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Pain relief and safety after major surgery
A prospective study of epidural and intravenous analgesia in 2696 patients

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Background: Adverse effects may still limit the use of continuous epidural and intravenous analgesia in surgical wards. This study postulated that postoperative epidural analgesia was more efficient, and had fewer side-effects than intravenous morphine. The aim was to investigate efficacy, adverse effects and safety of the treatments in a large patient population.
Methods: During a five-year period 2696 patients undergoing major surgery, received either epidural or intravenous analgesia for postoperative pain relief. The patients were prospectively monitored in surgical wards. Pain was evaluated with a numeric rating scale (0–10) at rest/mobilization. Treatment duration, respiratory depression, sedation/hallucinations/nightmares/confusion, nausea/vomiting, pruritus, orthostatism/leg weakness, and insufficient pain relief were registered. Pain relief for all patients aimed at a pain scoring of less than 4 at rest.
Results: Epidural analgesia was used in 1670 patients, and intravenous morphine in 1026 patients. Patients with epidural analgesia experienced less pain both at rest and during mobilization. Insufficient treatment effects such as dose adjustments, orthostatism/leg weakness, and pruritus were more common in the epidural group. Respiratory depression and sedation/hallucinations/nightmares/confusion occurred more often in the intravenous group. Thoracic epidural catheters caused a lower incidence of motor blockade compared to lumbar catheter placements.
Conclusion: In a large patient population the use of epidural and intravenous postoperative analgesia was considered safe in surgical wards, and the incidence of adverse effects was low. Patients with epidural analgesia experienced overall less pain, while opioid related side-effects were more common with intravenous morphine analgesia.

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Key words: adverse effects; epidural analgesia; intravenous morphine; patient safety; postoperative analgesia; respiratory depression.

INTRODUCING organized postoperative pain relief programmes is at present a major achievement for patients with a need for long-term postoperative analgesia. The most common techniques are epidural analgesia with local anaesthetics combined with opioids, or the administration of intravenous opioids.

Although the risk of sedation and respiratory depression initially limited the use of postoperative epidural opioids (1–4), it was later concluded that epidural analgesia can safely be used in surgical wards (5–9). Reported advantages of utilizing postoperative epidural analgesia are efficient pain relief (10), decreased overall cardiovascular morbidity (11), a reduced incidence of pulmonary infections (12) and less thrombo-embolic events (13). Although outcome variables may not be altered by intraoperative epidural/general anaesthesia followed by postoperative epidural analgesia (14), such benefits as less respiratory failure, better analgesia and fewer adverse effects have been demonstrated (15–17). However, despite the widespread use and potential side-effects of parenteral opioids, few large studies compare analgesic efficacy and adverse effects of epidural analgesia and intravenous opioids (18, 19). In small clinical studies epidural analgesia can be superior to intravenous opioids with less pain during mobilization (20), earlier enteral nutrition and discharge (21), and improved mental status (22).

In this clinical study of a large patient population we hypothesized that utilizing postoperative epidural

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analgesia would provide better pain relief, and cause fewer side-effects than intravenous opioids. Since 1996, patients at the Department of Surgery and Urology at the Lund University Hospital have been treated with either epidural administration of bupivacaine/morphine, or an intravenous infusion of morphine following major non-cardiac procedures. During a five-year period all patients with this treatment were prospectively monitored in the postoperative phase.

The aim of this non-randomized prospective study was to compare epidural analgesia and intravenous morphine following major surgery with regard to pain relief, side-effects, and with a special focus on serious adverse effects such as respiratory depression and sedation.

Methods and materials

The ethics committee at the Medical Faculty, Lund University approved the investigation. The study was conducted from January 1996 until January 2001, and included patients undergoing major abdominal or thoraco-abdominal surgery with a need for continuous postoperative epidural (EPI), or intravenous analgesia (IV). The study was not randomized. If contraindications to epidural blockade were present, patient refusal occurred, or the surgical procedure did not necessitate epidural analgesia, then a continuous intravenous morphine infusion was started postoperatively. Patients undergoing minor surgical procedures were given intermittent opioids postoperatively according to departmental routines and were not included in the study.

Surgery was defined as thoraco-abdominal (esophagectomy), upper abdominal (gastrectomy, liver resection, pancreatic resection, reflux and diaphragmatic surgery), lower abdominal (rectum amputation, radical prostatectomy, colon surgery, and cystectomy), and abdominal (explorative laparatomy, abdominal aortic aneurysm, nephrectomy), and miscellaneous procedures (i.e. open cholecystectomy, peripheral vascular surgery, intestinal surgery, spleenectomy, and abdominal wall hernias).

Perioperative management

Rectal/oral midazolam or parenteral opioids were used for premedication. The choice of premedication and general anaesthetic management was decided at the discretion of the attending anaesthesiologist and according to departmental routines. Induction of general anaesthesia was performed with propofol or thiopental, fentanyl, and a non-depolarizing muscle relaxant. Maintenance of general anaesthesia was performed with oxygen/nitrous oxide and a volatile agent, utilizing a low-flow (0.5–1.5 l min^{-1}) circuit and mechanical ventilation.

The selection of a thoracic or lumbar vertebral interspace for the epidural catheter was dependent on the dermatomal extent of the surgical procedure, ease of catheter insertion, and the attending anaesthesiologist. An early clinical impression was that a thoracic catheter placement was essential in order to reduce the incidence of lower limb weakness in the postoperative period when utilizing the 0.25% bupivacaine solution. Hence, the anaesthesiologists were then encouraged to perform a thoracic epidural catheter placement.

The epidural space was identified according to departmental routines with the patient in a sitting position, with a midline approach, and by the loss-of-resistance technique using a saline filled 10 ml plastic syringe. The epidural catheter was inserted approximately 4–6 cm into the epidural space in a presumed cranial direction (23, 24).

A 3-ml test dose of mepivacaine 20 mg ml^{-1} (Carbocain® 2%, AstraZeneca, Södertälje, Sweden) was injected. Intrathecal injection was ruled out before induction of general anaesthesia. The catheter was affixed by using a transparent adhesive dressing, thus enabling daily inspections of the insertion site. The rest of the catheter was taped along the midline of the back. The epidural blockade was established preoperatively during general anaesthesia with mepivacaine 20 mg ml^{-1}. A 20–30% decrease in systolic blood pressure and heart rate were interpreted as signs of an effective epidural blockade. Epidural morphine 2–4 mg (Morfin Special®, 0.4 mg ml^{-1}, AstraZeneca, Södertälje, Sweden) was injected subsequently. The epidural morphine dose was repeated for esophagectomies if surgery lasted longer than 8 h. In all patients the postoperative treatment was started at the end of surgery. A Deltec 5800® infusion pump (Deltec Inc, Minneapolis, MN) was used for both the epidural and intravenous treatments.

To improve safety, two sizes of infusion bags were used. For epidural analgesia 500 ml bags with bupivacaine/morphine (2.5 mg ml^{-1}–0.05 mg ml^{-1}) were used. Intravenous morphine (1 mg ml^{-1}) was provided in 250 ml bags. All infusion bags were prepared by the hospital pharmacy, and could be stored at room temperature for up to 1 month.

For the EPI-group the background infusion rate was set at 3–5 ml h^{-1} with a patient-controlled analgesia (PCA) option of 1.5–4 ml and a lockout interval of 30 min. In the IV-group, morphine was administered at 0.5–2 ml h^{-1}, with the PCA dose set at 0.5–3 ml with

a 10-minute lockout interval. Usually one infusion bag was sufficient for the treatment period. Exceptions were patients undergoing thoraco-abdominal esophagectomy who maintained their treatment for approximately 1 week until the chest drainage was discontinued.

Based on daily judgements, we tried to lower the preset maintenance dosage in both the EPI- and IV-group, respectively. We used the Numeric Rating Scale (NRS) scoring for pain as a primary end-point for the dosage, i.e. a NRS score for pain at rest at less than 4 (0–10) was considered adequate (25). As a precaution, a NRS score of ≤ 2 at mobilization resulted in a dose adjustment with lowering of the infusion rate. On the contrary, inadequate epidural or intravenous analgesia (NRS for pain at rest ≥ 4) was initially treated with a bolus dose with the pump and/or an increase of the background infusion. Supplemental oral or rectal doses of paracetamol, iv ketorolac, and iv tramadol were administered if the pump adjustment still resulted in insufficient pain alleviation.

Patient monitoring

Following surgery all patients were observed in the recovery room for at least 2 to 4 h, and then discharged to the surgical wards. The attending nurse monitored the respiratory frequency, pulse rate, and sedation every h during the first 12 postoperative hour. The monitoring was then performed every third hour. The monitoring was stopped 6 h after discontinuation of the treatment. As a safety precaution, the patients with epidural analgesia maintained their bladder catheterization during the treatment. The analgesic regime and protocol for each patient was terminated following consultation with the surgical staff. Further analgesic treatment was performed according to departmental routines.

Data collection

Dose-adjustments, documentation of NRS scores for pain at rest and during mobilization, and registrations of adverse effects were performed on a daily basis by an anaesthesiologist. Respiratory depression was defined as less than 8 breaths min^{-1}. Sedation was defined as difficulty arousing the patient verbally or by pain stimulation. Nightmares/hallucinations/confusion and orthostatism/dizziness reported by the patient or the attending nurse were registered. Nausea and vomiting reported by the nurse or the patient were noted. Only pruritus reported by the patient and necessitating treatment with iv clemastine was registered. Insufficient analgesic treatment effects necessitating dose adjustments, and epidural catheter displacements with a subsequent change of analgesic technique, were also registered.

Recording of lower limb motor blockade/leg weakness was defined as an inability to ambulate due to muscular weakness and patient discomfort from reduced limb control. Data were obtained during daily rounds on weekdays. Data obtained during weekends was retrieved from the patient's chart the following weekday. The information from our standardized protocol was then transferred to a database (Access®; Microsoft Corporation, Redmond, WA).

Statistical analysis

Continuous data were compared between groups by the unpaired *t*-test. Ordinal data were compared by the chi-squared test. NRS scores for pain were analysed by repeated analysis of variance (Hotelling's Trace), and pairwise comparisons were performed with the Mann–Whitney *U*-test. Data were expressed as mean ± SD unless indicated otherwise. Statistical significance was defined as a *P*-value less than 0.05.

Results

The study included 2696 patients with 998 participating women and 1698 men. Demographic data and surgical procedures are presented in Table 1. The analgesic treatment continued during 76 ± 42 h (range 1–330 h) in the EPI-group, and 71 ± 42 h (range 1–620 h) in the IV-group (Table 1).

Despite the aim with similar pain relief in both groups at rest, the NRS scoring was lower in the EPI-group compared to the IV-group both at rest and during mobilization ($P < 0.003$, and $P < 0.001$, respectively; Fig. 1). An additional limited analysis of patients with complete NRS scores (EPI: $n = 382$; IV: $n = 169$) confirmed the overall data when comparing

Table 1

Demographic data and surgical procedure.

	EPI-group	IV-group
Patients (*n*)	1670	1026
Mean age (±SD)	62 ± 15	60 ± 16
Gender (male/female)	1098/572	600/426
Duration (±SD) h	76 ± 42	71 ± 42
Thoraco-abdominal (*n*)	130	45
Upper abdominal (*n*)	203	117
Lower abdominal (*n*)	755	439
Abdominal (*n*)	347	231
Miscellaneous (*n*)	235	194

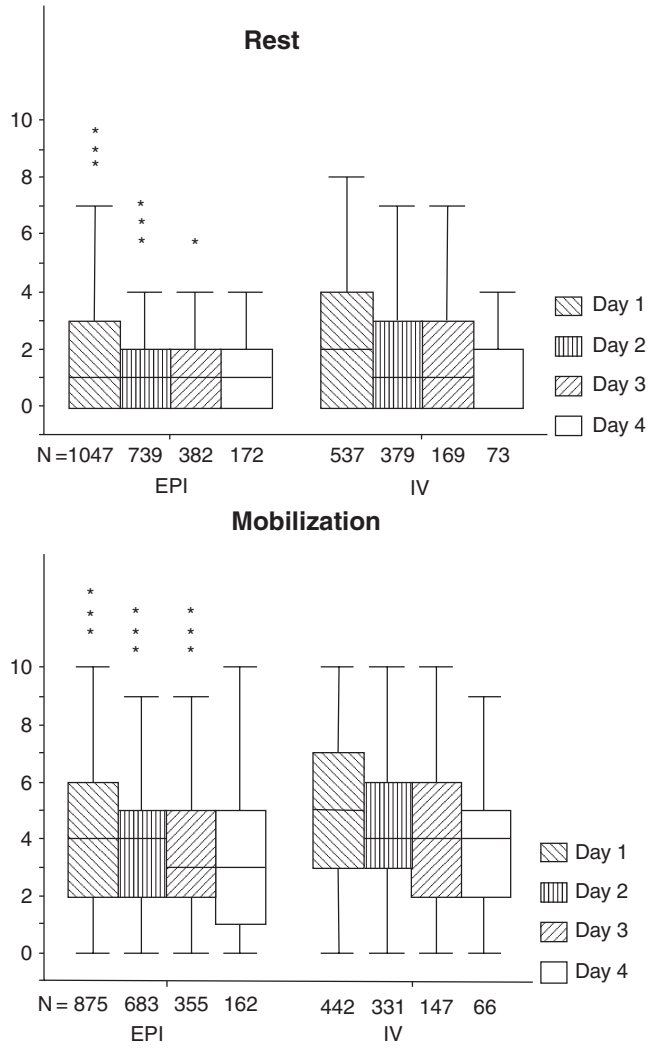

*Fig. 1 The Numeric Rating Scale (NRS) scoring presented during rest and mobilization in the epidural (EPI) and the intravenous (IV) groups, respectively. Summary plot based on the median, quartiles, and extreme values. The box represents the interquartile range, which contains 50% of the values. The whiskers are lines that extend from the box to the highest and lowest values, excluding outliers. A line across the box indicates the median value. A significant difference between the EPI and the IV treatment on the same postoperative day is indicated by: *** = $P < 0.001$, and * = $P < 0.05$.*

the groups. Another comparison including all patients did not reveal any differences regarding NRS scorings in relation to gender and analgesic technique.

In the EPI-group, such side-effects as orthostatism/dizziness (101 vs. 11 patients; $P < 0.001$), pruritus (73 vs. 19 patients; $P < 0.001$), and insufficient treatment effects necessitating dose adjustments (104 vs. 14 patients; $P < 0.001$) were more common than in the IV-group. Of the initially 104 patients with insufficient epidural analgesia, 55 patients continued the epidural treatment after dose adjustments. Among the remaining 49 patients, five patients experienced epidural catheter displacement, and eight patients were switched to iv morphine. Two patients received a new epidural catheter, and in addition one patient in the IV-group was switched to epidural treatment due to insufficient pain relief. Epidural analgesia was terminated in the remaining patients, and further analgesic treatment was provided according to departmental standards.

When utilizing the bupivacaine 0.25%/morphine 0.005% mixture, a thoracic epidural catheter placement above Th_{12} resulted a 2.4% incidence of leg weakness, while an epidural catheter placement below Th_{12} caused an 8.1% incidence of leg weakness (thoracic 33/1336 patients versus lumbar 22/272 patients; $P < 0.001$).

Compared to the EPI-group, the patients in the IV-group had a higher incidence of respiratory depression (7 vs. 13 patients; $P < 0.012$) (Table 2). Sedation and hallucinations/nightmares/confusion occurred more frequently in the IV-group (42 vs. 46 patients; $P < 0.005$).

There was a tendency that respiratory depression was more common on the day of surgery in the EPI-group (EPI vs. IV; 5/7 vs. 4/13 patients; NS), and on postoperative day 1 in the IV-group (EPI vs. IV; 2/7 vs. 9/13; NS) (Table 3).

The frequency of nausea and/or vomiting was similar in both groups (EPI vs. IV; 53/1670 vs. 38/1026; NS).

Major complications

Six patients died during the postoperative treatment period (EPI vs. IV; 2 vs. 4). Three of the patients had terminal cancer. Another patient was diagnosed with intestinal vascular obstruction, one patient died from a major retroperitoneal bleeding, and finally one patient died from circulatory failure due to severe cardiovascular disease. None of the deaths were attributed to the type of administered pain relief.

One patient with a thoracic epidural catheter placement at Th_{10-11} developed a 30-mm cranio-caudal epidural hematoma at the Th_{12} level. Paraplegia and pain in the lower extremities appeared on the first postoperative day after an emergent abdominal aortic aneurysm repair. The patient regained complete neurological recovery following laminectomy.

A perioperative thoracic vertebral disc herniation at Th_8 developed in one patient after a radical prostatectomy. The epidural catheter was inserted preoperatively without complications at the Th_{11-12} level. The reason for this complication was most likely explained

Table 2

Adverse treatment effects.

	EPI-group $n=1670$	IV-group $n=1026$	*P*
Respiratory depression (*n*)	0.04% (7)	1.2% (13)	<0.012
Nausea (*n*)	3.2% (53)	3.7% (38)	NS
Pruritus (*n*)	4.4% (73)	1.9% (19)	<0.001
Orthostatism/dizziness (*n*)	6.0% (101)	1.1% (11)	<0.0001
Insufficient treatment effects (*n*)	6.2% (104)	1.4% (14)	<0.0001
Sedation (*n*)	1.4% (23)	1.9% (20)	NS
Hallucinations/nightmares (*n*)	0.2% (3)	0.4% (4)	NS
Confusion (*n*)	0.4% (7)	1.2% (12)	=0.02
Total: Sed/Hall/Night/Conf/	2.5% (42)	4.5% (46)	<0.005

by the dorsal flexion of the patient's vertebral column in the supine position during surgery.

Discussion

The present prospective study monitored 2696 postoperative patients for efficacy of pain relief and adverse effects of postoperative epidural and intravenous analgesia. Patients treated with epidural analgesia experienced better pain relief both at rest and during mobilization. However, orthostatism, pruritus and insufficient treatment effects were more frequent with epidural analgesia. In comparison, intravenous morphine analgesia demonstrated a higher incidence of serious opioid related adverse effects, i.e. sedation and respiratory depression. This study illustrates the clinical challenge with providing efficient pain relief and simultaneously limiting the incidence of adverse effects.

The rationale for our use of background infusion combined with PCA in both groups was to maintain continuous adequate pain relief. In particular, breakthrough pain can be avoided with opioid bolus doses by maintaining therapeutic opioid blood levels (26–28). A recent study has confirmed that elderly patients have difficulties operating pure on-demand PCA-systems (29), and others have demonstrated beneficial effects of a continuous infusion (30). However, during an opioid infusion the opioid dosage may increase without improving pain relief (31). Furthermore, PCA combined with a background infusion provides effective analgesia, but with a higher frequency of adverse effects (26, 27). On the contrary, a continuous infusion during patient-controlled epidural analgesia could decrease postoperative pain without serious side-effects compared to PCA without background infusion (32). Despite the continuous intravenous infusion of morphine in our study, the pain relief was not as efficient as in the epidural group, and at the same time associated with adverse opioid effects.

We found a higher frequency of respiratory depression (1.2%) in the intravenous morphine group, compared with the epidural group. Respiratory

Table 3

Analgesic treatment in relation to onset of respiratory depression.

Pat	Postop pain treatment	Gender female/male	Age (years)	Type of surgery	Day of surgery	Onset of respiratory depression Postop day 1	Postop day 2	Postop day 3
1	EPI	m	67	Liver resection		X		
2	EPI	m	54	Radical prostatectomy	X			
3	EPI	m	63	Radical prostatectomy		X		
4	EPI	f	78	Liver resection	X			
5	EPI	f	62	Liver resection	X			
6	EPI	f	85	Gastrectomy	X			
7	EPI	f	70	Liver resection	X			
8	IV	f	70	Cystectomy		X		
9	IV	f	78	Gastrectomy		X		
10	IV	f	61	Pancreatic resection	X			
11	IV	f	64	Explorative laparotomy	X			
12	IV	f	74	Colectomy		X		
13	IV	f	76	Liver resection	X			
14	IV	f	77	Explorative laparotomy	X			
15	IV	m	72	Gastrectomy		X		
16	IV	m	64	Radical prostatectomy		X		
17	IV	m	84	Hemicolectomy		X		
18	IV	m	79	Thoracoabdominal esophageal resection		X		
19	IV	m	78	Hemicolectomy		X		
20	IV	m	67	Explorative laparotomy		X		

depression seemed to occur earlier in the epidural than in the intravenous morphine group, although no differences were found. A dose-related depression of the ventilatory drive can occur as early as 5 h after an epidural morphine injection (3). In contrast, patients treated with intravenous morphine seem to have a slower onset of respiratory depression, probably due to a gradual accumulation of morphine and its metabolites. If patients have an impaired renal function it may give rise to high levels of morphine-3-glucoronide and morphine-6-glucoronide that could influence the respiratory function (33). However, monitoring renal function and morphine metabolites was beyond the scope of the present study.

In two large retrospective surveys and one prospective study of epidural opioid treatment, the frequency of respiratory depression was 0.09–0.9% (2, 34, 35), and elderly patients are especially prone to respiratory depression (36). In a double blind multicentre study the incidence was as high as 2–7% (37), which also may reflect differences in epidural opioid dosage. Rarely, the incidence of respiratory depression is reported for parenteral opioid treatment, but it is important to remember when considering dosage and optimal choice of postoperative pain relief. In our experience and based on the findings in the present study, a continuous morphine infusion can be used if the patients are closely monitored and dose titration is performed early in the postoperative period avoiding side-effects due to opioid accumulation.

Pruritus was more common in the epidural group. This is in concordance with previous reports, and the incidence of pruritus after epidural administration of opioids may be as high as 50%. It should be emphasized that the low incidence in our study is based on pruritus reported by the patient or the nurse when there was a patient need for pharmacological treatment. Patients may experience pruritus which is not bothersome and not reported by the patient unless asked.

Nausea/vomiting occurred with a similar frequency in the groups. Given in equi-analgesic doses, all opioids may cause nausea and vomiting by triggering the medullary chemoreceptor zone (38). The early titration of an appropriate opioid dose seems crucial to avoid such adverse effects. There is no evidence that nausea and vomiting is more frequent with iv PCA than that with im opioids (39), and Zacharias et al. found that a properly supervised continuous infusion of morphine is equal to PCA regarding the incidence of side-effects (40).

In our study lumbar placement of the epidural catheter resulted in a higher incidence of lower limb motor blockade compared to thoracic catheter placement. For this reason, early mobilization was limited in some patients, despite adequate analgesia, due to the involvement of lumbar dermatomes in the epidural blockade (7, 41). The reasons for using the 0.25% bupivacaine/0.005% morphine mixture in the present study were the low drug dosage, few dose adjustments, low incidence of tachyphylaxis, and few infusion bag changes. Clinical studies describing an accelerated postoperative multimodal concept including epidural analgesia with the same epidural solution demonstrate adequate pain relief, improved pulmonary function, adequate physical performance (42), as well as earlier return of bowel function (43). Several epidural drug combinations can provide adequate postoperative epidural analgesia. Over the last years there has been a trend toward lower concentrations of epidural mixtures. Recent reports with epidural mixtures such as 0.1% bupivacaine or 0.1% ropivacaine mixed with fentanyl and epinephrine may also induce adequate postoperative pain relief (10, 44).

Although the incidence of ortostatism/dizziness in our study was higher for the epidural group than the intravenous morphine group, thoracic epidural analgesia with 0.25% bupivacaine does not necessarily adversely influence postoperative ambulation and risk of orthostatism (45). Thus, the choice of epidural solution plus a correct placement of the epidural catheter in relation to the surgical dermatomes are important prerequisites to minimize pain and side-effects.

Inadequate analgesic treatment effects necessitating dose adjustments were more common in the epidural group than in patients with intravenous analgesia. Malfunction and displacement of the epidural catheter is a contributing factor (5, 9, 46), and especially catheter displacement may occur during mobilization (47). D'Angelo et al. concluded in a large obstetric study that epidural catheters should be inserted at least 2 cm, and up to 6 cm to minimize catheter dislocation (24). The choice of dressing can also be important, and it is reported that adhesive plastic film covering the epidural catheter and filter causes the least catheter displacement (48). We aimed at inserting the catheter 4–6 cm into the epidural space and, as a result, we experienced relatively few catheter displacements. Only 7% of the epidural treatments caused insufficient analgesia. Less than half of these epidural treatments had to be terminated earlier than planned, since most initially insufficient epidural treatments only necessitated dose adjustments.

During the course of the present five-year study, one case of epidural hematoma developed in conjunction with epidural analgesia. The patient had a previous history of bilateral leg pain and underwent an emergent repair of an abdominal aortic aneurysm. The patient was circulatory stable preoperatively, and therefore had an epidural catheter inserted for postoperative pain relief. Intraoperatively the patient received 5000 units of heparin prior to aortic cross-clamping. Postoperatively, low-molecular weight heparin (enoxaparine, 40 mg, sc, once daily) was started. The patient complained of intermittent leg pain that eventually disappeared. However, pain reappeared with signs of leg weakness and anal sphincter dysfunction. The epidural infusion was stopped on the second postoperative day, and a subsequent MRI-scan demonstrated an epidural hematoma at the Th_{12} level. Due to aggravation of the neurological symptoms following a three-day observation period in the neurosurgical intensive care unit, the patient underwent laminectomy leading to full neurological recovery (49).

The true incidence of neurological dysfunction after hematoma formation associated with epidural anaesthesia has been estimated to be 1/150 000 (50). Since the introduction of low-molecular weight heparin the reported frequency in the United States has been set in the range 1/1000–1/10 000 hematomas following neuraxial blockades (51). This incidence was reported following a higher dosage than is commonly used in Europe. The introduction of national guidelines for regional anaesthesia with lower dosages of low-molecular weight heparins has further reduced the rate of reported epidural hematomas.

One previous report mentions paraplegia associated with disc herniation and epidural analgesia (52). The patient in our study undergoing radical prostectomy with a thoracic epidural catheter placement at Th_{11-12} reported postoperative back pain and paravertebral sensibility disturbances the day after surgery. A MRI-scan revealed a disc herniation at the Th_8 level with a mild compression of the spinal cord. However, this did not fully explain the symptoms, and it was thought that the condition had developed due to the duration of surgery combined with the hyper-extended supine position. The symptoms gradually disappeared without any further treatment and the patient was discharged from the hospital without any sequelae.

In summary, we found that continuous epidural and intravenous analgesia in a large patient population are safe in surgical wards. The present study demonstrates that epidural analgesia results in more efficient pain relief than intravenous morphine. The use of intravenous morphine causes a higher incidence of serious opioid related side-effects compared to epidural analgesia, even though intravenous morphine does not induce the same analgesic effect.

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