Epidural and spinal analgesia

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KEY LEARNING POINTS

- Neuraxial techniques are safe and provide better postoperative pain relief than parenteral opioids after a wide range of surgical interventions and across different patient populations.
- Co-administration of neuraxial local anesthetic agents and opioids enhances the quality of analgesia. New local anesthetic agents with improved safety profile and short-acting, highly potent opioids have been developed and licensed for neuraxial use.
- Different adjuvant drugs may have additional benefits in terms of analgesia and pharmacokinetic interaction with neuraxial local anesthetics and opioids.
- Specific indications exist for patient-controlled epidural analgesia, combined spinal-epidural analgesia and continuous spinal analgesia.
- In patients having neuraxial blockades, regular monitoring of analgesic efficacy and potential side effects is indispensable.
- Neuraxial analgesia appears to improve morbidity in specific settings, while its impact on mortality is not clear.
- Neuraxial techniques are associated with a high degree of patient satisfaction and procedure-related quality of life.

INTRODUCTION

Neuraxial analgesic techniques were first described in the late nineteenth and early twentieth century. The German surgeon August Bier reported the first intrathecal anesthesia in 1898,¹ while the first lumbar epidural probably dates back to 1921.² However, the safety and efficacy of neuraxial anesthesia and analgesia were only established in the 1970s.³

Over the following decades, significant progress was made in both surgical and anesthetic domains, enabling

more and more complex procedures to be carried out in more and more fragile populations. In this context, neuraxial techniques cannot only produce reliable and flexible analgesia, but they also have been advocated as a method of attenuating detrimental physiologic responses in the perioperative period and improving postoperative outcome. This chapter presents a summary of the recent evidence about epidural and spinal analgesia, evolving indications in specific settings, and the impact of neuraxial techniques on different outcome variables.

NEURAXIAL ANALGESIA: INDICATIONS AND CONTRAINDICATIONS

There are no formal indications, but rather clinical situations where patient preference and physiology make a neuraxial block the technique of choice. Thoracic and abdominal, inguinal, urogenital, rectal, and lower extremity surgery, including ambulatory surgical procedures, are suited for neuraxial anesthesia and analgesia. While epidural techniques are indicated for major surgery where lasting postoperative analgesia is required, spinal techniques produce rapid anesthesia and analgesia for up to 24 hours and have advantages in ambulatory surgery.

Contraindications to neuraxial blockade are patient refusal, clotting defects, sepsis, poor or limited cardiac function, and severe hypovolemia. Relative contraindications are immunocompromise, preexisting neurologic deficits, or spinal deformities. That preexisting central nervous system (CNS) disorders should not be regarded as an absolute contraindication to neuraxial blockade has been confirmed recently, when a survey found no increased frequency of complications.⁴ In contrast, clinicians should be aware that neuraxial blockade in patients with preexisting peripheral sensorimotor neuropathy or diabetic polyneuropathy may lead to worsening of neurologic function postoperatively; the incidence of such severe deterioration in a case series was 0.4 percent (95 percent confidence interval (CI), 0.1–1.3 percent).⁵

Regardless of formal indications or contraindications, the decision to perform a neuraxial block must be an individual one. Detailed physiological and pharmacological knowledge, as well as patient-informed consent prior to, meticulous technique during, and continuous follow up after performance of a neuraxial block are prerequisites for successful neuraxial analgesia.

MECHANISMS OF NEURAXIAL ANALGESIA

The precise sites of action and mechanisms of specific neuraxial drug effects are not known, but analgesia is likely to be mediated via extradural (radicular), subdural (spinal), and peripheral structures.⁶ Pharmacokinetic studies have shown that an epidurally administered drug diffuses down its concentration gradient into the epidural fat, where it acts at the spinal nerves that traverse the epidural space. In addition, the drug diffuses through the spinal meninges, into the cerebrospinal fluid (CSF) and into the white matter of the spinal cord dorsal horn where its central effects are mediated. Spinal analgesics are given directly into the CSF and correspondingly traverse fewer structures. Finally, neuraxial drugs reach the plasma compartment via venous uptake.⁷

Neuraxially administered local anesthetic (LA) agents penetrate nerve axonal membranes and bind to sodium

channels, thus reducing postsynaptic depolarization and nerve stimulus propagation. The effect is nonselective, involving both autonomic and somatic nerve fibers. In addition to sodium channels, multiple neurotransmitters are involved in nociceptive transmission in the dorsal horn of the spinal cord, such as tachykinins (for example, substance P), somatostatin, acetylcholine, γ -aminobutyric acid and *N*-methyl-D-aspartate (NMDA). Neuraxial administration of LA seems to decrease nociception by interference with these transmitters.

Clinically, a differential pattern of sensory and motor block can often be discerned with LA. Thinner C-fibers that convey pain and autonomic impulses are blocked first, followed by the preganglionic sympathetic B-fibers and finally the large A-fibers that transmit touch, pressure, and motor information.

The effects of neuraxial opioids are complex and are mediated by both peripheral and central mechanisms.^{3,8} At a spinal level, they bind to nonspecific presynaptic afferents to inhibit release of substance P. They also bind to specific μ (μ), κ (κ), and δ (δ) receptors in the substantia gelatinosa of the dorsal horn where they decrease transmission of nociceptive inputs by hyperpolarization of postsynaptic neurones and inhibition of various neurotransmitter releases. After cephalad transport via the CSF, opioids exert an analgesic action on central μ , κ , and δ receptors. After intravascular absorption, opioids have systemic antinociceptive effects on peripheral μ receptors.

DRUGS USED FOR NEURAXIAL ANALGESIA

Local anesthetic agents

Almost every LA agent can be administered neuraxially. The first LA drugs to be used on a larger scale in the 1980s were of the ester type, such as procaine and tetracaine. These were then replaced by amino-amides (for example, lidocaine, bupivacaine) with an improved safety profile. When it was found that bupivacaine was associated with cardiac arrest and life-threatening arrhythmias, levobupivacaine and ropivacaine were introduced. These are *S*-enantiomers with similar anesthetic efficacy and reduced toxicity when compared to the racemic mixture.⁹ While levobupivacaine is less cardiotoxic, ropivacaine also appears to cause less motor blockade. A meta-analysis of neuraxial ropivacaine in obstetric analgesia suggests clinical advantages, notably a differential block with improved motor function,¹⁰ but the clinical relevance of this aspect continues to be debated.

Overall, neuraxial LA alone have never become widely used because of significant block failure and early regression of sensory block with lower doses and because of the unacceptable incidence of motor block and hypotension with larger doses.

Side effects of neuraxial local anesthetics

Serious complications can result from systemic absorption or inadvertent intravascular injection of LA in large doses, such as CNS toxicity (alterations of consciousness, seizures) or cardiovascular toxicity (arrhythmias, conduction abnormalities). These side effects will not be detailed further as this review is centered on complications resulting specifically from neuraxial administration of LA.

A review by Hodgson *et al.*¹¹ about the neurotoxicity of drugs given intrathecally found that all LA have the potential to be directly neurotoxic.¹¹ In usual concentrations, lidocaine and tetracaine seem to be more neurotoxic than bupivacaine. In animal experiments, neurotoxicity with lasting histopathologic and electrophysiologic changes and neurologic deficits occurred only when LA were given in high doses and concentrations within a restricted area.^{12,13} The exact mechanism of nerve injury induced by neuraxial LA remains undetermined, but may be related to electrolytic imbalances at the neuronal membrane. Despite these preclinical concerns, extensive epidural and spinal use of LA agents has attested to their relative safety in clinical doses.¹⁴

Another more recent concern with intrathecal LA in clinical doses are transient neurologic symptoms (TNS). Various types of paresthesias, as well as unilateral or bilateral pain in the lower extremity pain, were first reported in 1993 after the intrathecal use of 5 percent hyperbaric lidocaine.¹⁵ Subsequent case series revealed an incidence of TNS between 4 and over 30 percent, depending on the type and concentration of LA, type of surgery, and patient position.^{16,17,18} Average onset of TNS was 12 to 24 hours after surgery with a duration between six hours to four days and largely spontaneous resolution.¹⁹ Proposed mechanism of TNS are disruption of the blood–nerve barrier by highly concentrated LA, decreased neural blood flow, and irritation of nerve cell membranes.²⁰ It is most likely not a manifestation of direct neurotoxicity, as neurological deficits are not part of the syndrome and all symptoms are fully reversible. In any patient presenting with neurologic symptoms, the exclusion of more sinister causes, such as nerve compression or infection, is mandatory.

Another concern, especially with spinal LA, are cardiovascular side effects. Blockade of sympathetic vasomotor fibers leads to a significant fall in peripheral vascular resistance by both arterial and venous dilation. If the block level is higher than T5, cardiac sympathetic outflow is affected, so that marked hypotension and bradycardia can occur. While hypotension is seen in over one-third of patients after spinal anesthesia, probably due to the sudden decrease in peripheral vascular resistance, the incidence is only between 0.7 and 6 percent with epidural LA.²¹

Motor blockade is the rule after intrathecal LA, but occurs rarely when low concentrations of local anesthetics

are used to provide epidural analgesia. Patients under epidural analgesia with significant motor impairment should be followed up carefully, as this might be a symptom of beginning spinal cord compression.

Opioids

Neuraxial opioids produce intense analgesia without significant motor impairment. Morphine, fentanyl, and sufentanil are the most commonly used epidural and intrathecal opioids, and there is extensive clinical evidence attesting to their efficacy.

Hydrophilic opioids, such as morphine, penetrate neural tissue slowly, resulting in slower onset, delayed elimination and a longer duration of action. Furthermore, hydrophilic opioids have a widespread CSF distribution with the potential of significant cephalad migration.²² Its prolonged analgesia (up to 24 hours) makes morphine suitable for single epidural or intrathecal bolus administration. However, respiratory depression limits the usefulness of intrathecal morphine doses over 300 µg and requires prolonged monitoring and some vigilance. Newer pharmacologic formulations of morphine were recently introduced into clinical practice, for example liposome-encapsulated morphine, which provides up to 48 hours of pain relief after total hip replacement surgery, but sedation and respiratory depression occurred frequently (4 percent of patients requiring naloxone) and requires careful monitoring and assessment for at least 48 hours.²³[II], ²⁴[III]

As opposed to the preferential CSF distribution of hydrophilic opioids, lipophilic opioids tend to diffuse into perineural fat and are then released back into the epidural space. While fentanyl is the neuraxial opioid most often employed in Australia and in the USA, the fentanyl analog sufentanil is extensively used in Europe. Sufentanil is a µ receptor selective, highly lipophilic synthetic opioid five to ten times more potent than fentanyl.²⁵ Because of their good bioavailability at the spinal cord, fentanyl and sufentanil have a rapid onset of action. Analgesia tends to be segmentally restricted because of rapid uptake by neural and fatty tissue. The limited duration of lipophilic opioids aids in recovery after short procedures.

Side effects of neuraxial opioids

In contrast to LA, even in large doses neuraxial opioids do not seem to be neurotoxic,²⁶ and motor impairment is not an issue. However, opioids have several class-specific side effects, as well as complications specifically related to their epidural and spinal use.

The incidence of pruritus with intrathecal opioids varies from 30 to 100 percent and is higher than with epidural administration.²⁷[II] While the exact mechanism

remains unclear, opioid-induced pruritus is probably not histamine-related, but rather due to activation of spinal μ receptors.²⁸ Reviews comparing the side effects of intravenous and epidural opioids concluded that epidural administration was associated with slightly more pruritus (16 versus 14 percent).^{29, 30}[I]

The treatment of opioid-related pruritus is difficult. 5-HT₃ antagonists should be the first choice (for example ondansetron 0.1 mg/kg i.v.).²⁸[V] Propofol has some efficacy (10 mg i.v., followed by a small continuous infusion), as well as opioid antagonists (for example, naloxone 1–2 μ g/kg i.v. per hour, naltrexone 6–9 mg p.o.) or low doses of an agonist/antagonist (for example, nalbuphine 4 mg i.v.). There is no evidence in favor of the traditionally administered antihistamines.

Although intrathecal opioids distribute rapidly within the CSF and about 10 percent of the dose can reach the cisterna magna within 30 minutes after lumbar injection,³¹ the overall incidence of respiratory depression with intrathecal opioids is less than 1 percent.⁷[V] Respiratory depression after epidural injection is reported in 0.24–1.6 percent of patients.²¹[V] As lipophilic opioids are highly potent with a rapid onset of action, they tend to cause early respiratory depression. In contrast, delayed respiratory depression is a concern with neuraxial morphine because of its high affinity to CSF with significant risk of late cephalad spread.

Urinary retention of up to 12 hours after neuraxial anesthesia is common; after epidural analgesia, urinary retention occurs in almost one-third of patients, compared to 15 percent with intramuscular opioids and 13 percent with intravenous patient-controlled opioids.³⁰[I] These figures may seem prohibitive. However, only patients after large surgical procedures are likely to require postoperative epidural analgesia, and urinary catheters are routinely inserted in these patients.

Nausea and vomiting are very distressing side effects of opioids and are probably mediated by direct stimulation of the chemoreceptor trigger zone. However, nausea and vomiting do not seem to be specifically related to neuraxial administration. In a recent review, the incidence was approximately 25 percent and was unaffected by route of administration (intravenous, intramuscular, or epidural).³⁰[I] Treatment of nausea and vomiting after neuraxial opioids follows the same principles as other types of opioid-induced nausea and vomiting.³²[V] It involves 5-HT₃ antagonists, such as ondansetron (4–8 mg i.v.), dopamine (D₂), antagonists, such as droperidol (0.625–1.25 mg i.v.), and corticosteroids, such as dexamethasone (5–10 mg i.v.).

Another common side effect of opioids is sedation. While 4.6–6.4 percent of patients on intravenous patient-controlled analgesia (PCA) complained of excessive sedation, the incidence was only 0.9–1.4 percent with epidural opioids.³⁰[I] Administration of the smallest possible doses of neuraxial opioids, close clinical

monitoring, as well as avoidance of additional intravenous sedatives are useful preventive measures.

Combination of local anesthetics and opioids

Various mixtures of neuraxial LA and opioids have been studied or are commonly used for both epidural and spinal analgesia; some are even commercially available in some countries. Compared with either component alone, such a combination achieves better analgesia with lower doses of each component.²¹ This particularly reduces the hypotension and motor block seen with LA. However, one should always bear in mind that co-administration of LA agents and opioids not only combines the advantages, but also the potential side effects of each drug.

Systematic dose-finding studies with regard to optimal concentrations and combinations of LA-opioid mixtures have not been undertaken. Clinically, in terms of pain relief and side effects, differences between modern LA, such as levobupivacaine or ropivacaine, mixed with opioids, such as fentanyl or sufentanil, are probably minor. Typically, lipophilic opioids are chosen over hydrophilic ones for epidural administration in combination with local anesthetics. In contrast, hydrophilic opioids can have advantages in situations where catheter level and level of incision are incongruent. Probably the most often used epidural is combination bupivacaine 0.05–0.1 percent with 2–4 μ g/mL of fentanyl. As co-administration of LA and opioids is routine practice, premixed solutions are available in many centers.

Other neuraxial drugs and adjuvants

EPINEPHRINE (ADRENALINE)

Epinephrine is a mixed α - and β -adrenergic receptor agonist. Its principal effect of interest in neuraxial use is the intense vasoconstriction it provokes. This markedly slows the systemic absorption of neuraxial LA and opioids, so that the sensory block is longer and more intense.³³[II] Addition of neuraxial epinephrine decreases the doses of LA and opioids used.³⁴[II] Epinephrine can be an adjunct to intrathecal, as well as epidural, analgesics; intrathecal doses are between 100 and 300 μ g, and epidural doses are 0.5–3 μ g/mL. Theoretical concerns have been raised about the detrimental effects of epinephrine on spinal cord blood flow, but these have been refuted in clinical studies.^{35, 36}

Besides its vasoconstrictive effects, epinephrine may also have an analgesic effect of its own.³⁷ Indeed, several studies have shown that the addition of epinephrine to thoracic epidural analgesia (TEA) with fentanyl and bupivacaine improved analgesia.³⁸[II]

ALPHA-ADRENERGIC AGONISTS

Clonidine is an α_2 -receptor agonist that was introduced for epidural use in the 1980s. It inhibits pain transmission by binding to pre- and postsynaptic receptors of nociceptive afferents, particularly in the dorsal horn of the spinal cord.³⁹ While having sympatholytic (anti-hypertensive) and sedative properties, the fact that clonidine is devoid of side effects such as respiratory depression, pruritus, and urinary retention makes it a potentially useful adjunct to neuraxial LA and opioid analgesia.

Several studies indicate that small doses of epidural clonidine (5–20 μ g per hour) may improve analgesia, increase motor block, and reduce the dose of LA required, but the evidence is mostly weak and inconsistent.⁴⁰[II] Significant side effects, particularly hypotension and sedation, limit the use of clonidine in greater doses.

In 1998, Armand *et al.*⁴¹[I] undertook a meta-analysis to analyze the efficacy of extradural clonidine to relieve postoperative pain. The authors found that meta-analysis was impossible due to serious methodological flaws in existing trials and due to lack of consistent study designs enabling direct comparison. They concluded that despite the frequent use of epidural clonidine, doses and indications remained widely a matter of personal habits and that no sound data for or against the use of epidural clonidine existed.

Dexmedetomidine is a more selective α_2 -receptor agonist than clonidine. In a recent study, dexmedetomidine has been described as equipotent to clonidine and as effective for prolongation of bupivacaine spinal block.⁴²[II] However, epidural dexmedetomidine is currently not in clinical use and further studies are needed to clarify its role.

KETAMINE

Ketamine, a phencyclidine derivative, had long been used as an anesthetic before it was discovered that it possessed significant analgesic properties in subanesthetic doses.⁴³ Among other target sites, ketamine acts as a noncompetitive antagonist at NMDA receptors where it is thought to play a role in blocking central sensitization, wind up, and pain memory. As ketamine is effective in both acute and chronic pain and has none of the side effects typically related to LA and opioids, it could be a very useful adjunct in neuraxial analgesia. Commercially available ketamine preparations contain potentially neurotoxic preservatives and should not be used for spinal or epidural analgesia, but preservative-free ketamine is well tolerated.

A systematic review assessed the effects of ketamine as adjuvant analgesic to various epidural regimens.⁴⁴[I] Eight trials were identified and five of these reported improved analgesia and opioid-sparing effects with no

increase in ketamine-related adverse events, such as excessive salivation or psychomimetic effects.

Studies on intrathecal ketamine are scarce; in association with bupivacaine it does not appear to improve analgesia, but to increase side effects.⁴⁵

More studies are warranted to identify the clinical applications of neuraxial ketamine.

NEOSTIGMINE BROMIDE

The acetylcholinesterase inhibitor neostigmine bromide reduces the breakdown of acetylcholine in the dorsal horn of the spinal cord. In animal experiments, it has been shown to potentiate muscarinic receptor-mediated analgesia, but human experience is limited. A multicenter study of intrathecal neostigmine after hysterectomy found that neostigmine reduced postoperative analgesic requirements, but this came at the price of increased and dose-dependent postoperative nausea and vomiting.⁴⁶[II] Epidural neostigmine is more promising and seems to have a LA-sparing effect, especially in labor analgesia with concurrent epidural clonidine.⁴⁷[II] Its routine use requires further evaluation.

MIDAZOLAM

Benzodiazepines act at GABA_A receptors, which are thought to be involved in antinociception at a spinal level. Preservative-free midazolam for neuraxial use is presented in an aqueous solution buffered to pH 3.5. At physiologic pH, it becomes more lipophilic, which facilitates tissue penetration. Nishiyama *et al.*⁴⁸ reported improved pain control with a combination of epidural midazolam and LA compared to LA alone, but increased sedation occurred with midazolam. In another study, intrathecal midazolam potentiated the analgesic effect of intrathecal fentanyl.⁴⁹ A recent report by Yaksh *et al.*⁵⁰ reviewed the current data about neurotoxicity of neuraxial midazolam and concluded that, although there seems to be a degree of safety, further research is necessary and routine clinical use is currently not recommended.

TIMING AND TECHNIQUE

Timing and duration

Elective surgery can be defined as a “planned physical aggression.” As the timing and extent of tissue injury are known, analgesic interventions can be given before, during, and after the noxious stimulation.

Over the last years, results of fundamental research and promising animal experiments have shaped the concept of preemptive analgesia, which means establishing an effective analgesic level before the actual noxious input

arises.⁵¹ Thus, central nervous perception of afferent nociceptive impulses could be blocked and acute pain, as well as central sensitization and pain memory, prevented. In order to provide preemptive analgesia, an analgesic intervention given before surgery must be shown to be more effective than the same analgesic intervention given after surgery. In this context, neuraxial regimens seem intuitively appealing because of their easy titrability and their combined peripheral and central actions. Various randomized controlled trials (RCT) of preemptive epidural analgesia have been conducted, but clinical benefit was marginal.⁵² Currently, there does not seem to be a role for routine preemptive epidural analgesia.⁵¹

Even if neuraxial techniques are not used preemptively, it is reasonable that analgesia be titrated to an adequate level during the intraoperative and immediate postoperative period. The optimal duration of postoperative epidural analgesia is not clearly defined and decisions should be made on individual grounds (patient comorbidities, extent of surgery, postoperative rehabilitation program). Commonly, epidural analgesia is maintained for two to four days after major surgery until the patient can be switched to a step down regimen of other analgesics.

Level of insertion of epidural catheters

The location of epidural catheters affects analgesic efficacy.⁵³ Since it has become standard practice to insert an epidural catheter at the level of the incisional dermatome, a shift from lumbar to thoracic epidurals for major thoracoabdominal interventions has been observed. Although there are no randomized controlled trials comparing the efficacy of the same epidural drugs administered via a thoracic or a lumbar approach, numerous studies have demonstrated effective pain relief with thoracic epidural analgesia (TEA), especially dynamic pain relief after extensive thoracic surgery.⁵⁴ [I]

Another advantage of TEA is that the sympathetic and sensory-motor innervation of the lower abdomen and the lower extremity remains intact. This translates into minimal motor blockade, less urinary retention, and less hypotension compared to lumbar epidurals. While there are theoretical concerns that the placement of a TEA may involve a greater risk of spinal cord injury, the current evidence does not support this view.⁵⁵

Patient-controlled epidural analgesia and continuous epidural infusion

In the era of patient-oriented outcome variables and individualized pain management, giving patients control of their own analgesia is an important principle. Analogous to patient-controlled intravenous analgesia, patient-controlled epidural analgesia (PCEA) has been developed

and has become a standard modality of postoperative analgesia. In most cases, a continuous epidural infusion of LA and opioids is combined with patient-controlled bolus administration of the same mixture. To minimize side effects of repeated bolus doses, a lockout period – mostly 10–20 minutes – is defined before the patient can self-administer the next bolus. While this provides reliable background analgesia during periods of low activity and at night, the patient can manage his or her pain “on demand” according to his or her individual needs and activities. Dedicated color-coded PCEA pumps are available and should be used in order to avoid confusion with other intravenous drugs and infusions. Automatic lock of the PCEA pump after a certain time, and need of an access code to unlock and modify parameters, are useful features of safe epidural analgesia.

Combined spinal–epidural analgesia

For performance of combined spinal–epidural (CSE) analgesia, a needle-through-needle technique is commonly employed. First, the larger epidural needle (for example, an 18-gauge Tuohy needle) is placed in the lumbar epidural space. Then, the smaller spinal needle (for example, a 20- or 22-gauge pencil point needle) is put through the epidural needle until CSF is seen. A single shot spinal is then given through the spinal needle, which is subsequently taken out, and a lumbar epidural catheter is placed.

While the subarachnoid bolus produces immediate and dense analgesia, the epidural catheter can be used to top up the block during longer interventions and for postoperative analgesia. The small dural puncture makes significant intrathecal diffusion of epidurally administered drugs unlikely.

CSE analgesia is an option in prolonged surgery of the lower extremity and has also been incorporated into the practice of obstetrical anesthesia, both for labor analgesia and surgical anesthesia. While the intrathecal component has a rapid onset of action and offers a dense neuraxial blockade, the epidural catheter provides prolonged surgical anesthesia and postoperative analgesia as needed.

Continuous spinal analgesia

Continuous spinal analgesia (CSA) can be used for lower abdominal and lower extremity procedures. Placement of a catheter into the subarachnoid space produces rapid and reliable analgesia. By repeated injection of small doses of LA (for example, hyperbaric bupivacaine by steps in 2.5 mg), the block height can be titrated and analgesia can be extended as required. Especially in the elderly or in patients with significant cardiovascular compromise, it makes sense to avoid the cognitive dysfunction associated with general anesthesia on the one hand and the

hemodynamic side effects associated with large intrathecal bolus administrations on the other. Orthopedic interventions, such as hip replacement surgery, are particularly suited for CSA.

Until the early 1990s, dedicated CSA microcatheters (<24 gauge) were available. After multiple case reports of cauda equina syndrome in 1992,^{56,57,58} the Food and Drug Administration (FDA) issued a safety alert and banned these microcatheters. Subsequently it was found that the neurological complications most likely resulted from direct neurotoxicity when high concentrations of lidocaine were administered through these small needles. Currently, there is a prudent revival of interest in CSA with emphasis on meticulous insertion techniques and use of small doses and low concentrations of LA. A recent review concluded that CSA is a safe modality when patients are carefully selected and appropriately managed.⁵⁹ However, CSA catheters are still not available in most countries so that epidural catheters are often used for this purpose. A disadvantage of these catheters is the large dural leak they create and the subsequent risk of postdural puncture headache (see below under Postdural puncture headache). This means that CSA should preferably be used in patients over 75 years where the incidence of headache is very low.

COMPLICATIONS OF EPIDURAL AND SPINAL ANALGESIA

Spinal hematoma

Among the most dreaded and devastating adverse events associated with neuraxial techniques are bleeding complications with resultant permanent damage of the spinal cord. Fortunately, despite a rising number of patients on chronic or perioperative anticoagulant drugs, spinal hematomas remain very rare, and estimations of its incidence are difficult. In a large Finnish study based on 23,500 patient insurance claims from 1987 to 1993, the overall incidence was 0.005 percent, with 0.003 percent of spinal hematomas occurring after epidural and 0.004 percent after spinal anesthesia.⁶⁰ Another Swedish report summarizes severe neurological complications after central neuraxial blockades between 1990 and 1999.⁶¹ Among 1,260,000 spinal blocks and 450,000 epidurals, spinal hematoma occurred in only 33 cases, 11 of which were associated with anticoagulation. However, the consequences of spinal and epidural hematoma in this review were severe. Only six patients made a full recovery and 27 suffered permanent neurological damage, such as paraparesis, cauda equina syndrome, and sensory deficits. A more recent review of 8120 patients with epidural catheters under the care of an acute pain service identified two epidural hematomas (incidence <0.05 percent) with no long-term neurological sequelae.⁶²

Technical difficulties with block performance seem to be the single most important risk factor for spinal hematoma.⁶³ Therefore, indications for neuraxial blockade must be weighed carefully and abandoning the procedure should be considered in case of difficulties or “bloody taps.”

Another risk factor for spinal–epidural hematoma is concurrent anticoagulation. In the late 1990s, after the introduction of low molecular weight heparin (LMWH) for routine thromboprophylaxis, a sharp rise in the incidence of spinal hematomas was observed.⁶⁴ This was mostly related to intraoperative or early postoperative administration of LMWH and a twice-daily, high-dose administration regimen, as practiced in the USA in contrast to the European once-daily administration.⁶⁵ Since then, there have been several consensus recommendations for safe practice of epidural and spinal blocks in anticoagulated patients. A summary of relevant guidelines according to the 2003 Second American Society of Regional Anesthesia and Pain Medicine Consensus Conference on Neuraxial Anesthesia and Anticoagulation will be given here.⁶⁶

- Intraoperative systemic heparinization in patients under neuraxial blockade is safe. The same applies to low-dose unfractionated heparin (for example, 5000 IU/12 hours subcutaneously). Indwelling neuraxial catheters should be removed two to four hours after the last heparin dose; unfractionated heparin can be started two hours after removal.
- For patients on LMWH, at least 12 hours should elapse after a standard dose and 24 hours after higher doses before neuraxial blockade is considered. After surgery under neuraxial anesthesia, the first dose of LMWH should be administered after six to eight hours and then every 24 hours. Epidural catheters can be removed 12 hours after the last dose, and the next LMWH dose can be given two hours later.
- Oral anticoagulants should be stopped four to five days before a neuraxial block. The international normalized ratio (INR) must be closely monitored and should be less than 1.5 for catheter insertion and removal. Low-dose oral anticoagulants (for example warfarin 3–5 mg per day) started after catheter insertion seem safe.
- With regard to antiplatelet drugs, low-dose aspirin (for example, 100 mg per day) and nonsteroidal anti-inflammatory drugs (NSAIDs) do not appear to add a substantial risk, whereas neuraxial blocks should never be undertaken in patients on clopidogrel, GPIIb/IIIa antagonists, and direct thrombin inhibitors. However, as these anticoagulants have been introduced only recently, no formal studies and risk calculations exist.

Even with adherence to these guidelines, routine neurologic monitoring should be undertaken in every patient

after neuraxial blockade, and more so in patients on any anticoagulant medication.

Infectious complications

Serious infectious complications related to neuraxial analgesia are very rare. A recent English survey of 8100 patients who had received epidural anesthesia between 2000 and 2005 identified six epidural abscesses and three cases of meningitis.⁶⁷ In another study which reviewed 17,372 epidurals, the overall incidence of infectious complications was 0.05 percent.⁶⁸ Risk factors, such as immunosuppression, diabetes, difficult insertion, or longer catheterization time (greater than three days), were present in 75 percent. No infections were seen when catheters were left in place for two days or less.⁶⁸ Similarly, a very recent review of 8120 patients with epidural catheters identified six epidural abscesses (incidence <0.1 percent) with no long-term neurological sequelae.⁶²

Epidural analgesia in patients with localized infections is controversial. Septicemia is generally considered a contraindication. Although the data situation is not clear, expert advice is against the use of neuraxial blockade, other than single-shot spinal anesthesia in patients with untreated systemic infections.⁶⁹ However, Jakobsen *et al.*⁷⁰ undertook a retrospective study of 69 patients with localized skin infections who underwent repeated epidural catheterization and reported no infection. Immunocompromise should be regarded as a relative contraindication.⁷¹

Full sterile technique for performance of neuraxial blocks is mandatory. Moreover, careful follow up and a high index of suspicion for infectious complications and recognition of associated symptoms, such as erythema, severe back pain, and progressive neurologic deficit, are required. Early involvement of a neurologist and liberal use of imaging procedures, such as magnetic resonance, are indispensable when in doubt. In cases of confirmed spinal-epidural abscess or meningitis, the most frequent etiologic organism is *Staphylococcus aureus*, and timely administration of probabilistic antibiotics is important.⁷² Surgical decompression must be realized as appropriate. The issue of infectious complications has been the topic of a recent practice advisory of the American Society of Regional Anesthesia and addressed in an accompanying editorial.⁷³

Unfortunately, the outcome of patients with spinal or epidural abscess is bleak. Due to late recognition, the risk of persistent neurological deficit from an epidural abscess is almost 50 percent. In an analysis of the literature, Kindler *et al.*⁷⁴ found that this has not improved since the 1970s.

Postdural puncture headache

Postdural puncture headache (PDPH) is a common complication of spinal anesthesia and occurs in 2 to 3

percent.⁷⁵ The risk of accidental dural puncture with epidurals is estimated at 1 percent. Predictive factors for PDPH are younger patient age, possibly female sex (parturients), and size and type of needles.⁷⁶

The pathophysiologic mechanism for PDPH is thought to be the dural defect induced by needle puncture with continuous transdural leakage of CSF. Headache occurs due to decreased CSF pressure, especially when the patient assumes an upright position because additional traction is then placed on the meninges.⁷⁶

Smaller needles decrease the risk of PDPH, but are technically more difficult to handle. Noncutting (pencil point tip) needles are associated with fewer dural leaks. If PDPH has occurred, treatment by epidural blood patch provides effective tamponade of the CSF leak and increases subarachnoid pressure. Alternative, albeit less successful, options are hydration and intravenous administration of caffeine or intake of caffeinated beverages. Spontaneous improvement of PDPH occurs in ten days in over 90 percent of patients.⁷⁶

EPIDURAL AND SPINAL ANALGESIA IN SPECIFIC SETTINGS

The use of neuraxial anesthesia and analgesia in obstetrics is the topic of Chapter 26, Pain in pregnancy, childbirth, and the puerperium and will not be discussed here.

Cardiac surgery

Cardiac surgery has several unique features that need to be considered before performing neuraxial analgesia. First, cardiac surgery is a highly invasive and stressful intervention that is carried out in a high-risk population. Second, intense postoperative pain can arise from sternotomy, thoracotomy, and chest tube insertion, and this can lead to chronic pain.⁷⁷ Third, intraoperative prolonged pulmonary collapse and postoperative atelectasis can cause significant pulmonary dysfunction. Fourth, a significant proportion of cardiac interventions is carried out under cardiopulmonary bypass. Significant platelet dysfunction or coagulopathy may arise from intraoperative anticoagulation. In addition, interventions, such as prosthetic heart valve surgery, warrant early long-term anticoagulation.

In this complex and unpredictable setting, it is difficult to evaluate the risks and benefits of neuraxial blockades for an individual patient. On the one hand, neuraxial analgesia seems attractive because it produces excellent analgesia and has the potential to attenuate the stress response and improve postoperative pulmonary dysfunction. On the other hand, a particular risk is associated with the use of epidural and spinal analgesia in anticoagulated patients. Several recent randomized controlled trials and meta-analyses have addressed this topic.

Intrathecal morphine given as a single-shot injection via a small needle provides effective postoperative analgesia up to 24 hours without the risk of spinal hematoma that might be associated with the use of large needles and the placement of indwelling catheters. Two reviews of intrathecal morphine in patients undergoing cardiac surgery found it to achieve good postoperative analgesia.^{78,79}[I] However, no additional benefits were observed, in particular no impact on the perioperative stress response. Larger intrathecal doses of morphine may attenuate the stress response, but they cause an unacceptable delay of extubation.

Epidural techniques provide effective analgesia after cardiac surgery.^{78,79}[I] Moreover, TEA has the potential to selectively block the cardiac sympathetic outflow (T1 to T5), which was found to attenuate stress-related increases in heart rate, blood pressure, inotropy, and myocardial oxygen consumption.⁸⁰ In a randomized controlled trial among patients with poor left ventricular function undergoing coronary artery bypass grafting, TEA was associated with improved cardiac index, reduced incidence of arrhythmias, and decreased inotropic requirements.⁸¹ [III] While these advantages have been demonstrated, their clinical relevance is currently not clear.

In contrast, a recent randomized controlled trial designed to compare thoracic PCEA with intravenous PCA after elective cardiac surgery found no significant differences.⁸²[II] There was only a lower intraoperative consumption of anesthetics and a trend towards reduced incidence of confusion and pneumonia in patients receiving PCEA. In 2006, Chaney⁷⁹ published a review about intrathecal and epidural anesthesia and analgesia for cardiac surgery. They found that while TEA induced thoracic sympathectomy and attenuated the postoperative stress response, its impact on patient outcome remained unclear, and TEA seemed to offer no benefits other than analgesia. Similar results were found in a meta-analysis by Liu *et al.* which looked at the effects of perioperative neuraxial analgesia on outcome after coronary artery bypass surgery.⁷⁸[I] While TEA was associated with faster extubation, slightly decreased pulmonary complications, decreased cardiac dysrhythmias, and reduced pain scores, no differences in major morbidity or mortality were detected.

In conclusion, intrathecal and epidural analgesia for cardiac surgery remains controversial. The only proven benefit is good postoperative analgesia, but this can also be achieved by a combination of intravenous or oral opioid and nonopioid analgesics. The risks of neuraxial blockade in the fully anticoagulated or coagulopathic patient are substantial.

Thoracic surgery

Thoracic interventions probably come close to cardiac surgery in terms of invasiveness and perioperative risk. There is also a high level of intraoperative stress and

postoperative pain after thoracic interventions. In addition, intercostal nerve dysfunction may result from incision, retraction, trocar placement, or sutures.⁸³ Intense pain on respiration can cause postoperative hypoventilation and atelectasis in patients who often present significant pulmonary compromise at baseline, and such acute pain may predict chronic postthoracotomy pain.⁸⁴

A meta-analysis by Ballantyne *et al.* concluded that TEA for thoracic surgery achieved good dynamic pain control, reduced pulmonary atelectasis, decreased the risk of infection, and increased oxygen saturation.⁸⁵[I] A more recent review found consistent evidence that TEA reduced perioperative pulmonary complications, especially in high-risk patients.⁸⁶[I]

In the future, less invasive surgical techniques, such as video-assisted thoracoscopy, are likely to be used more extensively. Whether the benefits of TEA will persist in this setting will be subject to reevaluation.

Apart from intravenous opioids, new analgesic techniques for thoracic surgery are emerging and compare favorably to epidurals. Davies *et al.* compared the efficacy of epidural and paravertebral blocks.⁸⁷[I] The latter were placed under direct vision by the thoracic surgeon. While both paravertebral and thoracic epidural blocks achieved good postoperative analgesia and dynamic pain control, the epidural group had significantly more adverse effects, such as block failure, hypotension, and urinary retention. Moreover, paravertebral blocks are less problematic with regard to anticoagulation.⁸⁸

Vascular surgery and coagulation

It has long been known that major surgery is associated with a hypercoagulable state, which persists into the postoperative period so that patients are at risk of vaso-occlusive and thrombotic events. Some decades ago it was proven that the vasodilatation associated with neuraxial blockades reduced such events.^{89,90}[II] A recent review, however, found minimal evidence that epidural analgesia affected the incidence of deep venous thrombosis or pulmonary embolism when state-of-the-art thromboprophylaxis was used.⁸⁶[I]

In a recent Cochrane review, epidural analgesia versus systemic opioids for abdominal aortic surgery was analyzed.⁹¹[I] Epidural analgesia provided better pain relief at rest and dynamic pain relief for up to three postoperative days, and it reduced the duration of postoperative intubation by 20 percent. Epidural analgesia, in particular TEA, reduced overall cardiac complications, myocardial infarction, and gastric and renal complications. However, TEA had no impact on postoperative mortality.

Gastrointestinal surgery

Ileus is common after major abdominal surgery and can be associated with significant postoperative morbidity. In

contrast, early enteral feeding reduces septic complications and improves wound healing.⁹² The avoidance of parenteral opioids and the blockade of sympathetic afferents resulting from epidural analgesia can potentially reduce postoperative ileus.

A Cochrane review of randomized controlled trials revealed reduced gastrointestinal paralysis in patients after major abdominal surgery who had epidural analgesia as compared to systemic opioids.²⁹[1] High lumbar and thoracic epidurals were more effective than lower lumbar epidurals.⁹³ Another more recent review found consistent evidence that epidural analgesia hastened bowel recovery by 24–37 hours.⁸⁶[1] Continuous epidural analgesia was superior to PCA in relieving postoperative pain, but was associated with a higher incidence of pruritus.²⁹[1] Benefits with regard to improved analgesia and shortened duration of ileus have also been confirmed by a recent meta-analysis of RCTs in the setting of colorectal surgery; however, specific complications were also identified and length of hospital stay was not shortened.⁹⁴[1]

There was no evidence that epidural analgesia increases the risk of anastomotic leakage.⁹⁵[1]

Orthopedic surgery

After hip or knee replacement, epidurals provide better analgesia, especially dynamic pain relief, than parenteral opioids.⁹⁶[1] A review published in 1995 found less deep venous thrombosis in patients undergoing total hip replacement or knee arthroplasty under epidural than general anesthesia.⁸⁶ However, as pointed out above, the preventive effect of epidural analgesia on thrombosis may be less relevant today. Another review found less postoperative delirium, reduced deep venous thrombosis, and less pneumonia with epidural analgesia for hip replacement surgery.⁹⁷

A recent meta-analysis in patients undergoing total hip replacement and spinal fusion surgery found that neuraxial techniques led to reduced blood loss and a reduced number of patients transfused.⁹⁸[1]

PROSPECT is a group which provides systematic reviews of randomized controlled trials leading to consensus recommendations for analgesia at a dedicated website (www.postoppain.org),⁹⁹ e.g. after total hip replacement.¹⁰⁰[1] The authors recommend general anesthesia combined with a peripheral nerve block, such as femoral nerve block, as the first option, because this combination provides reliable analgesia and has a favorable risk–benefit profile. An alternative recommendation is a single-shot spinal anesthesia with LA and opioids, followed by postoperative intravenous and oral analgesics. Epidural analgesia is recommended only for patients at particular risk for cardiopulmonary events.

Similar recommendations have been made by this group for the treatment of pain after total knee joint replacement, where again the evidence is more in favor

of peripheral nerve blocks, when benefits and risks are weighted.

SAFETY AND EFFICACY OF NEURAXIAL ANALGESIA

Postoperative pain may result in a variety of unfavorable short- and long-term outcomes, such as psychological distress, inability to perform physiotherapy, delayed return to normal function, and chronic pain.¹⁰¹ Over the last decades, the importance of aggressive pain management has been recognized and different forms of neuraxial analgesia with variable combinations of LA agents, opioids, and other adjuvants have been developed for treatment of postoperative pain. Numerous randomized controlled trials and meta-analyses have attested to the safety of epidural and spinal analgesia when performed according to recognized guidelines. Serious adverse events and mortality are so rare that it is difficult to obtain reliable data on their incidence.

As far as the efficacy of neuraxial analgesia is concerned, a study of almost 6000 patients who received intrathecal morphine for analgesia after different surgical procedures reported effective analgesia for up to 24 hours.¹⁰² In a survey of 1057 patients with postoperative PCEA, Wigfull *et al.*¹⁰³ reported that nearly 94 percent of patients had adequate analgesia with PCEA. Block *et al.* undertook a meta-analysis on the analgesic efficacy of epidural versus intravenous patient-controlled analgesia, which included 100 randomized controlled trials.¹⁰⁴[1] They found that the overall analgesia with epidurals was better than with parenteral opioids at all time points, across all patient populations, and after all types of surgery. Similarly, a meta-analysis by Wu *et al.* found that PCEA after different surgical interventions provided superior analgesia compared to intravenous PCA for overall pain, pain at rest, and pain with activity.¹⁰⁵[1]

OUTCOME AFTER SPINAL AND EPIDURAL ANALGESIA

Cost-effectiveness

Cost-related issues are important aspects of anesthetic decision-making in a time where healthcare resources are scarce. As demographic changes and financial restrictions are only recent developments, no comprehensive reviews of costs and benefits associated with neuraxial analgesia have been published. In addition, no consensus exists as to which costs should be measured, in which clinical settings, and at what points in time this should be done. Comparison of cost-effectiveness data is likely to be hampered by major differences in healthcare systems.

A cost evaluation of epidural versus intravenous PCA after major abdominal surgery in Sweden published in 1995 found that epidurals provided more effective pain control, but were three times more expensive.¹⁰⁶ The beneficial effect of better pain control was only seen in the immediate postoperative period, so that the authors judged epidural analgesia poorly cost-effective and not overall justified. In contrast, a German analysis of 6349 patients comparing postoperative PCEA, intravenous PCA, and brachial plexus blockade concluded that the higher initial costs of PCEA could be set off by better pain relief and earlier discharge from the intensive care unit.¹⁰⁷

In conclusion, a detailed cost-effectiveness analysis of neuraxial analgesia remains to be performed. It is most likely that neuraxial techniques become cost-effective by utilizing their advantages to permit aggressive postoperative rehabilitation.¹⁰⁸ Earlier discharge from high dependency wards, decreased postoperative complications, and long-term benefits, such as reduction in morbidity, may then outweigh the higher initial costs of epidural analgesia, especially in high-risk patients.¹⁰⁹ In low- and intermediate-risk patients undergoing less invasive interventions, neuraxial analgesia may not be cost effective.

Morbidity and mortality

Numerous studies have proven that major surgery and perioperative pain are powerful activators of the neuroendocrine stress response. Manifestations of this stress response include hypercoagulability, immunosuppression, increased myocardial workload and oxygen consumption, widespread inflammation, and increased catabolism with hyperglycemia, muscle breakdown and poor wound healing. Epidural analgesia has the potential to block this detrimental pathophysiology by improving analgesia and by blocking sympathetic afferents.

Indeed, many studies undertaken in the 1980s and 1990s found that epidural analgesia attenuated the postoperative stress response and improved outcome.^{110,111} [II] In 1987, Yeager *et al.* reported such a significant improvement in morbidity and mortality in high-risk patients receiving epidural analgesia that their study was stopped early by the local ethics committee.¹¹² [II] In 2001, Beattie *et al.* published a meta-analysis including 11 randomized controlled trials with 1173 patients from 1966 to 1988.¹¹³ [I] They found that epidural anesthesia and analgesia was associated with a 40 percent reduction of postoperative myocardial infarction.

Yet the most comprehensive meta-analysis in favor of neuraxial anesthesia is the CORTA analysis by Rodgers *et al.* that was published in 2000.¹¹⁴ [I] This review included 141 randomized controlled trials from 1977 to 1995 with almost 9600 patients, with the majority of trials coming from the 1980s. The authors observed a 30 percent reduction in overall mortality (1.9 versus 2.8

percent) with intraoperative neuraxial blockade compared to general anesthesia.

After much discussion of these impressive data, several large multicenter trials were undertaken with less striking results. In a study with 1021 patients published in 2001, epidural anesthesia and analgesia did not improve overall morbidity and mortality.¹¹⁵ [II] The only benefit was seen in a subgroup of patients undergoing abdominal aortic procedures. The MASTER trial (2002) analyzed data from 915 patients undergoing major abdominal surgery under combined epidural and general anesthesia or under general anesthesia alone.¹¹⁶ [II] Postoperative analgesia was either via epidural catheters or via intravenous PCA. There was no benefit in terms of mortality and only a slightly improved morbidity in the epidural group. In 2007, Liu *et al.* carried out a systematic update of the evidence to assess the effect of postoperative analgesia on major postoperative complications.⁸⁶ [I] They analyzed randomized controlled trials from 1996 to 2006 and found that there was insufficient evidence to confirm or deny the ability of postoperative analgesia to affect postoperative mortality or morbidity.

In conclusion, several randomized controlled trials and meta-analyses report reduced morbidity and even mortality with epidural anesthesia and analgesia, while others find no significant benefit apart from good pain relief. Several aspects may explain these seemingly contradictory results.

Methodological difficulties most certainly play a role. Comparison of various data sets from heterogeneous studies with different patient groups undergoing a variety of surgical procedures is not evident. It is equally difficult to differentiate which effects are due to general anesthesia and which are due to intraoperative or postoperative neuraxial analgesia.¹¹⁷ In the postoperative period, it is difficult to establish the exact impact of neuraxial analgesia amidst a multitude of therapeutic measures and individual patient factors. Therefore, the changes in mortality observed in several studies may not have been brought about by analgesia alone, but by a combination of different factors, such as optimization of preoperative medical status, use of short-acting anesthetic drugs and the laryngeal mask, less invasive surgical technique, modern thromboprophylaxis, and accelerated recovery. A corroborating aspect to this argument is that results of studies and meta-analyses seem to be affected by their publication date.¹¹⁸ [I] While older studies tend to find significant benefits from neuraxial analgesia, this effect is much attenuated in recent publications.

Modern anesthesia may also be a victim of its own success in that serious morbidity and mortality have become too rare to be measured in clinical trials of ordinary sample size. This aspect was addressed by Wu *et al.* in 2004, who analyzed a random sample of American Medicare beneficiaries undergoing different types of major surgery from 1997 to 2001.¹¹⁹ In their database of 12,780 patients, they found that epidural

analgesia was associated with a significantly lower odds ratio of death at 7 and 30 days postoperatively.

In conclusion, the impact of neuraxial analgesia on mortality remains to be determined and is likely to be less important than in the past due to surgical and anesthesiologic advances. However, epidural techniques, in particular, are very useful as part of a multimodal approach to control postoperative pain and hasten recovery.¹¹⁷

Nontraditional outcome measures

Over the last few years, patient-centered outcome variables have been introduced as monitors of anesthetic care and are likely to supplement or replace the traditional outcome measures, morbidity and mortality.

While many authors agree that patient satisfaction is an important outcome measure, no validated and standardized tools exist for rating patient satisfaction with regard to neuraxial analgesia.¹²⁰ Satisfaction is a complex psychosocial construct, which is likely to be influenced by numerous factors other than analgesia, for example patient expectations, level of information, baseline physical and psychological status, communication, and interaction with healthcare providers.¹²¹ While it seems inherently difficult to measure patient satisfaction, reproducibility and comparison of such data from different studies is highly problematic.

Nevertheless, several trials have addressed this complex issue. In a survey of 1057 patients receiving postoperative PCEA, Wigfull *et al.*¹⁰³ found that PCEA produced excellent analgesia and high patient satisfaction. Another study of almost 6000 patients who received intrathecal morphine for analgesia after a range of surgical procedures equally reported high patient satisfaction.¹⁰² A systematic review found that, compared with systemic opioids, epidural analgesia was associated with higher patient satisfaction.¹²² [1] Indeed, in a prospective seven-year survey of nearly 6000 surgical patients, neuraxial analgesia was associated with a high degree of patient satisfaction (mean satisfaction score of 8.5 on a scale from 0 to 10).¹⁰²

As far as measurements of health-related quality of life are concerned, these have not been carried out with regard to postoperative analgesia. "Analgesia-related quality of life" is not yet an issue in most clinical studies. However, if the goal after a surgical intervention is to get the patient "up and functioning" and back to his or her preoperative state as soon as possible, neuraxial techniques may play an important role because they provide better pain relief and contribute to early rehabilitation. In one study, Carli *et al.*¹²³ found that epidural analgesia enhanced postoperative quality of life. Another contribution of neuraxial analgesia to better quality of life may be the avoidance of chronic pain by aggressive management of early postoperative pain.¹⁰¹

RESEARCH AGENDA AND FUTURE DIRECTIONS

Despite many recent advances with insight into pain mechanisms, further basic and clinical research is needed in order to elucidate the phenomenon of acute pain and associated physiology, such as the pain-related stress response. Better knowledge of peripheral and central pain reception and modulation may lead to better use of existing neuraxial techniques and to the development of new epidural and spinal analgesics.

As far as practical conduct of neuraxial analgesia is concerned, safer techniques of insertion, such as ultrasound-guided techniques, need to be studied, and safe catheters for epidural and intrathecal use are needed.

Based on further randomized controlled trials and meta-analyses, it is likely that more procedure-specific guidelines for postoperative pain management will be developed and that indications and contraindications will be tailored to specific subgroups of patients.

Finally, systematic outcomes research with regard to neuraxial analgesia needs to be conducted, with special emphasis on nontraditional outcome measures, analgesia-related quality of life, and cost-effectiveness.

CONCLUSIONS

The last decades have witnessed important advances in all aspects of patient care. In parallel with the introduction of less invasive and individualized surgical methods, new techniques of postoperative pain relief have been added to the armamentarium of the anesthetist. Specific guidelines about indications, contraindications, and the technical performance of neuraxial procedures are available.

Standard intrathecal and epidural analgesia and their variations, such as combined spinal-epidural analgesia and continuous spinal analgesia, provide effective pain relief after various types of surgical procedures. Patient-controlled epidural analgesia is an important component of effective and individualized management of postoperative pain.

Appropriately administered neuraxial analgesia is a key component of multimodal rehabilitation programs after major surgery and has benefits in terms of patient satisfaction and health-related quality of life. Significantly decreased morbidity has been proven in selected patients. The exact impact of epidural and spinal analgesia on mortality remains to be determined.

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