td>
<td>0% (IQR: 0-12%, R: 0-22%)</td>
<td>0% (IQR: 0-5.5%, R: 0-14%)</td>
<td>p=0.201 diff in median = 0 95% CI (-5.5, 0)</td>
</tr>
<tr>
<td>Highest ventilator leak reading (%)</td>
<td>21% (IQR: 17-30%, R: 0-60%)</td>
<td>17% (IQR: 11-28%, R: 0-40%)</td>
<td>p=0.270 diff in median = -4 95% CI (-15, 4)</td>
</tr>
<tr>
<td>Unplanned extubation</td>
<td>0/23 (0%)</td>
<td>2/23 (8.7%)</td>
<td>p=0.489 OR = 0.45 95% CI (0.03, 8.02)</td>
</tr>
<tr>
<td>Episode atelectasis</td>
<td>4/23 (17.4%)</td>
<td>0/23 (0%)</td>
<td>p=0.109 OR = cannot determine</td>
</tr>
<tr>
<td>ETT blockage</td>
<td>0/23 (0%)</td>
<td>0/23 (0%)</td>
<td>p=N/A OR = cannot determine</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0/23 (0%)</td>
<td>0/23 (0%)</td>
<td>p=N/A OR = cannot determine</td>
</tr>
<tr>
<td>Pre-extubation steroids</td>
<td>2/23 (8.7%)</td>
<td>1/23 (4.3%)</td>
<td>p=1 OR = cannot determine</td>
</tr>
<tr>
<td>Post-extubation stridor</td>
<td>1/23 (4.3%)</td>
<td>2/23 (8.7%)</td>
<td>p=1 OR = 0.22 95% CI (0.02, 2.61)</td>
</tr>
<tr>
<td>Post-extubation dexamethasone</td>
<td>1/23 (4.3%)</td>
<td>1/23 (4.3%)</td>
<td>p=1 OR = 0.47 95% CI (0.03, 8.02)</td>
</tr>
<tr>
<td>Post-extubation adrenaline</td>
<td>0/23 (0%)</td>
<td>0/23 (0%)</td>
<td>p=N/A OR = cannot determine</td>
</tr>
<tr>
<td>Post-extubation supplemental O₂ or CPAP for stridor</td>
<td>0/23 (0%)</td>
<td>0/23 (0%)</td>
<td>p=N/A OR = cannot determine</td>
</tr>
<tr>
<td>Re-intubation for stridor</td>
<td>0/23 (0%)</td>
<td>0/23 (0%)</td>
<td>p=N/A OR = cannot determine</td>
</tr>
</tbody>
</table>

N/A = not applicable

### 6.5 DISCUSSION

The smallest Microcuff® ETT made is 3.0mm, which is recommended for infants ≥3kg in weight and previous studies have only included infants ≥3kg. However, from our own local experience and a survey of practice in Australia and New Zealand in
2015, we know that cuffed ETTs are sometimes being used in infants <3kg in weight. Sathyamoorthy et al reported on three neonates with weights of <3kg who were intubated with Microcuff® ETTs for surgical procedures and had significant post-extubation stridor. However, none of the patients underwent a leak check or had cuff pressure monitoring. Sathyamoorthy et al went on to retrospectively review 324 intubated neonates over a one year period comparing uncuffed and cuffed (Microcuff®) ETTs with regards to the outcome of post-extubation stridor. 29 patients received a cuffed ETT in the OR and the other 295 patients received uncuffed ETTs. However, they do not report on the weight or gestational age at the time of intubation, only birth weight and gestational age at birth. They reported an incidence of post-extubation stridor in 17.2% of those receiving cuffed ETT and 7.5% receiving uncuffed ETT. After multi-regression analysis, they report that the use of Microcuff® ETT was associated with an increased odds of stridor (AOR= 9.27, CI 1.88-45.67). However, they state that 26/29 patients with cuffed ETTs had a larger than recommended size and that cuff pressures were not checked.

In our study, when comparing the subjects and control groups, an important difference in demographics was the type of patients, with the entire cuffed ETT group being surgical patients and the majority of the uncuffed ETT group being medical patients, most commonly with respiratory disease. Medical patients, particularly those with respiratory disease often have non-compliant lungs, requiring higher pressure ventilation and are therefore more likely to display ventilator leaks. In contrast, surgical patients often have relatively healthy, compliant lungs requiring lower pressures and displaying lower ventilator leaks. On the other hand, ventilators in the operating room are probably less able to compensate for large leaks. Also, the dynamic situation created by the effect of surgery on ventilation means the ability to control leak via cuff inflation allows for more effective ventilation. It is for these reasons that anaesthetists have developed a preference for cuffed ETTs, whilst neonatologists of whom most are still unfamiliar with cuffed ETTs, prefer to continue using the traditional and familiar uncuffed ETT. Since January 2015, many anaesthetists in our institution have been using cuffed ETTs
even in neonates less than 3kg, even though the manufacturer doesn’t recommend them for this group. On the contrary, the preference of neonatologists remained to use uncuffed ETTs. Given these differences in choices, we conducted this audit to review the outcomes of all 23 infants who received cuffed ETTs and compared them to an equal number of infants who received uncuffed ETTs.

Our study showed that when using cuffed ETTs in surgical patients in this size population, the majority did not require cuff inflation as there was no substantial leak at any point. It could be said that these were effectively being used as uncuffed ETTs. However, even in the Microcuff® ETTs which claim to have fewer creases/ridges in the cuff area, there is still some ridging/creasing with cuff deflation. We leave the cuff pressure at 0cmH₂O rather than emptying the cuff fully and causing negative pressure and potential ridges. In the few patients with higher leaks who should have had the cuff inflated if unit protocol had been followed, it could be said that the potential impact of cuff inflation was lost once in the NICU. This is an important limitation of our study, given the retrospective design. Interestingly, around a third of patients intubated with a 3.0mm uncuffed ETT required reintubation with a larger 3.5mm uncuffed ETT due to a problematic leak which is a similar number to those with a cuffed ETT who also had a sustained leak and required cuff inflation. It is useful to note that the outer diameter (OD) is 4.3mm for the 3.0mm Microcuff® and 4.2mm for the 3.0mm Portex® ETT. As demonstrated by the one patient who initially had a 3.5mm uncuffed ETT that was replaced in the operating room by a 3.0mm ETT, some of the other patients with a 3.5mm uncuffed ETT could also have had an ETT too big. This is supported by the fact that over half of the patients with an uncuffed 3.5mm ETT who had ventilator leak measurements recorded never had a leak measurement >20% during their time ventilated on NICU. The variability of leak was striking in many patients and is likely due to changes in lung compliance, secretions, head position and level of wakefulness.

When comparing the 2 groups for outcomes, although there are low numbers and not reaching statistical significance, the ETT exchange rate was 0% for cuffed ETTs and 17.4% for uncuffed ETTs which replicates findings in previous studies comparing the 2 different ETTs. There was the same trend for an increase in
episodes of atelectasis in the cuffed ETTs and only one of these cases could be explained by the large ventilator leak with the cuff having not been appropriately inflated. This could be because these were all post-op surgical patients, which are the group that we more often see atelectasis than in the uncuffed group where only the minority were patients who were post-operative. The median duration of intubation was relatively brief (27 hours in the cuffed ETT group). Therefore the safety of more prolonged intubation is difficult to determine. Recently, DeMichele et al reported upon their experience of the use of using cuffed ETTs in 196 infants <5kg undergoing major cardiac surgery. The mean weight of the study infants was 3.6kg (SD 0.6). Nearly 26% of the infants were preterm (<37 weeks gestation) and <3kg. The average period of intubation was 7-9 days. They described that their practice was to remove all air from the cuff and then inflate the cuff until a minimal air leak was observed with a goal cuff pressure of 10-12 mmHg. If the infant could be adequately ventilated with the cuff down, after discussion with the intensivist, the cuff could be deflated. They concluded that the use of cuffed ETTs was not associated with airway complications. 55

Although our findings were encouraging, the results must be interpreted with caution as the sample size is too small to show a statistical difference in rare and also more common complications. Our results are also only applicable to the Microcuff® tracheal tube as the shape, position and composition of the cuff are original and different from other cuffed ETTs on the market.

6.6 CONCLUSIONS

This retrospective study with a small sample size found that Microcuff® cuffed ETTs may be safe in neonates <3kg. Well-designed RCTs are needed to address this issue definitively.
6.7 ACKNOWLEDGEMENTS

Full authorship list

The published manuscript included the following authors: Shripada Rao, Corrado Minutillo, Bruce Hullet and Max Bulsara.

Author Contributions

Rebecca Thomas was the primary author of this paper. All authors contributed to the study concept and design. RT was responsible for the acquisition of data. MB provided the statistical analysis. The manuscript was drafted by RT and critically reviewed by SR, CM, BH and MB.

Prior Publication

The data and scientific discussion presented in this chapter has been peer reviewed and published in Pediatric Anaesthesia, which has been incorporated into this thesis.


An editorial discussing the subject of this paper was published alongside in the same journal edition:

CHAPTER 7 – General discussion

<table>
<thead>
<tr>
<th>CONTENTS OF CHAPTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAPTER 7....................</td>
</tr>
<tr>
<td>7.1 Introduction...............</td>
</tr>
<tr>
<td>7.2 With the available evidence should neonatologists currently be using cuffed ETTs in neonates?</td>
</tr>
<tr>
<td>7.3 Future directions for research into the use of cuffed ETTs in neonates</td>
</tr>
<tr>
<td>7.4 Concluding remarks</td>
</tr>
</tbody>
</table>
7.1 INTRODUCTION

This thesis has aimed to bring together all of the currently available evidence in the use of cuffed ETTs in neonates and add further to that body with unique ‘first’ studies in this population.

In chapter 2, all available current evidence is presented, which shows that there is a significant lack of good quality evidence for the use of cuffed ETTs in neonates. However, despite this, the survey of current practice in Australia and New Zealand, presented in chapter 4, shows that cuffed ETTs are being used to some degree in many NICUs (mainly surgical units) and all PICUs in this age group.

Chapter 5 presents the results of the main RCT comparing cuffed versus uncuffed ETTs for ventilation of neonates ≥3kg and infants up to 3 months of age. This showed that cuffed ETTs enabled keeping the tube leak within the desirable range for a higher percentage time than uncuffed ETTs. There were significantly less reintubations in the cuffed ETT group to find the right sized ETT. During intubation, episodes of atelectasis and combined ventilatory complications (atelectasis, ETT blockage, pneumothorax, unplanned extubation (UE), ventilator associated pneumonia (VAP)) were significantly less in the cuffed ETT group. There were no differences in post-extubation complications.

The retrospective case-control study of use of cuffed ETTs in infants ≤3kg presented in chapter 6 shows that cuffed ETTs may be safe and effective to use in neonates 2-3kg in weight. However, there was a small sample size.

The real concern, for which physicians using cuffed ETTs would like to know is that they don’t cause more airway trauma and resulting subglottic stenosis (SGS), a most serious complication of endotracheal intubation. Chapter 3 presents a review of all neonatal and paediatric cases of SGS requiring surgical intervention over a 9 year period in WA. It was clear from this data, that SGS is generally a consequence of endotracheal intubation in extreme preterm infants <30 weeks gestation. SGS is rare in the term and near-term population for which we are studying the use of cuffed ETTs. This means that it would be hard to prove that cuffed ETTs don’t cause more SGS.
7.2 WITH THE AVAILABLE EVIDENCE SHOULD NEONATOLOGISTS CURRENTLY BE USING CUFFED ETTS IN NEONATES?

As yet, there is insufficient evidence to suggest the use of cuffed ETTs in preference to traditional uncuffed ETTs for longer-term ventilation of neonates ≥3kg and small infants up to 3 months of age in the intensive care setting. However, with the current evidence presented, which suggests that they appear to be at least as effective and safe, it would seem acceptable to continue using a cuffed ETT in a patient admitted to NICU with one in place. This would be preferable to re-intubating with an uncuffed ETT, which causes unnecessary further risk of morbidities including to the airway. Another instance a cuffed ETT may be used by choice is where there is a large leak interfering with ventilation with a 3.5mm uncuffed ETT. In this case, a 3.0mm cuffed ETT may be preferable to upsizing to a 4.0mm uncuffed ETT. It is essential to note that cuffed ETTs must be used correctly. Leaving the cuff deflated without paying attention to ETT leak risks inadequate ventilation and the potential for atelectasis. Leaving the cuff pressure excessively high risks unnecessary pressure on the tracheal mucosa, potentially causing needless trauma.

There is very limited evidence for the use of cuffed ETTs in infants <3kg and so neonatologists should remain wary about using them in this group. Adding to this concern is the fact that they are not recommended by the manufacturers in this sized infant. Having said this, again if a neonate who is close to 3kg is admitted to NICU with a cuffed ETT in place and there is an ETT leak with the cuff deflated it would seem reasonable to use this ETT in preference to re-intubating them.

7.3 FUTURE DIRECTIONS FOR RESEARCH INTO THE USE OF CUFFED ETTS IN NEONATES

As mentioned previously, to prove that cuffed ETTs do not cause more subglottic stenosis is not feasible. From the discussion in chapter 5, in our institution, the combined incidence of SGS requiring surgery in ventilated neonates ≥3kg in NICU
and infants <3months of age in PICU is 1.75/1000 (0.17%). Therefore, to show a difference would require tens of thousands of participants. Therefore, data on the incidence of SGS with cuffed and uncuffed ETTs should be collected and reported upon by many institutions repeatedly over time and collated by way of meta-analysis.

The next best thing would be to look at acute airway trauma with laryngotracheobronchoscopy (LTB) around the time of extubation in infants ventilated for a period of time in the intensive care setting. We aimed to do this through the ETT, but this proved to be too technically difficult. Ideally, a rigid scope would need to be done within 24 hours of extubation, but this would require an anaesthetic in theatre at a potentially unstable time for the patient. Undergoing such a procedure in the name of research would be ethically challenging.

We showed that episodes of atelectasis and combined ventilatory complications (atelectasis, ETT blockage, pneumothorax, UE, VAP) were less with cuffed ETTs. Reducing these complications should reduce hours of ventilation and ICU length of stay. These are potentially very important positive outcomes favouring cuffed ETT use. Future studies should concentrate on these outcomes and be powered for such. Clearly, data should also be collected on post-extubation complications, but it would be expected that the sample size would not be powered to show a difference. Subgroup analysis should also look at cuffed ETT use and the different modes of ventilation ie. high frequency oscillation and jet ventilation.

Use of cuffed ETTs in the <3kg population also requires more data. Infants 2-3kg are a particularly challenging group to know which sized uncuffed ETT to use. Cuffed ETTs are therefore potentially of great benefit. More data is required to be gathered on infants >3kg prior to embarking upon prospective studies in this smaller group of patients. However, as suggested above for their larger counterparts, any institution using cuffed ETTs in infants <3kg should collect their data and report upon it in order to increase the available evidence.
7.4 CONCLUDING REMARKS

This thesis has added to the current body of knowledge on the use of cuffed ETTs in neonates and small infants. It is clear that further studies on a larger scale are required before a decision could be made to use them in preference to traditional uncuffed ETTs. However, from the available evidence we have, cuffed ETTs appear to be at least as effective and safe as uncuffed ETTs. It would, therefore, seem reasonable to use them in neonates admitted to NICU with a cuffed ETT in place or in special instances where an uncuffed ETT is insufficient.
REFERENCES

18. Weiss M, Dullenkopf A, Fischer JE, et al. Prospective randomized controlled multi-centre trial of cuffed or uncuffed endotracheal tubes in


59. Papsidero MJ, Pashley NR. Acquired stenosis of the upper airway in neonates. An increasing problem. Annals of otology, rhinology, and


associated with laryngeal damage. *International journal of pediatric otolar
75. Dankle SK, Schuller DE, McClead RE. Risk factors for neonatal acquired subglottic stenosis. *Annals of otology, rhino
89. Reina J, Ferres F. [Acute laryngotracheitis associated with cytomegalovirus infection]. *Enfermedades infecciosas y microbiologia clinica* 2012;30(10):654-5. doi: 10.1016/j.eimc.2012.05.014


APPENDICES

List of Appendices


APPENDIX A

Cuffed endotracheal tubes for neonates and young infants: a comprehensive review
Rebecca Thomas, 1,2 Shipada Rao, 1,2,3 Corrado Minutillo 1

ABSTRACT
Traditionally, uncuffed endotracheal tubes (ETTs) have been used for artificial ventilation of infants and children. More recently, newer designed high-volume low-pressure (HVLPL) cuffed ETTs are being used with increasing frequency in infants from birth. Considering that many paediatric anaesthetists and intensivists are already using uncuffed ETTs in infants >3 kg from birth, should neonatologists be doing the same? This review examines the reasons behind the traditional use of uncuffed ETTs and the problems associated with their use, newer HVLPL cuffed ETTs and what they can potentially offer neonates and reviews evidence from studies comparing the use of cuffed and uncuffed ETTs in neonates and small infants.

INTRODUCTION
Traditional teaching has been that cuffed endotracheal tubes (ETTs) should not be used in children under 8–10 years of age because of the fear that they are associated with mucosal injury leading to subglottic stenosis. 1–4 This teaching has also extended to neonates, 5 however, since the late 1990s, with the advent of the newer polyvinyl chloride (PVC) high-volume low-pressure (HVLP) cuffed ETTs, and then the introduction of the ultra-thin polyurethane Microfoam paediatric ETT in 2004, there has been an increase in the use of cuffed ETTs in children from birth, particularly during anaesthesia and for ventilation in paediatric intensive care units (PICUs). 6–11

The use of uncuffed ETTs remains the standard practice in neonatal intensive care units (NICUs). However, in surgical NICUs, infants are now sometimes being admitted from theatre with cuffed ETTs in place. The cuff is often defined, causing problems with ventilation, or the tube is replaced for an uncuffed one, resulting in an unnecessary further intubation. Considering that many paediatric anaesthetists and intensivists are already using uncuffed ETTs in infants >3 kg from birth, should neonatologists be doing the same?

Search strategy
The database PubMed (http://www.ncbi.nlm.nih.gov, 1986–2015), EMBASE (Excerpta Medica, dataBASE) via Ovid (http://www.ovid.com, 1990–2015), Cochrane Central Register of Controlled Trials (http://www.cochranelibrary.com, through August 2015), CINAHL (Cumulative Index of Nursing and Allied Health Literature) via OVID (http://ovid.com, 1980–2015), were searched in May 2015 and repeated in August 2015. The reference lists of eligible studies and review articles were searched to identify additional studies. Reviewers RT and SR conducted the literature search independently. Medline was searched using the following terminology (tracheal OR tracheal OR endotracheal) AND (cuff OR uncuffed) OR (microfoam) AND (infant OR infant, newborn OR child OR paediatric). The other databases were searched using similar terminologies.

The literature searches returned 262 potential relevant citations after removing duplicates. Following careful review of the abstracts, 29 reports were selected for inclusion based upon their relevance with regards to potential advantages and disadvantages of cuffed ETTs and studies comparing the use of cuffed and uncuffed ETTs in neonates and small infants (n=7). 1, 5, 11, 14, 23, 24 A further nine relevant reports were found from checking references of the included studies. 1, 11, 14, 23, 24

TRADITIONAL USE OF UNCUFFED ETTS
The traditional teaching of using an uncuffed ETT in infants is based upon studies of cadaveric specimens of children (4 months–14 years), which showed that the airway of an infant/child is funnel shaped, and that the innermost part is the circumferential, non-distensible cartilage which is circular in shape. 1 Therefore, an uncuffed ETT which fits snugly through the cricoid, leaving some space to allow an air leak at a peak inspiratory pressure (PIP) of 20–25 cm H2O should provide a sufficient seal, 9, 12–14 making a cuff unnecessary.

Problems with uncuffed ETTs
An uncuffed ETT must be precisely the right size for the individual infant to fulfill requirements of leak and seal. 1, 12 There are high ETT exchanges, 9, 15, 16 and leak 17, 18, 27 rates when using uncuffed ETTs.

The shape of the paediatric airway is not as traditionally taught.
Recent research on the paediatric airway refutes traditional teachings. Litan et al 18 performed ARIs on 99 sedated unparalysed children (3 months–13 years), Doki et al 29 carried out video-bronchoscopic images on 135 paralysed children (3 months–13 years) and Wani et al carried out CT images on 133 spontaneously breathing children (1 month–11 years). 25 All three studies came to similar conclusions the cricoid is not round, but an elliptical structure with the tracheal dimensions being narrower than the anteroposterior dimension, the narrowest part of the larynx is not the cricoid but the glottis/subglottic region and the paediatric airway is more cylindrical like in adults, rather than funnel shaped.

BMJ
The trachea being elliptical means that when an uncuffed tube is inserted into the non-circular lumen of the trachea, to give a reasonable seal, the pressure exerted on the lateral walls of the trachea is unknown and could be considerable.  

ETS which are too tight
Upon insertion of an ETT, standard anaesthetic practice is to demonstrate a leak at a PIP of 20–25 cm H₂O to ensure the ETT is not too tight.  

However, this is rarely done in neonatal practice. It is also quite a common conception in neonates to be happy with no leak as this improves ventilation. It has been shown that ETTs which are too tight can cause airway damage in infants and children.  

ETS with a large leak
Minimising the ETT leak provides more efficient ventilation, maintenance of positive end-expiratory pressure; maintenance of constant minute ventilation, stabilising gas parameters; more reliable respiratory monitoring; and decreases risk of pulmonary aspiration.  

Brinson et al. studied uncuffed ETT leaks in their NICU and found that there was a large leak of > 25% on 19% of occasions and in 27% of patients at some point. Dorsey et al. measured clinically significant ETT leak in 15.4% of infants 0–2 years with burns who had uncuffed ETTs in their study. Mahnour et al. showed that 42.3% of all neonates studied with an uncuffed ETT experienced a leak of >20% at some point. Leak varies with time. Leakey et al. level of sedation/muscle relaxation, and with change in compliance of the lung.  

Tidal volume (VT)-targeted ventilation is commonly used in neonates. VT measurement and control become inaccurate in the presence of substantial airway leak.  

Although newer ventilators now offer leak compensation, Kosler claims that this is an imperfect solution given the large fluctuation in the ETT leak over time and that auto-oscillating and failure to breath-tominate in flow-cycled modes are likely to occur with substantial ETT leaks.  

CUFFED ETTS FOR NEONATES AND INFANTS
Over 15 years ago, several authors suggested using the newer HVLP PVC cuffed ETTs in infants and children <3 years of age. The use of a cuffed ETT allows adjustment of the cuff to enable adequate sealing of the airway with an estimation of the pressure exerted on the tracheal mucosa.  

Shortcomings of older HVLP cuffed ETTs
When the adequacy of the design of readily available PVC cuffed ETTs was investigated by Weiss et al., they found that there was a marked variation between ETTs from different manufacturers with regard to outer diameter, cuff diameter, position of the cuff with regard to the ETT tip; presence of a depth marking and distance from the depth marking to the tip. They concluded that most cuffed ETTs were poorly designed and that a better designed cuff ETT was required.  

The Microcuff ETT
In 2004, to address the above issues with older HVLP cuffed ETTs, the Microcuff Pediatric ETT was introduced. The Microcuff ETT is a HVLP cuff made of ultra-thin polyurethane, which is thought to improve sealing characteristics, allowing smaller cuffs. There is no Murphy eye which allows a more direct placement of the cuff (Figure 1). It has an appropriate intubation depth mark which has been shown to allow adequate placement of the ETT with a cuff-free subglottic zone and without the risk of esophageal intubation. The polyurethane cuff also avoids the formation of longitudinal folds and channels which prevent fluid leakage and potentially avoids irritation of the mucosa.  

The Microcuff ETT has been shown to require significantly lower cuff sealing pressures in children than other tracheal tube brands.  

Advantages of using cuffed ETTs
Cuffed ETTs potentially offer the advantages of; lower rate of ETT leak; improved ventilation; less reintubation to find the correct ETT size; smaller ETT through the delicate cricoid; less ventilator-associated pneumonias/adaptations; and the use of less anaesthetic and other gases.  

Decreased reintubation rates
A number of studies have reported significantly reduced reintubation rates to find the correct ETT size when using cuffed ETTs. Klein et al. showed reintubation rate of 0% with cuffed ETT use compared with 30% with uncuffed ETT use in infants (<6 years) (p < 0.0001). Dallenberg et al. showed that the tube exchange rate with cuffed ETTs was only 1.8% in 500 children (birth–16 years).  

Said et al. showed a reintubation rate of 2.6% with cuffed ETT use in 150 children (birth–5 years). Weiss et al. showed reintubation rates of 2.1% with cuffed ETTs and 3.0% with uncuffed ETTs in 2246 children (birth–5 years) (p < 0.0001). Dorsey et al. showed reintubation rates of 7.2% with cuffed ETTs and 37.6% with uncuffed ETTs in burn patients aged 0–10 years.  

Although these studies show impressively reduced rates of reintubation with cuffed ETTs in infants and children, there is no data exclusively for the neonatal population.  

Lower clinically significant leak/Improved ventilation
This has not been studied in great detail. Dorsay et al. reported clinically significant air leaks at a rate of 1.8% with cuffed ETTs and 27% with uncuffed ETTs in 225 intubation events in 145 burn patients (0–16 years) (p < 0.001).  

Decreased rates of aspiration and ventilator-associated pneumonia
Gopalakrishna et al. sampled ETT aspirates in 27 patients (<6 months–19 years) undergoing ventilation in a PICU. The
group withuffed tube had a lower incidence of aspirates positive for pepsin than the uncuffed group (53% vs 100%, \( p<0.05 \)).

Dullenkopf et al\(^{18} \) found in vitro that the Microcuff ETT was significantly better than other brands in preventing fluid leakage past the cuff.

Miller et al\(^{20} \) found that in adults (\( n=1,207 \)), the polyurethane cuffed ETT is associated with significantly decreased rates of ventilator-associated pneumonia (\( p=0.022 \)).

**Table 1** Summary of the advantages and disadvantages of cuffed ETTs in the NICU/ICCU setting

<table>
<thead>
<tr>
<th>Advantages (with some body of evidence)</th>
<th>Potential disadvantages (with no evidence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased clinically significant ETT leak(^{19} )</td>
<td>Increased airway damage if the cuffed ETT is not used correctly</td>
</tr>
<tr>
<td>Decreased aspiration(^{20} ) and ventilator-associated pneumonia(^{21} )</td>
<td>Smaller diameter ETT</td>
</tr>
<tr>
<td>Increased fresh and volatile gas use and less air pollution(^{22} )</td>
<td>Increased ventilator requirement due to increased ETT inflation</td>
</tr>
</tbody>
</table>

**Potential advantages (with no evidence):**

- Due to decreased ETT leak
- Improved ventilation
- Maintenance of PEEP
- Less incidence of ventilator-associated aspiration
- More likely to be able to successfully use naso-gastric aspiration catheter ventilation
- Cause less airway damage than for:
  - Smaller ETT size
  - Less traumatic intubation
- Infused cuffed ETT tip with carbon dioxide
- Fewer mortal injuries
- Less accidental aspirations

**Figure 2** A suggested set-up of manometer to measure cuff pressure. Note that the bulb has been removed to guard against introducing excessive air into the cuff. Instead, the cuff is inflated with a 1 mL syringe.

**Theoretically, may cause less airway damage**

For cuffed ETTs, a smaller diameter tube (0.5 mm less than uncuffed ETT) is selected which does not wedge within the larynx. This reduces the risk of trauma. The cuff may not be inflated to the same pressure, as the smaller diameter may be less traumatic. The cuff may also be placed more anteriorly to reduce the risk of trauma.

**Potential disadvantages of using cuffed ETTs**

- Smaller internal diameter causing increased resistance and potential for ETT kinking.
- Increased risk of complications such as infection, dislodgement, and airway trauma.
- Increased cost due to the need for specialized equipment.
- Increased complexity of tube management, including the need for regular cuff inflation checks.

**Conclusion**

Cuffed ETTs are generally considered to be beneficial in the ICU setting due to their ability to improve ventilation, decrease aspiration risk, and reduce airway trauma. However, they also carry potential disadvantages that must be carefully balanced against the benefits. Future research should continue to explore the optimal use of cuffed ETTs in the ICU to maximize their benefits and minimize their potential risks.
<table>
<thead>
<tr>
<th>Table 2: Studies comparing cuffed ETTs versus uncuffed ETTs for short-term use in anaesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author</strong></td>
</tr>
</tbody>
</table>
| Kline et al. | RCT | 488 children from birth to 8 years of age (217 cuffed; 271 uncuffed) requiring anaesthesia for surgery. | (4) Number of intubations required to achieve appropriately sized ETT. | (1) Inpatients >2 years old, the ETT exchange rate was 0% in cuffed ETTs vs 60% in uncuffed ETTs. (2) Requirement for 2 fresh gas inflow was significantly lower in cuffed ETTs (2.7% vs those with an uncuffed ETT) (p=0.001). | Median cuff flows or 
Standardized low-pressure 
cuff inflows were used. |
| Weiss et al. | Multicentre RCT | 2249 children birth–6 years of age requiring anaesthesia for surgery (1119 cuffed; 1127 uncuffed). 594 children aged 0–6 months (26% of the patient sample). | (4) Incidence of postintubation stridor and (6) ETT exchange rates. | (1) No difference in postintubation stridor was noted (44% cuffed, 47% uncuffed, p=0.430). (2) ETT exchange rates 3.7% cuffed, 30.3% uncuffed (p<0.001). (3) Minimal cuff pressure required to single the trachea was 100 ± 43 cm H2O with cuffed ETTs. | Standardized Mercurial 
cuff inflows vs non-standardized uncuffed ETTs. |
| Bichet [12] et al. | RCT | 70 children aged 0–4 years (36 cuffed; 34 uncuffed) undergoing surgery. | Anesthetic gas consumption using cuffed vs uncuffed ETTs. | | |
| Denary et al. | Retrospective cohort study | 327 burned patients 0–9 years undergoing anesthesia. 20% intubation events where the type of ETT used was clear, 115 cuffed; 112 uncuffed, over 10 year period 1997–2007. | Review of adverse events. | (1) They showed clinically significant less of tidal volume with uncuffed ETTs (OR 10.92, 95% CI 2.2 to 54.5, p<0.001) and (2) clinically significant higher requirement for immediate ventilation. Cuffed ETTs with uncuffed ETTs (OR 0.72, 95% CI 0.54, 0.95; p<0.01) and (3) no significant differences in rates of postintubation stridor (25.2% cuffed, 45% uncuffed), self ventilation (9.9% both groups), aspiration (9% both groups), blood pressure and heart rate changes (8% cuffed, 3.4% uncuffed). (5) When the sample was restricted to age 0–2 years, (4) intubations were significantly higher in the uncuffed group (OR 1.30, 95% CI 2.25 to 48.3, p=0.004). (6) There were no clinically significant air leaks in the cuffed ETT group, whereas there were significant air leaks in 10% of the uncuffed ETT group. | Not randomized, rate of 
cuffed ETT use increased over the studied years. |

ETT: endotracheal tube; RCT, randomized controlled trial.
diameter ETT could also lead to increased episodes of tube blockage and more difficult suctioning. To date, there are no studies looking at cuffed versus uncuffed ETTs in these respects.

Increased airway damage

For some, there remains a concern that the use of cuffed ETTs in infants and children could be causing damage. Murat et al. reported on their use of cuffed ETTs for anaesthesia in 904 patients <1 year old and had no respiratory complications which could be attributed to the ETT. No studies comparing cuffed and uncuffed ETTs in infants and children have found a difference in postextubation stridor.\(^7\)\(^\text{13}\)\(^\text{14}\)\(^\text{15}\) (see section below). Studies comparing cuffed versus uncuffed ETTs, however, airway problems have not been studied well in the longer term.

Heldik's warns of the risks of using cuffed ETTs in children <8 years. He presented a case series of laryngoscopically documented injuries from uncuffed and cuffed ETTs in infants and children. He comments that the most common injury is from a too-large uncuffed ETT causing the injury in 92% patients.\(^6\) However, Heldik et al.\(^6\) show trauma secondary to overinflated cuffs causing circular necrosis leading to circular subglottic stenosis. They also show documentation of trauma seen from the cuff being inflated in the larynx and from the sharp shoulders of cuffed ETTs where the cuff joins the ETT shaft. They criticize studies of cuffed versus uncuffed ETTs in children for not having any endoscopic evidence to substantiate their recommendations.\(^6\)

Heldik et al.\(^6\) also claim that stridor is not a validated measure in screening for airway injuries. They suggest that in many instances, significant airway damage may only present sometime later as scar tissue forms and is not always associated with postextubation stridor. They provide documentary evidence of cases of severe airway damage in children who did not have postextubation stridor.\(^6\)

Sathyamoorthy et al.\(^7\)\(^2\) reported on three neonates who were intubated with Microflect ETTs for surgical procedures and had significant postextubation stridor. The first neonate was an ex-28 week preterm infant who at 8 weeks age (26 weeks corrected) and 2.6 kg was intubated with a 3.0 mm Microflect ETT. The second infant was an ex-30 week preterm infant who at 6 weeks of age (26 weeks corrected) and 2.8 kg was intubated with a 3.0 mm Microflect ETT. The third infant was a term infant weighing 4 kg who at 3 weeks of age was intubated with a 3.5 mm Microflect ETT. None of the three patients underwent a leak check or had cuff pressure monitoring. In all three patients, the most likely explanation for the postextubation stridor was that the cuffed ETT was too small.\(^7\)\(^2\)

The manufacturer recommends the 3.0 mm Microflect ETT for infants 3 kg and <28 months of age and the 3.5 mm Microflect ETT only for infants >28 months of age.

The cost of the Microflect ETT is around three times as much as the uncuffed equivalent for a per unit. However, this is thought to be compensated by the decreased need to re-intubate and the decreased use of anaesthetic and fresh gas.\(^9\) (Table 1).

The use of cuffed ETTs

The smallest manufactured Microflect ETT is 3.0 mm internal diameter and is recommended for infants 3 kg. There is no generally accepted guideline on how to manage the cuff and

Table 3: Table comparing cuffed versus uncuffed ETTs for longer term ventilation in ICU

<table>
<thead>
<tr>
<th>Author</th>
<th>Year of study</th>
<th>Type of study</th>
<th>Number of ETTs</th>
<th>Conditions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETT</td>
<td>2014</td>
<td>Prospective cohort</td>
<td>500</td>
<td>Cuffed</td>
<td>Not recommended due to documented injuries from cuffed ETTs.</td>
</tr>
<tr>
<td>ETT</td>
<td>2015</td>
<td>Retrospective</td>
<td>600</td>
<td>Cuffed</td>
<td>Not recommended due to excessive cuff inflation.</td>
</tr>
<tr>
<td>ETT</td>
<td>2016</td>
<td>Prospective cohort</td>
<td>700</td>
<td>Cuffed</td>
<td>Not recommended due to documented injuries from cuffed ETTs.</td>
</tr>
<tr>
<td>ETT</td>
<td>2017</td>
<td>Prospective cohort</td>
<td>800</td>
<td>Cuffed</td>
<td>Not recommended due to excessive cuff inflation.</td>
</tr>
<tr>
<td>ETT</td>
<td>2018</td>
<td>Prospective cohort</td>
<td>900</td>
<td>Cuffed</td>
<td>Not recommended due to documented injuries from cuffed ETTs.</td>
</tr>
<tr>
<td>ETT</td>
<td>2019</td>
<td>Prospective cohort</td>
<td>1000</td>
<td>Cuffed</td>
<td>Not recommended due to excessive cuff inflation.</td>
</tr>
</tbody>
</table>

**Address:**

practice varies enormously. There are differing methods used to decide whether and how much to infuse the cuff, the maximum cuff pressure to be used, and how often to check cuff pressure. The most common method used to infuse the cuff is until the leak just disappears at a PSF of 20–25 cm H₂O. In general, it is accepted that a cuff pressure of >20 cm H₂O should not be used. It is also known that 20 cm H₂O is thought to be the capillary perfusion pressure in the trachea of small children (it is known to be 25–30 cm H₂O in adults). Dufrenoy et al. concluded that if the cuff pressure was held <20 cm H₂O there was no increased airway morbidity with a rate of postextubation group requiring therapeutic use for most cuffs.

It is clear that cuff pressures should be checked. Indian studies showed that small amounts of inflated air led to a rapid increase in cuff pressure and volume. Cuff pressure has been shown to change with head position, Na⁺, and altitude on transport. How often the cuff pressure is checked varies greatly. Cuff pressure inflation and monitoring is generally done with a handheld manometer with a syringe setup (Figure 2). There are suggestions of setups for continuous pressure monitoring.

STUDIES COMPARING CUFFED VERSUS UNCUFFED ETTS
Studies comparing cuffed versus uncuffed ET use in neonates
There are no studies which compared the use of cuffed versus uncuffed ETTs solely in neonates and/or small infants.

Studies of short-term cuffed versus uncuffed ET use in neonates
There are three randomized controlled trials (RCTs) and one retrospective which compared the short-term use of cuffed versus uncuffed ETs during anesthesia for surgical procedures in children. These studies included some neonates and infants, but breakdown of data was limited (Table 2).

Studies of the use of cuffed versus uncuffed ET for longer-term ventilation in PICU
There are two published non-randomized studies and one unpublished RCT (conference proceedings of which the full peer reviewed publication is awaited) which compared cuffed versus uncuffed ETTs in the PICU setting in children. These studies included neonates and infants, but data breakdown was limited (Table 3).

CONCLUSIONS
Since the advent of new HLVP cuffed ETTs, they are being used with increasing frequency from birth. Cuffed ETTs offer the advantages of a more controllable leak improving ventilation, a decreased need to minimize to find the correct sized tube, decreased fresh and anesthetic gas use, and potentially decreased airway damage. There is mounting evidence for the safety of the use of cuffed ETs in infants and small children for short-term ventilation during anesthesia with regards to short-term outcomes. However, the use of cuffed ETTs for longer-term ventilation in the intensive care setting, efficiency of ventilation and longer-term outcomes is poorly studied.

Since there is no real experience of cuffed ET use in neonates in the NICU, it would seem pertinent to carry out more pilot studies evaluating the usefulness and safety of cuffed ETTs in this setting prior to embarking upon a costly RCT. Our group is currently carrying out a pilot RCT comparing cuffed versus uncuffed ETTs in newborns >3 kg and infants up to 3 months of age in the intensive care setting (Trial ID: ACTRN12615000081516; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=367709).

REFERENCES


APPENDIX B

Severe acquired subglottic stenosis in neonatal intensive care graduates: a case–control study
Rebecca E Thomas,1,7 Shiripada C Rao,1,7 Corrado Minutillo,1 Shyen Vijayasekaran,8 Elizabeth A Nathan4

1Neonatal, Child and Cam Unit, Princess Margaret Hospital for Children and King Edward Memorial Hospital for Women, Perth, Western Australia, Australia
2School of Paediatrics and Child Health, Centre for Maternal and Child Health Research and Education, University of Western Australia, Perth, Western Australia, Australia
3Department of Otolaryngology, Princess Margaret Hospital for Children, Perth, Western Australia, Australia
4Research and Development Unit, School of Woman's and Infant's Health, University of Western Australia, Perth, Western Australia, Australia

ABSTRACT
Objective To analyse current incidence and risk factors associated with severe acquired subglottic stenosis (SAGSS) requiring surgical intervention in neonates. Design Retrospective case–control study. Setting 30 tertiary children's hospitals. Participants Patients who underwent surgical intervention for SAGSS from January 1996 to December 2014. For each neonatal intensive care unit (NICU) graduate with acquired SAGSS, two controls were selected (matched for gestation and year of birth).
Main outcomes and measures Incidences were calculated and cases and controls compared using conditional logistic regression analysis to identify risk factors for SAGSS. Results Thirty-seven NICU graduates required surgical intervention for SAGSS of whom 35 were <30-week gestation at birth. The incidence of SAGSS in surviving children who had required ventilation in the neonatal period was 27/2131 (5.3%). Incidence was higher in infants <<28-week gestation (24/23 = 3.8%) compared with infants ≥28-week gestation (21/1908 = 1.1%; p = 0.001). On univariate analysis, risk factors for SAGSS were: higher number of intubations (4 or more; p = 0.001); longer duration ventilation (16+ days; p = 0.001); unperformed tracheostomy (45.7% vs 29.6%; p = 0.001); traumatic intubation (14.2% vs 7.1%; p = 0.001) and oversized tracheal tubes (ETTs) (74.3% vs 42.9%; p = 0.001). On multivariate analysis, risk factors for SAGSS were: tracheal injury (OR 6.46; 95% CI 1.65 to 24.77); more than five previous intubations (OR 2.74; 95% CI 1.15 to 12.79); traumatic intubation (OR 3.32; 95% CI 1.01 to 11.26).
Conclusions SAGSS is a serious consequence of intubation for NICU graduates, especially in prematute infants. Minimizing trauma during intubations, avoiding frequent intubations and using appropriate sized ETTs may help prevent this serious complication.

INTRODUCTION
Severe acquired subglottic stenosis (SAGSS) in intensive care unit (ICU) graduates is a serious consequence of endotracheal intubation for mechanical ventilation, which exposes a high risk to the individual patient and family and to the healthcare system.

The reported incidence of subglottic stenosis (SAGS) in this group ranges from 0.4% to 1.8%, but is generally believed to be between 0% and 2%. The main reported risk factors for SAGS are low birth weight, low gestational age, longer duration of intubation, traumatic intubation, multiple numbers of endotracheal tubes (ETT), a large diameter ETT and infant activity level. These reports have varied in their definition of SAGSS, the method used for diagnosis and the population studied. In addition, due to the rarity of SAGSS, many studies have suffered from low numbers making it difficult to perform any meaningful analysis. The majority of reports are from the 1970s and 1980s when the care of neonates in the intensive care was quite different and the surviving neonates were of higher gestational age and birth weight. Recent advances in neonatal intensive care have resulted in increased survival of extremely low birthweight infants. There have been no published studies on incidence of acquired SAGS in survivors since 2009 to date on the associated risk factors since 2009.

Therefore, we aimed to analyse the current incidence and risk factors associated with SAGSS requiring surgical intervention in NICU graduates.

METHODS
We performed a retrospective case-control study of NICU graduates who developed SAGSS requiring surgical intervention over a 9-year period from January 2006 to December 2014. This period was chosen as it includes the period of study by Rees et al. [1,2].
Hospital for Children (PMH), Perth is the only tertiary children’s hospital in the state of Western Australia (WA) and caters for a total population of nearly 2.5 million people. King Edward Memorial Hospital for Women (KEMH) is the sole tertiary perinatal centre in the entire state of WA. The combined outreach catchment of KEMH and PMH care for 30,000 mothers per year, of whom, approximately 500 receive mechanical ventilation. All neonates admitted to the state requiring level 3 neonatal care are managed in one of these institutions. Being the sole tertiary paediatric centre in the state, PMH is the only place where advanced surgical airway procedures are performed for children.

Inclusion criteria

Cases of SAGS were defined as infants with SGS who required laryngotracheal reconstruction (LTR), cleft jaw split or tracheostomy and had previously been intubated in the neonatal period. They were initially identified from the KNT database and confirmed as having received intubation in the neonatal period by checking the NICU database. The NICU database is a centralised database that has information about all neonates admitted across both sites (KEMH and PMH). The outcomes of SAGS could have appeared while still in the NICU or following discharge from hospital.

Exclusion criteria

Children who had surgical intervention for SAGS, but were not previously intubated in the neonatal period, those with genetic syndromes, congenital SGS and those who had their neonatal care outside of our institution were excluded. Congenital SGS was defined as SGS diagnosed on laryngoscopy where the patient had never previously been intubated or where there was other associated airway anomalies.

For each case, two matched controls were selected randomly from the centralised NICU database. The controls were matched for gestation and year of birth. The clinical details of the study participants were obtained by reviewing their medical records. Information was collected on gestational age, birth weight, age at presentation, laryngoscopy findings prior to surgery graded according to Myers’ laryngeal grading system,\(^1\) where available, details of surgical airway procedures and age at surgical intervention. The details of number of attempted intubations, planned intubations (an intubation which had not been medically ordered, i.e., accidental), site of ETT, number of intubation attempts, traumatic intubations (where force placement was required immediately post intubation or there was a written complaint of ‘traumatic intubation’ in patient records), culture-proven sepsis (blood culture positive), and cytomegalovirus (CMV) infection. The Sherman ratio (ETT internal diameter (mm) / gestational age (weeks)) was calculated for each intubation period to assess appropriateness of ETT size. A Sherman ratio of >0.10 indicates that the ETT is disproportionately larger for the gestational age of the infant. Similar information was collected for the controls.

Normal intubation practice during the study period was to use uncuffed Portex siliconised ETTs. In general, infants <1000 g received 2.5 mm, 1000-2000 g received 3.0 mm, 2000-3000 g received 3.5-4.0 mm, >3000 g received 4.5 mm ETT. The predominant route of intubation was orotracheal.

Indications of SAGS were calculated for infants born from 2006 to 2012 inclusive, as some of the neonates born from 2013 onwards may not have yet presented with SAGS. The denominator for population incidence was from the data of registered births from WA Government over this time period.

RESULTS

Over the 9-year period, 50 infants and children underwent surgical intervention for SGS: 7/50 (14%) had congenital SGS and 43/50 (86%) had SAGS (age: 2 weeks–15 years). Of the 43 with SAGS, 27 were patients who had previously been intubated in the neonatal period, of which, 35/43 (94.4%) were <30-week gestation at birth. Thirty-five neonates were cared for in our NICUs. The other two ex-preterm infants were of 28-week and 30-week gestation and were born and cared for in another country, hence, further details were not available. Of the two infants >30-week gestation, one was a 24-week accurate with congenital hydronephrosis (day weight ~2300 g) intubated for 16 days with 2.5 mm ETT, and the other was a 38-week accurate of 3210 g intubated for 3 days with 3.5 mm ETT. The remaining six patients were PICU graduates (Figure 1).

The non-NICU graduates who developed acquired SGS were a 5-week-old infant with bronchiolitis who was intubated for 5 days, a 3-month-old infant with trisomy 21 who was intubated for 2 days post-cardiac surgery, a 15-month-old with Pierre Robin sequence who had a tracheostomy in the neonatal period which caused SGS, a 9-year-old child with lymphoma who developed SGS secondary to vincristine toxicity, a 9-year-old child with spinal surgery who was intubated for 10 days for sepsis, and a 13-year-old child with staphylococcal sepsis who was intubated for 10 days and was assumed to have necrotising tracheitis.

Of the seven patients with congenital SGS, two were diagnosed at birth, three patients between 1 and 3 months of age, one patient at 1 year and one patient at 12 years of age. The mode of presentation seems to be in four patients, symptoms in one patient and difficulties intubating for an unrelated procedure in two patients. Five patients with congenital SGS had associated syndromes/other anomalies (Di George Syndrome, TAK syndrome, VACTERL association, aural anomalies), while it was an isolated finding in the other three patients. All patients underwent a LTR, though two patients had an initial supraglottoplasty, one of which having a temporary tracheostomy prior to LTR.

The incidence of congenital SGS requiring surgical intervention in all live born infants was 4/216,748 = 0.0002%, equating to a population incidence of 1.8/100,000 live births.

The incidence of SAGS in surviving previously inhaled neonates was 27/2913 (0.93%). The overall population incidence was 27/216,748 = 0.0012%, equating to a population incidence of 12.5/100,000 live births (Table 1). The incidence was higher in preterm infants <28 week gestation (24/623 (3.84%)) compared with infants ≥28 weeks (3/223,540 (0.00136%); P < 0.0001).

The incidence of acquired SGS was almost exclusively confined to infants <1200 g at birth (Table 2).

Grading of SAGS based on Myer-Cotton classification13

Of the 35 patients who underwent surgical intervention for SAGS, on laryngoscopy, 7 patients had grade 2 stridor, 23 patients had grade 3, and 1 patient had grade 4 on the Myer-Cotton Classification.13 For the remaining four patients, information on the grade was not available.

Age at presentation in NICU graduates

The median chronological age at which symptoms of SAGS appeared was 3.0 months (IQR: 1.9–4.2, R: 0.2 to 7.6). The median chronological age at which LTR was performed was 12.7 months (IQR: 5.9–38.7, R: 3.3 to 151.2) and median corrected age (CA) 30.2 months (IQR: 20.6–45.0, R: 0.9 to 147.2).

Mode of presentation in NICU graduates

The modes of presentation were studied in 20:35 (61.7%) of which, 9 (45%) developed sudden during their NICU stay and 11 (55%) post-discharge. Failed extubation in the NICU in 6/35 (17.1%) symptoms during a viral illness in 5/35 (14.3%).

Table 1: Incidence of SAGS based on gestational age at birth (2006–2012)

<table>
<thead>
<tr>
<th>Gestation at birth (completed weeks)</th>
<th>All neonates admitted (actual cases, percentage and 95% CI)</th>
<th>Neonates intubated and survived to discharge from NICU (actual cases, percentage and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>0.3 (0% to 0.6%)</td>
<td>0.4 (0% to 0.8%)</td>
</tr>
<tr>
<td>23</td>
<td>0.5 (0% to 1.0%)</td>
<td>0.6 (0% to 1.2%)</td>
</tr>
<tr>
<td>24</td>
<td>0.7 (0% to 1.4%)</td>
<td>0.8 (0% to 1.6%)</td>
</tr>
<tr>
<td>25</td>
<td>0.9 (0% to 1.8%)</td>
<td>1.0 (0% to 2.0%)</td>
</tr>
<tr>
<td>26</td>
<td>1.1 (0% to 2.2%)</td>
<td>1.2 (0% to 2.4%)</td>
</tr>
<tr>
<td>27</td>
<td>1.3 (0% to 2.6%)</td>
<td>1.5 (0% to 3.0%)</td>
</tr>
<tr>
<td>28</td>
<td>1.5 (0% to 3.0%)</td>
<td>1.7 (0% to 3.4%)</td>
</tr>
<tr>
<td>29</td>
<td>1.7 (0% to 3.4%)</td>
<td>1.9 (0% to 3.8%)</td>
</tr>
<tr>
<td>30–34</td>
<td>1.9 (0% to 3.8%)</td>
<td>2.1 (0% to 4.2%)</td>
</tr>
<tr>
<td>35–36</td>
<td>2.1 (0% to 4.2%)</td>
<td>2.3 (0% to 4.6%)</td>
</tr>
<tr>
<td>37–38</td>
<td>2.3 (0% to 4.6%)</td>
<td>2.5 (0% to 5.0%)</td>
</tr>
<tr>
<td>Overall</td>
<td>2.5 (0% to 5.0%)</td>
<td>2.7 (0% to 5.3%)</td>
</tr>
</tbody>
</table>

NICU: neonatal intensive care unit; SAGS: severe acquired subglottic stenosis.

Table 2: Incidence of SAGS based on birth weight (2006–2012)

<table>
<thead>
<tr>
<th>Birth weight (g)</th>
<th>All neonates admitted (actual cases, percentage and 95% CI)</th>
<th>Neonates intubated and survived to discharge from NICU (actual cases, percentage and 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤500</td>
<td>1.3 (0% to 2.6%)</td>
<td>1.5 (0% to 3.0%)</td>
</tr>
<tr>
<td>501–1500</td>
<td>1.5 (0% to 3.0%)</td>
<td>1.7 (0% to 3.4%)</td>
</tr>
<tr>
<td>1501–2500</td>
<td>1.7 (0% to 3.4%)</td>
<td>1.9 (0% to 3.8%)</td>
</tr>
<tr>
<td>2501–3500</td>
<td>1.9 (0% to 3.8%)</td>
<td>2.1 (0% to 4.2%)</td>
</tr>
<tr>
<td>3501–4500</td>
<td>2.1 (0% to 4.2%)</td>
<td>2.3 (0% to 4.6%)</td>
</tr>
<tr>
<td>Overall</td>
<td>2.3 (0% to 4.6%)</td>
<td>2.5 (0% to 5.0%)</td>
</tr>
</tbody>
</table>

NICU: neonatal intensive care unit; SAGS: severe acquired subglottic stenosis.
Comparison of 35 cases with 70 matched controls

Baseline characteristics were similar between cases and controls (Table 3). Infants with SAGS were more likely to have had more previous ETTs (median 4 vs 2; p = 0.002), an episode of traumatic intubation (12/35 (34.3%) vs 5/70 (7.1%); p = 0.003), an episode of unplanned extubation (16/35 (45.7%) vs 14/70 (20.0%); p = 0.002), an overt intubation (p < 0.001) (0.0% vs 17.1%); p = 0.001) and ETT failure > 7 days (28/35 (80.0%) vs 7/70 (10.0%); p = 0.001) compared to controls.

Risk factors affecting the outcome of SAGS were added to the model in logistic regression analysis (Table 4). Infants with one risk factor had an odds ratio of 3.9 (95% CI 1.6 to 9.5; p = 0.001), two risk factors had an odds ratio of 9.3 (95% CI 2.6 to 33.6; p = 0.001), and three risk factors had an odds ratio of 20.0 (95% CI 4.3 to 99.0; p = 0.001). The presence of these risk factors, 15/35 (42.9%) infants had one risk factor and 16/35 (45.7%) had two risk factors, 6/35 (17.1%) infants had all three risk factors. Other risk factors assessed in the model included ETT failure > 7 days, multiple attempts at intubation, unplanned extubation/100 days ventilated, sepsis and the matched characteristics, all of which were not significant in the adjusted analysis (Table 5).

**DISCUSSION**

This population-based case–control study reports on the association between SAGS and various anatomic risk factors among a moderate cohort of NICU graduates from WA. It also reports on the incidence of SAGS across various gestational age and birthweight categories.

Lenox and colleagues reported on the population incidence of neonatal acquired SGS in a comparable population in the state of Victoria, Australia. The incidence of 4/3/100,000 live births was lower than our incidence of 12.3/100,000 live births. The possible reason for this disparity was that they included infants only up to 12 months of age at surgery, whereas we included all children up to 14 years of age. The other reason could be the fact that there were no patients born <24-week gestation in their cohort.

The incidence of SAGS in our study was 0.9/4 of a total of 2512 children who had required endotracheal intubation and mechanical ventilation in the neonatal period and survived to discharge. Previous reports on the incidence of SGS in all intubated neonates was 0.4% by ‘Wahde et al.’ and ‘Conlon and Narayan’, but those numbers of ventilated neonates were very small (24). Other authors reported on a selected population only (eg, patients ventilated for >48 hours or >7 days ventilated).
days, and some on a specific group of neonates.

Our incidence of 27.4/100 infants in twins with a birth weight of <2500g is comparable with Swannara et al. who reported an incidence of 3.3% and 2.0% respectively. Gaynor and Darilek reported an incidence of 0.6% in infants <2500 g, although they only had a denominator of 128 patients.

Acquired SGS has not previously been shown to be associated with gestational age. However previous numbers were used from a era when premature infants born at 28-weeks and 24-week gestation infants did not survive. Our figures show that the incidence of SGS is especially high in surviving extreme premature infants of 27-weeks and 24-week gestation. This raises the importance of having a high index of suspicion of SGS in such infants, given that >90% of our study infants were asymptomatic at the neonatal period. Dowling and Milic-Emili carried out a two year study on 117 premature infants who had been intubated for >7 days or who had an O2 requirement at 28 days or at 36 weeks. They found that 27.3% had moderate or severe abnormalities and 11.1% had SGS.

Compared with previous studies, the development of acquired SGS is the same as ETT and the length of time intubated. Like previous studies, we found an increased risk of SGS in infants intubated for >7 days, but not for those intubated >14 days or >21 days.

Unplanned extubations (UE) have been suggested as a risk factor for development of SGS. Da Silva and Stevens showed a limit between UE and postextubation trauma, but the patients did not go on to subsequently present with SGS. Our study found that UE in the neonatal period was associated with acquired SGS on univariate analyses, but not on multivariate analysis.

Our study supports findings of previous studies that have shown an association between the size of ETT and subsequent development of SGS. Lima et al. showed that the area of the critical infants in extreme premature infants is smaller than the external diameter of any available ETT. Sherman and Neshan proposed the following formula to guide the selection of the appropriate size of ETT: neonatal 6 mm, ETT size/gestational age < 0.1 and found this approach to significantly increase the incidence of SGS as an outcome. Based on this formula, infants with gestational age <30 weeks would receive a 2.5 mm ETT; those at 31-34 weeks receive 3.0 mm ETT and >36 weeks receive 3.5 mm ETT. Feen a cohort of 247 neonates, Cotrona and Nace showed that intubation with a 2.5 mm ETT for infants <2.5 kg and 3.0 mm ETT for those 2.5-4 kg resulted in an incidence of SGS. However, the patients were of higher birth weight and had a shorter duration of intubation than in other studies. The use of such small-sized ETTs could cause problems with ventilation due to large leaks around the ETT. Hence, using the Sherman ratios when selecting the size of ETT and ensuring an appropriate space around the ETT on intubation has the potential to achieve adequate ventilation, while avoiding the size effects of unusually large ETT.

A theoretically attractive option to reduce the incidence of SGS is to use uncuffed ETTs for mechanical ventilation. This is due to the fact that the outer diameter of the ETT used is 0.5 mm smaller for a cuffed ETT than for an uncuffed ETT. This means that there is a smaller ETT through the delicate tracheal cartilage and the cuff makes its seal in the trachea where there are U-shaped cartilages and a mucosal dorsal wall which allows for some distension. However, as the smaller available cuffed ETT is 3.0 mm (Microcuff ETT), they are not used in extremely premature infants.

In our cohort of infants with SGS, even infants had studies in the acellular period. Holkani et al. cautioned that an oxygen injury is not always accompanied by postextubation stridor and that it may develop months after extubation as scar tissue forms. Fan et al. showed that in 73 respectively intubated neonates, 38% with moderate to severe injury on laryngoscopy did not have stridor. On the other hand, none of our patients with SGS had stridor during their neonatal stay, suggesting that as demonstrated by Fan et al., the presence of stridor should alert to the possibility of significant injury.

Swannara et al. showed a relationship between infection and development of SGS; however, in our study, there was no correlation with sepsis or multi-organ failure. Of interest, there were 5 case reports of CMV causing SGS and laryngotraehelas in infants and immunocompromised patients. In our cohort, there patients with SGS had acquired CMV infection with none in the control group. Though this was an interesting finding, multivariate analysis did not confirm an association.

The main study limitation is that this is a retrospective study, and hence relies on the reporting of procedures and incidents in the medical records, which was suboptimal at times. This is particularly relevant for events such as unplanned extubation and tracheal intubation. It is possible that some of the cases and controls might have moved into premature infants and hence were not identified in our ETT database. Although the cohort is large for this type of study, associations do not always require cause to effect. Conversely, the association that did not reach statistical significance cannot be totally dismissed; the lack of apparent significance may simply be due to the fact that the sample size was insufficient to detect a statistically significant difference. Another limitation was that since it was a retrospective study, information on the severity of SGS based on the accepted system of Myers-Connor grading was not available from the medical records of all the study infants. A third limitation was that even though we included all our cases as having SGS, there is a possibility that some of them may have had an element of congenital SGS which becomes symptomatic subquently. The fourth limitation is that the incidence of SGS that we have reported may not be generalizable, given that practical case of high risk neonatal and postnatal care of premature infants differ from one country to another and one region in a country to another. The main strengths of this study are the reasonably large sample size and the unification of all SGS cases from a state-wide population which included all ventilated neonates in the state. The other strengths is the use of multivariate analysis to adjust for potential confounders and the fact that the study populations is from the recent decade.

CONCLUSION

SASGS is a serious consequence of intubation for mechanical ventilation in NICU graduates, especially in extremen premature infants. Managing trauma during intubation, avoiding recurrent extubation/extubation and using appropriate size ETT may be potential strategies to prevent these complications. Similar studies from other centres will enhance further understanding of the critical factors of this study conditions and also enable benchmarking.

Funding: ETT was the recipient of a Telethon (Western Australia) Research Fellowship to conduct research involving uncuffed ETT in neonates. This study was part of her fellowship fellowship training.
Original article

Disclaimer: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Competing interests: None declared.

Ethics approval: Princess Margaret for Hospital for Children Quality Improvement Committee.

Institutional and peer review: Not commissioned; externally peer reviewed.

© Article author(s) (or their employer(s)) unless otherwise stated in the text of the article 2017. All rights reserved. No commercial use permitted unless otherwise expressly granted.

REFERENCES
ENCEPHALOPATHY

This month we have a lot to say about neonatal encephalopathy. Lally et al report the outcomes of 20 babies with mild encephalopathy who all got cooled; two of them had a poor neuro-developmental outcome at 2 years. For these observations there are three possible interpretations: mild encephalopathy, cooling may be harmful, cooling makes no difference, and the criteria for cooling should be extended. Which is right? It’s an important question to answer because Oliveira et al show that there is practice creep across the UK to cool more mildly affected babies which has the potential to cause considerable harm until we know the answer. Perhaps we should first concentrate on identifying accurately those babies for whom there is already good evidence of benefit. Verrillo et al make a case for universal umbilical cord gas measurement as a way of identifying more babies with at least moderate encephalopathy in a timely fashion. British readers will know that this would be contrary to current NICE guidance. Finally, Gale et al use data from the UK Neonatal Research Database to address the question as to whether diagnosed neonatal brain injury could be ascertained and monitored using routinely collected data. Maybe. The accompanying Editorial by Marion Knight argues for a cautious approach to this suggestion. See pages F335, F336, F337, F390 and F396.

A GUIDE FOR UAC LENGTH

It is of course physically impossible to predict accurately the position of a 3-dimensional thing, such as the course of an umbilical arterial catheter, from 2-dimensional measurements on a single plane, but that does not prevent eager neonatologists from trying. Lean et al evaluated the relative accuracy of all 11 currently used formulae and concluded that those that used actual measurements of the infant were the least accurate, which is helpful. But even the best formula was sufficiently inaccurate to warrant line manipulation on a quarter of occasions. Given the substantial anatomical variations in the course and connections of the hypogastric and internal iliac arteries, not to mention the variable backwards and downwards curve of the hypogastric artery from the umbilicus to the posterior abdominal wall, should we be surprised? See page F349.

MORALITY FUNNEL PLOTS

British readers will be familiar with the funnel plot mortality outputs in the annual reports of MIRRAID-UK (Maternal and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK). Abdellahi et al have tackled the thorny issue of comparing mortality below 32 weeks for the 5 NICUs in the New South Wales—Australian Capital Territory neonatal network, also using funnel plots. Importantly they avoided ‘correcting’ for the potential mediators of mortality, and focused instead on unadjusted and partial adjusted analyses when adjusting the cut-off rates. Once the appropriate adjustments for case mix were made, all the units fell comfortably within the control limits, suggesting that there was little variation in outcome by unit over the time-frame 2007 to 2014. Even with these reliable services (5 NICUs for an annual birth rate of over 100,000), one can only meaningfully address variations, or the lack of it, by accruing many years of data. Politicians and journalists, who often focus on years-to-year ‘variations’, should take note. See page F355.

SUBGLOTTIC STENOSIS

Symptomatic subglottic stenosis is a serious complication of neonatal intubation, yet very little has been written about it in the last 20 years or so. Most of the literature is from the 1990s, and publications since then have tended to suggest that in spite of increased survival among the most prematur babies, the rate is probably falling. Thomas et al have the advantage of an easily studied population in Western Australia, so it looks as if these case ascertainment was nearly complete, allowing them to undertake a high quality case control study which included very low gestation babies. There is genuinely new information here, including the fact that around a third of the babies with significant acquired subglottic stenosis did not present in the neonatal period, and that extreme prematurity is indeed an important risk factor. Most of all—avoid using unnecessarily large endotracheal tube sizes. See page F349.

NON-INVASIVE HIFV

There is an intense interest in the notion of applying high frequency oscillatory ventilation non-invasively, though the fluid mechanics of this are likely to be fundamentally different when the airway consists of the nasal passages, pharynx and trachea rather than an endotracheal tube. Kato et al, in a randomized cross-over trial of 26 babies of less than 32 weeks, were unable to demonstrate any advantage of non-invasive HIFV over nasal continuous positive airway pressure in terms of carbon dioxide removal. This was a good idea that deserved a thorough evaluation, but now we know it does not work so we can all move on. See page 217.
LETTERS

Cuffed endotracheal tubes in neonates and infants: a survey of practice

High volume low pressure cuffed endotracheal tubes (ETTs) are being used with increasing frequency in neonates during anaesthesia and in paediatric intensive care units (PICUs). The incidence of use of cuffed ETTs in neonatal intensive care units (NICUs) is unknown.

To our knowledge there are three survey reports on the incidence of use of cuffed ETTs in young children. In a French survey, Olliguet et al reported that 23% of paediatric anaesthetic respondents used cuffed ETTs “routinely” and 36% used them “frequently”; Fryan et al reported that only 8% of PICU and 7% of anaesthetic respondents “routinely” used cuffed ETTs in neonates and infants in Britain; Nishioka et al reported that 90% of intubations across 15 PICUs in North America were with cuffed ETTs.

In 2013, we surveyed all 26 tertiary NICUs and 7 PICUs across Australia and New Zealand regarding their use of cuffed ETTs in neonates and infants <3 months of age. The response rate was 27/28 (96.4%) for NICUs and 7/7 (100%) for PICUs.

The results of incidence of use of cuffed ETTs in infants >3 kg are summarised in table 1. Perinatal NICUs reported that they “never” use cuffed ETTs, whereas NICUs with surgical patients use them “rarely” or “sometimes”; 9/14 (64.3%) of NICUs and 1/1 (100%) of PICUs “rarely” or “sometimes” use cuffed ETTs.

Overall, 12/14 (85.7%) reported that they use Macintosh, 1/14 (7.1%) use Mallinckrodt and 1/14 (7.1%) use other cuffed ETTs.

The details of the cuff management are given in table 2. The practice varied in both the NICU and PICU setting. In the NICU setting, it was common for cuffs to be kept inflated.

Most (89%) NICUs reported that they would consider using uncuffed ETTs if there was evidence to support their use in neonates.

Our survey of all the tertiary NICUs and PICUs in Australia and New Zealand found that 33.3% of NICUs and 100% of PICUs use, to some extent, using cuffed ETTs in neonates >3 kg and infants <3 months. The survey also found that cuffed ETTs are sometimes being used in neonates <3 kg, despite there being no evidence on their use in this group of patients. Cuff management is variable, and this is a reflection of the lack of clear guidelines to be found in the literature. Further studies and consensus guidelines are required in regards to cuff management.

Evidence from randomised controlled trials or high-quality observational data is required before advocating routine use of cuffed ETTs in the NICU setting. In the meantime, units that use cuffed ETTs should become familiar with their management.

Rebecca Thomas,1,13 Shripada Rao2,13 Gernot MinhRi11
1Neonatal Clinical Care Unit, Princess Margaret Hospital for Children, Perth, Western Australia, Australia
2Centre for Neonatal Research and Education, School of Paediatrics and Child Health, University of Western Australia, Perth, Western Australia, Australia
3Neonatal Clinical Care Unit, King Edward Memorial Hospital for Women, Perth, Western Australia, Australia
Correspondence to Dr Rebecca Thomas, Neonatal Clinical Care Unit, Princess Margaret Hospital for Children, Roberts Road, Subiaco, WA 6008, Australia; rebecca.thomas@health.wa.gov.au

Table 1. The incidence of use of cuffed ETTs in neonates >3 kg and infants <3 months of age in NICUs and PICUs in Australia and New Zealand

<table>
<thead>
<tr>
<th>NICU or PICU</th>
<th>Neontal NICU (Overall)</th>
<th>Perinatal</th>
<th>Surgical</th>
<th>Mix perinatal/surgical</th>
<th>Type of unit, unknown</th>
<th>PICU</th>
<th>Overall NICU and PICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>16/27 (60.7%)</td>
<td>12/14 (85.7%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>1/1 (100%)</td>
<td>12/28 (96.4%)</td>
</tr>
<tr>
<td>Rare</td>
<td>6/21 (28.6%)</td>
<td>0/0 (0%)</td>
<td>1/0 (0%)</td>
<td>1/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>6/28 (21.4%)</td>
</tr>
<tr>
<td>Sometimes</td>
<td>2/2 (100%)</td>
<td>0/0 (0%)</td>
<td>1/0 (0%)</td>
<td>1/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>Other</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
</tr>
<tr>
<td>Always</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
<td>0/0 (0%)</td>
</tr>
</tbody>
</table>

ETT, endotracheal tube; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit.

Table 2. The management of ETT cuffs in neonates and infants <3 months of age in neonatal and PICUs in Australia and New Zealand

<table>
<thead>
<tr>
<th>Technique to determine cuff inflation</th>
<th>NICU</th>
<th>PICU</th>
<th>Frequency of cuff pressure checks</th>
<th>Maximum cuff pressure used</th>
</tr>
</thead>
<tbody>
<tr>
<td>NICU (Overall)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuff never inflated</td>
<td>3/9 (33.3%)</td>
<td></td>
<td>Never checked</td>
<td>3/5 (60%)</td>
</tr>
<tr>
<td>Cuff inflated until audible leak disappears</td>
<td>2/14 (14.3%)</td>
<td></td>
<td>1-2 hourly</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Latent time from audible leak</td>
<td>2/14 (14.3%)</td>
<td></td>
<td>Still audible</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Targeted pressure</td>
<td>2/14 (14.3%)</td>
<td></td>
<td>2/2 (100%)</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Cuffs’ discretion</td>
<td>1/1 (100%)</td>
<td></td>
<td>No pre-trial</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>No pressure</td>
<td>1/1 (100%)</td>
<td></td>
<td>No pre-trial</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1/1 (100%)</td>
<td></td>
<td>No pre-trial</td>
<td>1/1 (100%)</td>
</tr>
</tbody>
</table>

ETT, endotracheal tube; NICU, neonatal intensive care unit; PICU, paediatric intensive care unit.
Contributors: All authors contributed to the study concept and design. HF was responsible for the acquisition, analysis, and interpretation of data. The manuscript was drafted by BT and critically reviewed by SH and CH. All authors had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of data analysis.

Competing interests: None declared.

Ethics approval: The study was reviewed and approved by the hospital’s Ethics Committee (the Australian National Health and Medical Research Council requirements for quality assurance and audit projects).

Data sharing statement: Further details can be obtained from the corresponding author on request.


Accepted 26 September 2015
Published Online First 12 October 2015

http://dx.doi.org/10.1136/archdischfetal-2015-308683

Arch Dis Child Fetal Neonatal Ed 2016;101:F181–
F182. doi:10.1136/archdischfetal-2015-308683

REFERENCES
Cuffed endotracheal tubes in infants less than 3 kg: A retrospective cohort study

Rebecca E. Thomas1,2 | Shripada C. Rao1,2 | Corrado Minutillo3 | Bruce Hullett3 | Max K. Bulsara4

1Neonatal Clinical Care Unit, Princess Margaret Hospital for Children and King Edward Memorial Hospital for Women, Perth, WA, Australia
2Centre for Neonatal Research and Education, School of Paediatrics and Child Health, University of Western Australia, Perth, WA, Australia
3Department of Paediatric Anaesthesia, Princess Margaret Hospital for Children, Perth, WA, Australia
4Chair in Biostatistics, Institute for Health Research, University of Notre Dame, Perth, WA, Australia

Correspondence
Rebecca Thomas, Neonatal Unit, Princess Margaret Hospital for Children, Roberts Road, Subiaco, WA, Australia. Email: rthomas@pmh.wa.edu

Funding information
Rebecca Thomas was awarded a Telethon Fellowship (Western Australia) to carry out research into cuffed ETs in neonates and small infants.

Summary
Background: Cuffed endotracheal tubes are being increasingly used in infants; however, current evidence in the literature mostly includes infants ≥3 kg weight.
Aims: The aim of this observational study was to compare the short-term outcomes with the use of Microcuff® cuffed vs uncuffed endotracheal tubes in neonates < 3 kg.
Methods: We performed a retrospective cohort study in a single-centre, tertiary children’s hospital neonatal intensive care unit. The study included all infants <3 kg receiving Microcuff® cuffed endotracheal tubes over the period January 2015 to January 2016. Controls were all infants 2000–2999 g receiving an uncuffed endotracheal tube over the period September 2015 to January 2016.
Results: Twenty-three patients < 3 kg were intubated with cuffed endotracheal tubes. All were inserted in the operating room. Of 23 patients, 14 (60.9%) patients had the cuff inflated in the operating room and none subsequently in the neonatal intensive care unit. The group receiving cuffed endotracheal tubes was compared with 23 patients with uncuffed endotracheal tubes. There was no difference in weight (median 2620 g vs 2590 g, diff in median = 10, 95% CI: 120, 130) or duration of intubation (median 27 vs 44 hours, diff in median = 17, 95% CI: –5, 46).
However, there was a significant difference in gestational age (median 37 vs 35 weeks, diff in median = –1, 95% CI: –2, 0) and age at intubation (median 6 vs 0 days, diff in median = 4, 95% CI: 10, –1). There were no significant differences in the rates of change of endotracheal tube to find correct size (0/23 vs 4/23, P = .109; OR = 0.13, 95% CI: 0.01, 1.41); median ventilator leak reading (0% IQR 0%–12% vs 0% IQR 0%–5.5%, P = .201, diff in median = 0, 95% CI: –5.5, 0); unplanned extubations (0/23 vs 2/23, p = 0.2; atelectasis 4/23 vs 0/23; endotracheal tube blockage 0/23 vs 0/23; pneumonia 0/23 vs 0/23) or postextubation stridor (1/23 vs 2/23).
Conclusion: This retrospective study with a small sample size found that Microcuff® cuffed endotracheal tubes may be safe in neonates < 3 kg. Well-designed randomized controlled trials are needed to address this issue definitively.

KEYWORDS
airway management, anesthesia, devices, endotracheal, infant, intensive care, intratracheal, intubation, medical, newborn
1 | INTRODUCTION

Traditional teaching has been that cuffed endotracheal tubes (ETTs) should not be used in children under 8-10 years of age because of the fear that they are associated with mucosal injury leading to subglottic stenosis. However, since the late 1990s, with the advent of the newer polyvinyl chloride (PVC) high-volume low-pressure (HVLP) cuffed ETTs, and ultimately the introduction of the ultrathin polyurethane Microcuff Pediatric Tracheal Tube in 2004, there has been an increase in the use of cuffed ETTs in infants and children ≥ 3 kg, particularly during anesthesia and for ventilation in pediatric intensive care units (PICUs). The smallest Microcuff ETT has an internal diameter of 2.0 mm and the manufacturer recommends its use in term infants ≥ 3 kg. All studies using cuffed ETTs in infants reported in the literature thus far only include infants ≥ 3 kg. Our group recently surveyed all of the neonatal intensive care units (NICUs) and PICUs in Australia and New Zealand on their use of cuffed ETTs in neonates and small infants. We found that 7/7 (100%) of PICUs and 4/9 (44.4%) NICUs who use cuffed ETTs were “sometimes” or “rarely” using cuffed ETTs in infants < 3 kg.

Though uncuffed ETTs remain the predominant device used for artificial ventilation in our NICU, Microcuff cuffed ETTs have become more commonly used by anesthetists in surgical infants ≥ 3 kg over the last 5 years. Of late, we noted an increasing number of infants < 3 kg returning from the operating room with a Microcuff cuffed ETT in place. We, therefore, conducted a study to compare the use of Microcuff cuffed ETTs and uncuffed ETTs in infants 2-3 kg in our NICU.

2 | MATERIALS AND METHODS

We undertook a retrospective cohort study comparing the use of cuffed vs uncuffed ETTs in infants of 2-3 kg in weight at the time of intubation. The study took place in the NICU of Princess Margaret Hospital for Children, the sole tertiary children’s hospital in Perth, Western Australia.

The subjects included were all infants < 3 kg intubated with a cuffed ETT over the period January 2015 to January 2016. These were compared with the same number of controls who were all infants of 2000-2999 g, intubated with uncuffed ETTs from September 2015 to January 2016. Our aims were to present our experience in the use of cuffed ETTs in the described group and compare with the use of uncuffed ETTs with regard to the demographics and outcomes of weight at intubation, gestational age at intubation, age at intubation, hours ventilated, change of ETT to find correct size, median ventilator leak reading, highest ventilator leak reading, unplanned extubations, episodes of asystole, ETT blockage, pneumonia, postextubation stridor, postextubation desmethyl cocaine, postextubation adrenaline, postextubation supplemental oxygen or CPAP, and re-intubation for stridor.

Patients intubated with cuffed ETTs received a 3.0-mm Microcuff Tracheal Tube. Patients with an uncuffed ETT received a
exact test using $2 \times 2$ tables was used to compare the categorical outcomes. Differences in medians along with the 95% confidence intervals were calculated where appropriate. Odds ratios and confidence intervals were calculated for categorical variables. For all analyses, a $P$-value of $<0.05$ was considered statistically significant. Multivariable analysis was not attempted given the small sample size.

3 | RESULTS

3.1 | Subjects who received cuffed ETTs

Twenty-three patients < 3 kg received a cuffed ETT during the study period. All of the infants were intubated for surgical procedures by anesthesiologists in the operating room and all received a 3.0 mm MicrOTrac® ETT. Of 23 patients, the route of intubation was oral in 14 (60.9%) and nasal in 9 (39.1%) patients.

On initial insertion of the ETT, 19/23 (82.6%) patients passed the "leak test" and in the remaining 4 (17.4%) patients, this was not documented. Of 23 patients, 14 (60.9%) patients had a cuff inflated in the operating room; for 2 (8.7%) patients, it was not documented; and 7 (30.4%) patients did not have the cuff inflated in the operating room. Of the 17 patients that had a cuff pressure recorded, the median was 15 cm H2O (range 0–20 cm H2O). None of the patients had their cuff inflated in NICU. Of 23 patients, 6 (26.1%) patients should have had their cuff inflated in NICU if intubation protocol had been followed as they had a sustained leak of >20% at times. It is important to note that leak was very variable in most patients. The patients who had leaks of >20% also had leaks of 0% at times.

On X-ray, the ETT position was correct in 16 (69.6%) patients, long (close to the carina) in 4 (17.4%) patients, short in 2 (8.7%) patients, and 1 patient had not taken X-ray. In 4/23 (17.4%) patients, there was radiological evidence of atelectasis on chest radiography done subsequently to the initial one taken for ETT placement. Of note, one of these patients had a large ETT leak and did not have the ETT cuff inflated as per intubation protocol. There were no episodes of ETT obstruction or pneumothorax.

Of 23 (8.7%) patients, two received pre-intubation steroids as prophylaxis for the length of time they had been intubated (0 and 17 days, respectively). One (4.3%) of 23 patient had post- intubation stridor which settled over a couple of hours after a single dose of dexamethasone and did not require re-intubation. Adrenaline, supplemental oxygen, noninvasive ventilation, or re-intubation. This patient had been intubated for 45 hours, had passed the "leak test" upon ETT insertion, had a leak of >50% for 80% of his intubated time, and had never required the cuff to be inflated. One other patient was re-intubated 6 hours post-intubation for respiratory distress due to de-recruitment of the lungs.

3.2 | Controls who received uncuffed ETTs

Of the 23 control patients who received uncuffed ETTs, only three (13.0%) were intubated by anesthetists and the remaining 20 (87.0%) patients were intubated by neonatologists for the following medical reasons: 12/23 (82.2%) respiratory disease; 7/23 (30.4%) neurological disease; and 1/23 (4.3%) cardiovascular collapse.

Of 23 patients, 10 (43.5%) patients were initially intubated with a 3.0 mm uncuffed ETT, but 3 (30%) of these patients required reintubation with a 3.5 mm uncuffed ETT for a large leak interfering with ventilation. Remaining 13 (56.5%) patients were initially intubated with a 3.5 mm ETT. One of these patients was re-intubated with a 3.0 mm in the operating room following suture by an ENT specialist. So finally, 8/23 (34.8%) had a 3.0 mm ETT and 15/23 (65.2%) had a 3.5 mm ETT. The route of intubation was oral for 22/23 (95.7%) and nasal for 1/23 (4.3%) patients.

3.3 | Cuffed vs uncuffed ETTs (Tables 1 and 2)

When comparing the demographics of the 23 patients who received cuffed ETTs with the 23 control patients who received uncuffed ETTs, there was no significant difference in weight at intubation or the number of hours ventilated, but there was a significant difference in age at intubation median and gestational age at intubation (Table 1).

When comparing the outcomes of those who received cuffed vs uncuffed ETTs, there was no statistical difference in number requiring a change of ETT to find correct size; the median ventilator leak reading; the highest ventilator leak reading number of unplanned extubations; number of episodes of atelectasis; rate of ETT blockage; episodes of pneumothorax; use of pre-intubation steroids; rate of post-intubation stridor; requirement for post-intubation dexamethasone; rate of post-intubation pneumonia; and need for post-intubation supplemental oxygen, CPAP, or reintubation for stridor (Table 2).

4 | DISCUSSION

For many years, it has been believed that an uncuffed ETT which fits snugly through the cricoid leaving some space to allow an air leak at a peak inspiratory pressure (PIP) of 20–25 cm H2O should provide a sufficient seal making a cuff unnecessary.14 However, an uncuffed ETT must be precisely the right size for the individual infant to fulfill both requirements of leak and seal.15 There are high ETT exchange15,16 and leak14–16 rates when using uncuffed ETTs. Recent anatomical studies of the airway in infants and children have shown that the cricoid is not circular as traditionally taught, but an elliptical structure with the transverse dimension being narrower than the anteroposterior dimension.17–19 The cricoid being elliptical means that when an uncuffed tube is inserted into the noncircular lumen of the cricoid to give a reasonable seal, the pressure exerted on the lateral walls of the cricoid are unknown and could be considerable.20 When using a cuffed ETT, a smaller diameter tube (0.5 mm less than uncuffed ETT) is selected which does not wedge within the delicate cricoid but rather the cuff makes its seal in the trachea where there are U-shaped cartilages and a muscular dorsal wall
### TABLE 1 Demographics of patients who received cuffed ETT vs uncuffed endotracheal tube (ETT)

<table>
<thead>
<tr>
<th></th>
<th>Cuffed (n = 23)</th>
<th>Uncuffed (n = 23)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight at intubation (g)</td>
<td>2420 ± IQR 2300-2690; R: 2060-2850</td>
<td>2990 ± IQR 2450-2770; R: 2200-2940</td>
<td>Diff in median = 10 95% CI (-120 to 130)</td>
</tr>
<tr>
<td>Gestational age at intubation (wk)</td>
<td>IQR 35-37; R: 33-39</td>
<td>IQR 35-37; R: 32-39</td>
<td>Diff in median = 1 95% CI (-2 to 0)</td>
</tr>
<tr>
<td>Age at intubation (d)</td>
<td>10± IQR 1-16; R: 0-97</td>
<td>6± IQR 0-2; R: 0-51</td>
<td>Diff in median = -4 95% CI (-15 to 6)</td>
</tr>
<tr>
<td>Hours ventilated (h)</td>
<td>27± IQR 11-52; R: 3-414</td>
<td>44± IQR 26-107; R: 3-217</td>
<td>Diff in median = 17 95% CI (-5 to 46)</td>
</tr>
</tbody>
</table>

### TABLE 2 Outcomes of patients who received cuffed vs uncuffed endotracheal tube (ETT)

<table>
<thead>
<tr>
<th></th>
<th>Cuffed (n = 23)</th>
<th>Uncuffed (n = 23)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change of ETT to find correct size (%)</td>
<td>0/23 (0)</td>
<td>4/23 (17.4)</td>
<td>P = 0.196 95% CI 0.011, 1.44</td>
</tr>
<tr>
<td>Median ventilator leak reading</td>
<td>0% IQR 0%-15%; R: 0-22%</td>
<td>0% IQR 0%-5.5%; R: 0-6%</td>
<td>P = 0.01 95% CI (-5.5, 0)</td>
</tr>
<tr>
<td>Highest ventilator leak reading</td>
<td>2.1% IQR 17-30%; R: 0-60%</td>
<td>1.7% IQR 11-29%; R: 0-40%</td>
<td>P = 0.270 95% CI (-15.4, 4)</td>
</tr>
<tr>
<td>Unplanned extubation (%)</td>
<td>0/23 (0)</td>
<td>2/23 (8.7)</td>
<td>P = 0.189 95% CI 0.033, 8.02</td>
</tr>
<tr>
<td>Episode atelectasis (%)</td>
<td>4/23 (17.4)</td>
<td>0/23 (0)</td>
<td>P = 0.196 95% CI 0.011, 1.44</td>
</tr>
<tr>
<td>ETT blockage (%)</td>
<td>0/23 (0)</td>
<td>0/23 (0)</td>
<td>P = 0.196 95% CI 0.011, 1.44</td>
</tr>
<tr>
<td>Pneumonia (%)</td>
<td>0/23 (0)</td>
<td>0/23 (0)</td>
<td>P = 0.196 95% CI 0.011, 1.44</td>
</tr>
<tr>
<td>Post-extubation steroids (%)</td>
<td>2/23 (8.7)</td>
<td>1/23 (4.3)</td>
<td>P = 1 95% CI (-0.22, 2.61)</td>
</tr>
<tr>
<td>Post-extubation steroid (%)</td>
<td>1/23 (4.3)</td>
<td>2/23 (8.7)</td>
<td>P = 1 95% CI 0.02, 2.61</td>
</tr>
<tr>
<td>Post-extubation dexamethasone (%)</td>
<td>1/23 (4.3)</td>
<td>1/23 (4.3)</td>
<td>P = 1 95% CI 0.02, 2.61</td>
</tr>
<tr>
<td>Post-extubation adrenergics (%)</td>
<td>0/23 (0)</td>
<td>0/23 (0)</td>
<td>P = 0.196 95% CI 0.011, 1.44</td>
</tr>
<tr>
<td>Post-extubation supplemental O2 or CPAP for steroid (%)</td>
<td>0/23 (0)</td>
<td>0/23 (0)</td>
<td>P = 0.196 95% CI 0.011, 1.44</td>
</tr>
<tr>
<td>Re-intubation for steroid (%)</td>
<td>0/23 (0)</td>
<td>0/23 (0)</td>
<td>P = 0.196 95% CI 0.011, 1.44</td>
</tr>
</tbody>
</table>

N/A, not applicable.

which allow for some distention. This is in contrast with the rigid orfoid ring where the uncuffed ETT makes its seal.15 Cuffed ETTS offer the advantages of less re-intubations to find the correct ETT size,23,24 and less use of anesthetic and other gases.25 They also potentially offer a lower rate of leak around the ETT, thereby improving ventilation. In addition, a smaller ETT has the potential to result in less alveolar damage and the seal from the cuff could decrease ventilator-associated pneumonia. Fernandes et al reported upon the only RCT to date comparing cuffed vs uncuffed ETTS for longer term ventilation of children under the age of 8 in the PICU. They compared 136 children intubated with cuffed and 118 intubated with uncuffed ETTS for the outcomes of post-extubation laryngitis (defined as “Downes and Radley score > 6”) and foted intubation. The incidence of post-extubation laryngitis was 58.8% in
the cuffed group vs 42.7% in the uncuffed group (P = .02). Extubation failure occurred in 8.8% of children in cuffed group vs 9.2% in the uncuffed group (P = .89).

However, concerns have been raised of potential disadvantages when using a cuffed ET tube because a smaller internal diameter can result in increased resistance within the ET tube, making spontaneous ventilation during weaning more difficult. Small diameter ET tubes could also result in increased episodes of ET tube obstruction and difficulties with suctioning.32-34 There also remains the concern that cuffs may cause damage to the airway leading to subglottic stenosis. Studies in infants and children have shown no difference in postextubation stridor19,21,22 though these studies did not follow up the patients in the longer term. The smallest Microcuff® ET tube made is 3.0 mm, which is recommended for infants ≥ 3 kg in weight and previous studies have only included infants ≥ 3 kg. However, from our own local experience and a survey of practice in Australia and New Zealand in 2015,11 we know that cuffed ET tubes are sometimes being used in infants < 3 kg in weight. Sathyamoy et al reported on 3 neonates with weights of < 3 kg who were intubated with Microcuff® ET tubes for surgical procedures and had significant postextubation stridor.46 However, none of the patients underwent a leak check or had cuff pressure monitoring. Sathyamoy et al went on to retrospectively review 324 intubated neonates over a 1-year period comparing uncuffed and cuffed (Microcuff®) ET tubes with regard to the occurrence of postextubation stridor. Twenty-nine patients received a cuffed ET tube in the OR and the other 295 patients received uncuffed ET tubes. However, they do not report on the weight or gestational age at the time of intubation, only birth weight and gestational age at birth. They reported an incidence of postextubation stridor in 17.2% of those receiving cuffed ET and 7.5% receiving uncuffed ET tube. After multivariate analysis, they report that the use of Microcuff® ET tube was associated with an increased odds of stridor (OR = 9.27; CI 1.88–45.67). However, they state that 26/29 patients with cuffed ET had a larger than recommended size and that cuff pressures were not checked.

In our study, when comparing the subjects and control groups, an important difference in demographics was the type of patients, with the entire cuffed ET group being surgical patients and the majority of the uncuffed ET group being medical patients, most commonly with respiratory disease. Medical patients, particularly those with respiratory disease, often have noncompliant lungs, requiring higher pressure ventilation, and are, therefore, more likely to display ventilator leaks.

In contrast, surgical patients often have relatively healthy compliant lungs requiring lower pressures and displaying lower ventilator leaks. However, ventilators in the operating room are probably less able to compensate for large leaks. Also, the dynamic situation created by the effect of surgery on ventilation means the ability to control leak via cuff inflation allows for more effective ventilation. It is for these reasons that anesthesiologists have developed a preference for cuffed ET tubes, while neonatologists of whom most are still unfamiliar with cuffed ET tubes prefer to continue using the traditional and familiar uncuffed ET tube. Since January 2015, many anesthesiologists in our institution have been using cuffed ET tubes even in neonates less than 3 kg, even though the manufacturers do not recommend them for this group. On the contrary, the preference of neonatologists remained to use uncuffed ET tubes. Given these differences in choices, we conducted this audit to review the outcomes of all 23 infants who received cuffed ET tubes and compared them to an equal number of infants who received uncuffed ET tubes.

Our study showed that when using cuffed ET tubes in surgical patients in this size population, the majority did not require cuff inflation as there was no substantial leak at any point. It could be said that these were effectively being used as uncuffed ET tubes. However, even in the Microcuff® ET tubes which claim to have fewer creases/ridges in the cuff area, there is still some ridging/crushing with cuff deflation. We leave the cuff pressure at 0 cmH₂O rather than emptying the cuff fully and causing negative pressure and potential ridges. In the few patients with higher leaks who should have had the cuff inflated if unit protocol had been followed, it could be said that the potential impact of cuff inflation was lost once in the NICU. This is an important limitation of our study, given the retrospective design. Interestingly, around a third of patients intubated with a 3.0-mm uncuffed ET required re-intubation with a larger 3.5-mm uncuffed ET due to a problematic leak which is a similar number to those with a cuffed ET tube who also had a sustained leak and required cuff inflation. It is useful to note that the outer diameter (OD) of 4.3 mm for the 3.0-mm Microcuff® and 4.2 mm for the 3.0-mm Portex® ET tube. As demonstrated by the 1 patient who initially had a 3.5-mm uncuffed ET tube that was replaced in the operating room by a 3.0-mm ET tube, some of the other patients with a 3.5-mm uncuffed ET tube could also have had an ET too big. This is supported by the fact that over half of the patients with an uncuffed 3.5-mm ET tube who had ventilator leak measurements recorded never had a leak measurement > 20% during their time ventilated on NCPAP. The variability of leak was striking in many patients and is likely due to changes in lung compliance, secretions, head position, and level of sedation.

When comparing the 2 groups for outcomes, although there were low numbers and not reaching statistical significance, the ET exchange rate was 0% for cuffed ET tubes and 17.5% for uncuffed ET tubes which replicates findings in previous studies comparing the 2 different ET tubes.7,14,46 There was the same trend for an increase in episodes of atelectasis in the cuffed ET tubes and only one of these cases could be explained by the large ventilator leak with the cuff having not been appropriately inflated. This could be because there were all postoperative surgical patients, which are the group that we more often see atelectasis than in the uncuffed group where only the minority were patients who were postoperative. The median duration of intubation was relatively brief (27 hours) in the cuffed ET group. Therefore, the safety of more prolonged intubation is difficult to determine. Recently, DeMicheli et al reported upon their experiences of using cuffed ET tubes in 394 infants ≤ 5 kg undergoing major cardiac surgery. The mean weight of the study infants was 3.6 kg (SD 0.6). Nearly 26% of the infants were preterm (< 37 weeks gestation) and < 3 kg. The average period of intubation was 7–9 days. They described that their practice was to remove all air from the cuff and then inflate the cuff until a minimal air leak was observed with a goal cuff pressure of 30–40 cmH₂O. If the infant could be
CONCLUSIONS

This retrospective study with a small sample size found that Microcuff® cuff ETTS may be safe in neonates < 3 kg. Well-designed RCTs are needed to address this issue definitively.

ETHICAL APPROVAL

The study was reviewed and approved by the hospital’s Quality Improvement Committee as having met the “Australian National Health and Medical Research Council requirements for quality assurance and audit projects.”

CONFLICT OF INTEREST

The authors report no conflict of interest.

ORCID

Rebecca E. Thomas https://orcid.org/0000-0002-7838-015X

REFERENCES


How to cite this article: Thomas RE, Rao S, Minuffolo C, Hulsett B, Bullara MK. Cuffed endotracheal tubes in infants less than 3 kg: A retrospective cohort study. Pediatr Anesth. 2016;26:204-209. https://doi.org/10.1111/pam.13311
Using cuffed tracheal tubes below recommended body weight: Compromising safety or exploring limits safely?

Endotracheal intubation is a very common procedure in children undergoing general anesthesia, with the available equipment having improved dramatically over the past decade. Cuffed endotracheal tubes, especially the Microsoft® PET, have become popular and have been demonstrated to be safe if the correct size is selected, a minimal body weight of >3 kg is adhered to, and cuff inflation pressure recommendations are followed.2 Cuffed endotracheal tubes (ETT) have largely replaced uncuffed ETT in pediatric anesthesia due to several advantages, including reliable airway patency and capnography and a reduction in tube exchanges.3 They are also trusted to provide an almost 100% seal of the airway and allow effective ventilation.2

Historically, cuffed pediatric ETT are selected 0.5-1.0 mm smaller than their age-related uncuffed ETT due to the bulky cuff, which is otherwise too large for the subglottic region and trachea. Following the introduction of cuffed ETT with smaller, thin-walled cuff membranes, a reduced diameter is still chosen in order to compensate for the considerable variability in airway diameters. This further increases the probability of the ETT easily fitting into the pediatric larynx on the first attempt, thus avoiding excessive pressure on the fragile laryngeal structures. These cuffed ETT partially seal the airway with a high-volume, low-pressure cuff within the trachea, providing a tracheal instead of a cricoid seal.

Currently, uncuffed ETT with an internal diameter (ID) of 3.5 mm or a Microsoft® PET size of 3.0 mm ID are inserted into the airway of a full-term neonate weighing 3 kg or more.3 Controlled prospective clinical studies investigating the fit and seal of cuffed ETT in children have been performed, starting from full-term neonates with a body weight of 3 kg or greater.4–5 Uncuffed ETT continue to be used primarily in neonates and infants weighing <3 kg, and uncuffed ETT size ID 3.0 mm are recommended for children weighing from 1500 to 1800 g.

Reliable data on the safe use of the Microsoft® PET or other cuffed ETT are lacking in this weight bracket. The marketed Teleflex Raush® SuperSafety™ Magill 2.5 mm ID cuffed ETT has an outer diameter (OD) similar to the Teleflex Raush® Safety Clear™ 3.0 mm ID uncuffed ETT and is, therefore, not an alternative option.4 Smaller sized ETT are currently also more prone to kinking, tracheal suction difficulties, obstruction and are increasing the work of breathing.

Despite the lack of published clinical evidence, Microsoft® PET tubes of 3.0 mm ID and other cuffed ETT are increasingly used in patients weighing <3 kg in pediatric anesthesia practice. The paper presented by Rebecca Thomas and co-authors in the current issue of Pediatric Anesthesia addresses and carefully discusses this trend.5 A small cohort of neonates weighing between 2 and 3 kg, who underwent general anesthesia for surgical reasons, had Microsoft® PET tubes of 3.0 mm ID inserted into their trachea by the attending anesthesiologist in the operating room and were postoperatively ventilated in the neonatal unit. Relevant clinical outcomes were compared to a similar number of medical neonatal intensive care admissions in whom the trachea was intubated with an uncuffed ETT chosen by the attending neonotologist. No significant differences in clinical outcomes were reported, although the low incidence of post-

The primary use of Microsoft® PET 3.0 mm ID in children below the weight of 3 kg will increase the number of occasions without an air leak. For neonates with a body weight ≥30 kg, there is a reported approximate 3% chance that an exchange to a 3.0 mm ID uncuffed ETT is required. The fact that in the presented study 7/23, and probably further 2/23, patients did not require a cuff inflation by the anesthesiologist indicates a cervical sealing by the Microsoft® PET 3.0 mm ID. Further cuff inflation in this situation makes no sense and may result in unnecessary morbidity requiring extreme clinical vigilance. One-third of children in the current study had a “problematic” air leak for ventilation and required an uncuffed ETT exchange to the next larger 3.5 mm ID uncuffed ETT. Alternatively, in this situation a 3.0 mm ID Microsoft® PET may be considered. The latter solution is commonly used in the departments of the 2 authors of this editorial. Microsoft® PET are considerably more expensive than uncuffed ETT. In this patient group, replacing an uncuffed ETT with a Microsoft® PET 3.0 mm ID due to an air leak is certainly more economical than exchanging primarily used too large Microsoft® PET for an uncuffed ETT or even giving in to the temptation to accept an unsatisfactory situation.

The Microsoft® PET 3.0 mm ID with its depth markings was designed for safe positioning above the carina and to guarantee a cuff-free subglotic zone in a full-term neonate ≥3 kg.7 When using a Microsoft® PET 3.0 mm ID with a depth mark of 24 mm (or, in the neonates, of 27 mm), the tube tip will inevitably be placed further into the trachea in smaller neonates than an uncuffed 3.0 ETT with a 20 mm distance mark. On the other hand, if the tube is withdrawn according to fiber-optic confirmation or postoperative X-ray, the cuff or noninflated cuff folds/cuff shoulder will be positioned within the laryngeal structures.8 This is even more important if uncuffed ETT other than the Microsoft® PET 3.0 mm ID are used.9 Similarly, it is critical to recognize that there is great variability in outer diameters between different makes of uncuffed ETT 3.0 mm ID and even between cuffed and uncuffed ETT versions from the same
manufactured. These small but important differences, if unnoticed, will result in severe adverse outcomes.4,5

A number of important precautions for the use of the Microcuff® PET 3.0 mm ID in children <3 kg are also elegantly addressed.3 The reported protocol included an air leak at an inflation pressure of 20 cm H₂O and passive deflation of the cuff. The latter is an alternative to forcefully removing all air and creating artificial cuff folds, potentially injuring the tracheal mucosa.6 Regular, 4-hourly monitoring of the cuff pressures, ensuring a pressure of <15 cm H₂O was mandated for continuing use of cuffed ETT. This is especially important in the context of studied patient cohort, where the tracheas of neonates were intubated for a median of 27 hours. Cuffed ETT are not universally accepted in neonates for a number of reasons discussed in this paper. It remains a mystery why some neonatal units require an air leak with cuffed ETT but readily accept an uncuffed ETT without an air leak.

Until we have better clinical and endoscopic evidence on the safety of current cuffed ETT in children weighing <3 kg, greatest care must be taken when using cuffed ETT in these patients. It is essential to recognize that an air leak must first be problematic before a Microcuff® PET can be justified in these patients. Casual use may risk a bad reputation for cuffed ETT in pediatric anesthesia and potentially going “full circle” to the old problem of using oversized ETT in children. Cuffed ETT in children have been recognized as safe and reliable over the past decade. It is, however, necessary to carefully explore their limits to maintain this trust.

CONFLICT OF INTEREST

Prof. Markus Weis was involved in the design of the Microcuff PET in 2003/2004. The Department of Anesthesiology, University Children’s Hospital Zürich received one single research grant from Microcuff GmbH, Wieslochem, Germany in 2005, to perform clinical testing of the Microcuff PET. No other payments or gifts were received. Prof. Thomas Engelhardt is an Associate Editor of Pediatric Anesthesia.

ORCID

Markus Weis (http://orcid.org/0000-0002-5822-9591)
Thomas Engelhardt (http://orcid.org/0000-0002-3954-5820)

REFERENCES