Effect of postoperative analgesia on surgical outcome

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Despite improvements in perioperative care, major surgical operations are still followed by sequelae such as pain, organ dysfunction and prolonged convalescence. It has been assumed that sufficient pain relief will improve the surgical outcome with reduced morbidity, need for hospitalization and convalescence, and there is a common consensus that optimal (dynamic) pain relief is a prerequisite for early postoperative recovery. However, in recent years it has been realized that several other factors in perioperative management are important in the control of postoperative recovery and rehabilitation, and that these factors must be considered and revised in order to achieve the advantageous effects of pain relief on outcome.[39] Among the most commonly used pain-relieving techniques [patient-controlled analgesia (PCA) with opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and epidural analgesic techniques], there is evidence that the epidural local anaesthetic or local anaesthetic–opioid techniques are the most effective on providing dynamic pain relief after major surgical procedures.[43 79] This paper reviews data from randomized controlled trials on the effects of these analgesic techniques on postoperative morbidity and hospital stay (with emphasises on epidural analgesia) in order to derive useful conclusions on the relationship between optimal pain relief and postoperative outcome.[39] The effect of peripheral nerve blocks on postoperative morbidity will not be dealt with in this review.

Effect of postoperative pain relief on surgical stress responses

It has been hypothesized that a reduction in the surgical stress responses (endocrine, metabolic and inflammatory) will lead to a reduced incidence of postoperative organ dysfunction and thereby to an improved outcome.[39] As afferent neural stimuli and activation of the autonomic nervous system and other reflexes by pain may serve as a major release mechanism of the endocrine metabolic responses and thus contribute to various organ dysfunctions, pain relief may be a powerful technique to modify surgical stress responses. However, there is a pronounced differential effect of the various postoperative pain-relieving techniques on surgical stress responses (Table 1). Only regional anaesthetic techniques, and preferably continuous techniques with local anaesthetic, may lead to a substantial reduction in the surgical stress response.[40] Thus, several studies investigating lower extremity surgery have shown continuous lumbar epidural local anaesthetic techniques to be most effective, probably because of a more effective afferent blockade. In abdominal procedures, there is a somewhat smaller efficacy of thoracic epidural local anaesthetic techniques in modulating endocrine-metabolic responses, probably due to insufficient afferent blockade as well as the presence of other release mechanisms in eliciting the surgical stress response. The duration of epidural local anaesthetic analgesia is important; it should be at least 24 h and preferably 48 h.[40]

Epidural opioid techniques are less effective on the stress response, and are comparable with systemic opioid techniques and the use of NSAIDs. High-dose opioid anaesthesia suppresses intra- but not postoperative responses.[40] There are insufficient data on the use of multimodal analgesic techniques with combinations of different analgesics. It will be emphasized here that analgesic management predominantly will reduce endocrine metabolic responses[40] and that other techniques, such as minimally invasive surgery and the use of high-dose glucocorticoids, are needed to reduce the inflammatory responses.[39]

Effect of patient-controlled analgesia on postoperative outcome

PCA is widely used for many surgical procedures and is of clear benefit as patient satisfaction is improved,[5] and

Table 1 Effects of analgesic techniques on postoperative surgical stress responses (adapted from reference 40). =no effect; ↓=small effect; ↓↓=moderate effect; ↓↓↓=major effect

Type of analgesia	Endocrine–metabolic responses	Inflammatory responses
Systemic opioid (PCA or intermittent)	↓	
NSAID	↓	↓
Epidural opioid	↓	
Lumbar epidural local anaesthetics (lower extremity surgery)	↓↓↓	
Thoracic epidural local anaesthetics (abdominal surgery)	↓↓	

nursing time somewhat decreased.[10 14] However, PCA will not provide optimal dynamic pain relief after major procedures[38] and a meta-analysis[5] and more recent randomized studies[10 14 16 20 25 44 59] have demonstrated clearly that postoperative morbidity (pulmonary-, cardiac- and thromboembolic complications and hospital stay) is not improved by PCA compared with intermittent opioid therapy. These rather disappointing findings are consistent with the lack of effect of PCA on surgical stress responses and organ dysfunction.[39 40]

Non-steroidal anti-inflammatory agents

NSAIDs are widely used for perioperative pain control but have little effect on surgical stress responses and organ dysfunction.[39 40] On the other hand, it is well established that NSAIDs provide moderate postoperative analgesia and thereby an opioid-sparing effect of 20–30%.[61] This may be of clinical importance as NSAIDs may reduce the incidence of opioid-related side-effects (respiratory depression, sedation, nausea and vomiting, ileus, urinary bladder dysfunction and possibly sleep disturbances). Many randomized, controlled studies of perioperative NSAID treatment have been performed, but they have often included a variety of surgical procedures and a relatively small number of patients, thereby preventing firm conclusions about the clinical implications of opioid-sparing therapy.[42 61] A meta-analysis of these studies has not been performed, but in narrative reviews a significant reduction in opioid-related side-effects has been obtained in only 20–30% of the reported randomized studies with opioid sparing and NSAIDs.[42 61] Future large-scale randomized studies are required in well-defined surgical procedures to quantify the clinically relevant effects of NSAID-induced opioid-sparing on postoperative outcome.

Epidural analgesic techniques

Because continuous epidural local anaesthetic techniques are the most effective in reducing surgical stress responses, autonomic reflex responses and subsequently organ dysfunctions, a substantial reduction in postoperative morbidity may be expected.[23 40 48] Furthermore, they are the most effective method of providing dynamic pain relief after major procedures.[38 79]

However, the literature has been confounded by many misunderstandings in different narrative reviews and meta-analyses. Studies with different types of epidural analgesic techniques have been combined. This is not rational as opioid-based regimens have less or no effect on stress responses and organ dysfunction compared with local anaesthetic-based regimens.[40] Furthermore, a variety of surgical procedures have been included in these studies, which may limit interpretation of the findings as the effects on stress responses and organ dysfunction are less pronounced in major abdominal and thoracic procedures compared with lower body procedures.[40] Thus, the level of epidural blockade is of major importance, in particular the distinction between thoracic and lumbar blockade. Also, definitions of adverse outcomes have varied. Finally, outcome effects have to be distinguished for single-dose and continuous regional anaesthetic/analgesic techniques.

The outcome of intra- and early postoperative analgesia by single-dose regional anaesthetic techniques (epidural and spinal anaesthesia) has been discussed for decades. A recent meta-analysis of all randomized studies,[65] including 141 trials in a total of 9559 patients, concluded that central neuraxial blockade reduces the risk of deep venous thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39%, respiratory depression by 59% and myocardial infarction by 30%. Mortality was reduced by 30%. These positive findings were obtained predominantly after major orthopaedic procedures, whereas no significant effects were found in other procedures (urological, abdominal and thoracic). Because most studies involved single-dose regimens, the data did not allow any conclusions about the effect of continuous regional anaesthetic techniques on postoperative morbidity.[65] In this article, an updated review of the effect on continuous epidural techniques (including local anaesthetics, local anaesthetic–opioid combinations and opioids) compared with opioid techniques as assessed in randomized, controlled studies is presented with respect to postoperative complications/morbidity. The data focus primarily on pulmonary and cardiac complications, postoperative paralytic ileus, thromboembolic and cerebral complications, and hospital stay.

Pulmonary complications

The impairment of pulmonary function observed after all major procedures may contribute to the development of hypoxaemia, atelectases and pneumonia. The superior pain relief provided by thoracic epidural local anaesthetic techniques may therefore be expected to reduce pulmonary morbidity by modifying these responses as well as by reducing opioid requirements. In a meta-analysis from 1998[6] on the effect of epidural versus systemic analgesia in

Table 2 Effects of epidural analgesia on pulmonary complications. We define pulmonary complications as clinically diagnosed pneumonia and/or respiratory failure occurring after recovery from anaesthesia. Respiratory failure is defined as reintubation, not prolonged mechanical ventilation. Respiratory depression, reversible by naloxone, is not considered as respiratory failure but as a side-effect of the analgesia administered. Studies which only evaluated atelectasis, non-specified clinical complications or radiologically diagnosed lung changes are marked [a]. In studies marked [b], a well-defined clinical assessment scale to evaluate pulmonary adverse outcome was developed. However, these scales are not widely accepted clinically and may hinder exact comparison between studies. We counted the number of patients with pneumonia and/or respiratory failure. As several studies count the number of complications and not the number of patients with complications, it cannot be excluded that patients with pneumonia also developed respiratory failure, thus being counted twice. Congruent epidural catheter placement is defined as thoracic placement (epidural catheter placed entirely in the thoracic column) for abdominal and thoracic procedures, and lumbar placement for lower extremity surgery. Because of the established central effects of epidural opioid administration, congruent catheter placement is only relevant when administering epidural local anaesthetics. As the effects of epidural saline are unclear, we have chosen not to include study groups receiving epidural saline in our analysis. Studies in which several types of epidural analgesia were evaluated (against the same control group) are marked [c]. In one study [d], surgery consisted of a mixture of aortic surgery and lower extremity vascular surgery. In one study [e], respiratory failure consisted of a mixture of prolonged ventilation and reintubation, and the incidence of pneumonia was counted together with other major infections, and is therefore not available for analysis. Lower extremity procedures includes vascular surgery (Table 2A). Major abdominal surgery includes colorectal surgery, major upper abdominal procedures, gynaecological surgery and intra-abdominal vascular surgery (Table 2B and C). Major thoracic surgery includes all non-cardiac intrathoracic procedures (Table 2C). LA=local anaesthetic; MX=low-dose local anaesthetic–opioid; OP=opioid. Compiled data are shown with 95% confidence intervals

A. Lower extremity surgery

Reference	Congruent epidural catheter placement	Intra-operative epidural	Postoperative epidural	Pulmonary complications	
				Epidural analgesia	Opioid analgesia
60	Yes	None	LA	1 of 7 patients[a]	3 of 9 patients
15	–	LA	OP	6 of 49 patients[e]	14 of 51 patients

B. Major abdominal surgery

Reference	Congruent epidural catheter placement	Intra-operative epidural	Postoperative epidural	Pulmonary complications	
				Epidural analgesia	Systemic analgesia
Epidural local anaesthetics					
75	Yes	None	LA	2 of 11 patients[a]	7 of 10 patients
60	Yes	None	LA	6 of 13 patients[a]	9 of 11 patients
1	Yes	None	LA	1 of 25 patients	5 of 25 patients
17	Yes	None	LA	0 of 15 patients[a c]	2 of 18 patients
18	Yes	LA	LA	1 of 25 patients	11 of 50 patients
29	Yes	LA	LA	2 of 60 patients	1 of 40 patients
64	No	LA	LA	0 of 24 patients[a]	3 of 24 patients
66	Yes	LA	LA	4 of 45 patients	4 of 35 patients
19	Yes	LA	LA	3 of 25 patients	2 of 25 patients
Epidural local anaesthetic–opioid mixtures					
17	Yes	None	MX	0 of 15 patients[a c]	2 of 18 patients
32	No	LA	MX	9 of 44 patients	14 of 50 patients
76	Yes	LA	MX	0 of 40 patients[d]	5 of 40 patients
36	Yes	LA	MX	21 of 78 patients[b]	23 of 75 patients
22	No	MX	MX	2 of 48 patients	2 of 51 patients
51	Yes	MX	MX	4 of 31 patients[b]	3 of 33 patients
Total EPI-LA/MX vs systemic analgesia (pneumonia and respiratory failure). References 1, 17–19, 22, 29, 32, 36, 51, 66, 76				47 of 451 patients (10.4%, 7.6–13.2%)	74 of 442 patients (16.7%, 13.3–20.2%)
Total EPI-LA/MX vs systemic analgesia with thoracic epidural analgesia (pneumonia and respiratory failure). References 1, 17–19, 29, 36, 51, 66, 76				36 of 329 patients (10.9%, 7.6–14.3%)	54 of 323 patients (16.7%, 12.6–20.8%)
Total EPI-LA/MX vs systemic analgesia (atelectasis and other not well defined pulmonary outcome). References 60, 64, 75				8 of 48 patients (16.7%, 6.1–27.2%)	19 of 45 patients (42.2%, 27.8–56.7%)

C. Major abdominal surgery

Reference	Congruent epidural catheter placement	Intra-operative epidural technique	Postoperative epidural technique	Pulmonary complications	
				Epidural analgesia	Systemic analgesia
67				3 of 14 patients[a]	10 of 15 patients
62	–	LA	OP	1 of 15 patients	6 of 15 patients
17	–	None	OP	0 of 18 patients[a c]	2 of 18 patients
83	–	LA	OP	3 of 28 patients	11 of 25 patients
35	–	LA	OP	19 of 74 patients[b]	15 of 72 patients
45	–	LA	OP	0 of 23 patients	5 of 41 patients
Total EPI-OP vs systemic analgesia (pneumonia and respiratory failure). References 35, 45, 62, 83				23 of 140 patients (16.4%, 10.3–22.6%)	37 of 153 patients (24.2%, 17.4–31.0%)
Total EPI-OP vs systemic analgesia (atelectasis and other not well defined pulmonary outcome). References 17, 67				3 of 32 patients (9.4%, 0.0–19.5%)	12 of 33 patients (36.4%, 20.0–53.0%)

Table 2 *Continued.*

D. Thoracic surgery

Reference	Congruent epidural placement technique	Intraoperative epidural technique	Postoperative epidural technique	Pulmonary complications	
				Epidural analgesia	Systemic analgesia
Epidural local anaesthetic or local anaesthetic–opioid					
49	Yes	LA	LA	1 of 10 patients[a c]	1 of 10 patients
49	Yes	MX	MX	2 of 11 patients[a c]	1 of 10 patients
4	Yes	MX	MX	1 of 25 patients[a]	0 of 25 patients
Total LA/MX vs systemic analgesia				4 of 46 patients (8.7%, 0.5–16.8%)	2 of 25 patients (8.0%, 0–18.6%)
Epidural opioid					
26	–	LA	OP	9 of 83 patients[a]	23 of 80 patients
49	–	OP LA to systemic group	OP	3 of 12 patients[a c]	1 of 10 patients
27	–	None to epidural group	OP	7 of 58 patients[a]	27 of 71 patients
68	–	None	OP	5 of 20 patients[a]	5 of 20 patients
24	– (thoracic)	None	OP	2 of 16 patients[a c]	3 of 16 patients
24	– (lumbar)	None	OP	4 of 16 patients[a c]	3 of 16 patients
74	-	OP	OP	2 of 15 patients[a]	7 of 15 patients
Total EPI–opioid vs systemic analgesia				30 of 205 patients (14.6%, 9.8–19.5%)	66 of 212 patients (31.1%, 24.9–37.4%)

various surgical procedures, epidural local anaesthetics were found to reduce postoperative complications compared with epidural or systemic opioid techniques. Intercostal and intrapleural blockade and wound infiltration with local anaesthetic had no effect on pulmonary outcome.[6] Furthermore, it was demonstrated that surrogate outcome measures, such as pulmonary function, did not correlate with a clinically relevant outcome (pneumonia).[6] However, because of the limited number of studies, no distinction was made in this meta-analysis between the magnitude and location of surgery and the level of epidural blockade. Another factor that may limit the final interpretation of the effect in different operative procedures is the different definitions of pneumonia used in the various studies (see legend of Table 2).

The effects of continuous epidural analgesic techniques on pulmonary morbidity are shown in Table 2. In lower extremity surgery (Table 2A), the limited data do not allow the different epidural techniques to be separated, but overall there is a non-significant reduction from 17 of 60 patients (28.3%) to 7 of 56 patients (12.5%) in pulmonary complications by epidural analgesia compared with systemic opioid analgesia. In major abdominal and vascular surgery (Table 2B), continuous epidural local anaesthetic techniques led to a significant reduction in pulmonary complications from 16.7% to 10.4%. However, when consideration was restricted to studies in which thoracic epidural analgesia was used (which is rational in abdominal procedures), the reduction in pulmonary complications—from 16.7% to 10.9%—was not significant. Similarly, the risk of less well-defined pulmonary complications (atelectasis and others) was reduced insignificantly. Furthermore, there was only a non-significant reduction with the epidural opioid techniques (24.2% to 16.4%) (Table 2C). However, these latter data should be interpreted with caution, as the results have been influenced by the small number of studies. Thus, the study by Yeager and colleagues,[83] which was mainly a study of a continuous postoperative opioid technique, is difficult to interpret as it includes a variety of major procedures with different aetiology. In thoracic (non-cardiac) surgery, most of the epidural studies have involved a postoperative epidural opioid-based regimen, which led to a significant reduction in pulmonary morbidity from 31.1% to 14.6% (Table 2D). However, it should be emphasized that this positive effect was predominantly caused by the results of two studies from the same group.[26 27] No difference in pulmonary outcome was observed in the small number of local anaesthetic trials in thoracic surgery (8.0% versus 8.7%) (Table 2D).

In conclusion, continuous epidural local anaesthetic or local anaesthetic–opioid mixtures have only been demonstrated to provide a reduction in postoperative pulmonary morbidity in major abdominal procedures. Epidural opioid-based regimens also reduced pulmonary morbidity in abdominal (non-significantly) and thoracic procedures (significantly), but these results were largely influenced by a few studies. More work is required to validate these conclusions, as the number of patients studied was very limited and there was considerable variation in pulmonary morbidity in the individual studies. Furthermore, definitions of pulmonary outcome often differed between these studies, which further limits interpretation and a formal meta-analysis.

Cardiac morbidity

Cardiac morbidity is a major cause of perioperative death.[50] Epidural analgesic techniques, which include local anaes-

Table 3 Effects of epidural analgesia on cardiac complications in patients undergoing major non-cardiac surgery and lower extremity vascular surgery. Complications are counted as incidents, not patients. Cardiac complications are defined as heart failure, clinically significant ischaemic events (angina, acute myocardial infarction) and/or arrhythmias. LA=epidural local anaesthetic; MX=epidural low-dose local anaesthetic–opioid; OP=epidural opioid. In one study [a], surgery consisted of a mixture of aortic surgery and lower extremity vascular surgery. In one study [b], the type of arrhythmia was not specified. Lower extremity surgery includes vascular surgery. Major abdominal surgery includes colorectal surgery, major upper abdominal procedures, gynaecological surgery and intra-abdominal vascular surgery. Major thoracic surgery includes all non-cardiac intrathoracic procedures

Reference	Congruent epidural catheter	Intra-operative epidural technique	Postoperative epidural analgesia	Number of cardiac complications with epidural analgesia	Number of cardiac complications with systemic analgesia
Lower extremity procedures					
72	Yes	LA	MX	3 of 26 patients[b]	0 of 25 patients
15	Yes	LA	OP	4 of 49 patients	8 of 51 patients
Major abdominal surgery: epidural local anaesthetic or local anaesthetic–opioid					
28	Yes	LA	LA	5 of 60 patients	5 of 40 patients
19	Yes	LA	LA	8 of 25 patients	7 of 25 patients
32	No	LA	MX	2 of 44 patients	5 of 50 patients
76	Yes	LA	MX	6 of 40 patients[a]	21 of 40 patients
22	No	MX	MX	19 of 48 patients	22 of 51 patients
9	Yes	None	MX	8 of 55 patients	9 of 59 patients
13	Yes	LA	MX	0 of 21 patients	1 of 21 patients
Total EPI-LA/MX vs systemic analgesia.				48 of 293 patients	70 of 286 patients
References 9, 13, 19, 22, 28, 32, 76				(16.4%, 12.1–20.6%)	(24.5%, 19.5–29.5%)
Total EPI-LA/MX vs systemic analgesia with thoracic epidural analgesia.				27 of 201 patients	43 of 185 patients
References 9, 13, 19, 28, 76				(13.4%, 8.7–18.1%)	(23.2%, 17.2–29.3%)
Major abdominal surgery: epidural opioid					
83	–	LA	OP	4 of 28 patients	19 of 25 patients

thetics, may reduce sympathetic responses and have a favourable effect on cardiac outcome.[48] Unfortunately, the effect of postoperative epidural analgesic techniques on cardiac complications is controversial, because of lack of the data from major studies, differences in definitions of cardiac adverse outcomes, the use of different analgesic techniques and the small number of studies investigating high-risk patients.

In lower extremity procedures (Table 3), the only study available has shown a reduction in cardiac complications with epidural opioid.[15] However, intraoperative epidural local anaesthetic was also used, which may have contributed to the reduced risk of myocardial infarction.[65] The data from major abdominal surgery (Table 3) derive mostly from the use of epidural local anaesthetic techniques, while the regimen used in the study by Yeager and colleagues[83] was predominantly based on epidural opioid analgesia (but with intra-operative local anaesthetics). However, this study is controversial as the patient population was not well defined (underlying disease and type of surgery). In another, often-cited study in a high-risk population scheduled for major surgery,[8] the group receiving postoperative epidural opioid analgesia had a lower incidence of ventricular tachycardia than the group receiving systemic opioid analgesia. However, as this study was not randomized, it was excluded from the final data analysis. The epidural regimens based on local anaesthetics led to a non-significant reduction in postoperative cardiac morbidity from 24.5% to 16.4% in major abdominal procedures. When the two studies[22 32] with inappropriate use of lumbar epidural local anaesthetic for abdominal procedures were excluded, the conclusion was not altered (non-significant reduction with thoracic epidural from 23.2% to 13.4%). The two opioid-based epidural regimens in the lower extremity and in mixed surgical procedures also led to a reduction in cardiac morbidity.[15 83] The cumulative data may therefore suggest a clinically relevant reduction in cardiac morbidity, but further data are required from well-defined surgical procedures and patients, preferably including cardiac high-risk patients, in order to reach useful and statistically valid conclusions.

Thromboembolic complications

A recent meta-analysis comparing regional anaesthesia with general anaesthesia showed that the regional anaesthetic techniques reduced postoperative thromboembolic complications and pulmonary embolism.[65] These effects may be mediated by a reduction in intraoperative blood loss, an increase in venous blood flow, decreased coagulability and increased fibrinolysis after epidural or spinal local anaesthetics.[40] As mentioned above, the overall results from the meta-analysis did not differentiate between the effects of single-dose and continuous administration of epidural analgesia. In a specific analysis of randomized studies of continuous epidural analgesic techniques, a significant reduction in thromboembolic complications (assessed by phlebography or iodine–fibrinogen scans) from 62.0% to 28.7% was found in four randomized trials in hip surgery,[21 53–55] knee surgery,[37] prostatectomy[30] and low extremity vascular surgery.[15] All of these studies except one[15] investigated postoperative epidural local anaesthetic techniques. In contrast, five randomized clinical trials in abdominal surgery, also diagnosing thromboembolic com-

Table 4 Randomized, controlled trials in which the effect of epidural analgesia on thromboembolic complications was assessed. For thromboembolic complications, we counted patients with peripheral thrombosis because additional pulmonary embolism was always combined with peripheral thrombosis. In addition, two vascular studies[15 76] were included. We assumed that thromboembolic complications led to regrafting, which was assessed in both studies. One study[76] was a mixture of lower extremity vascular surgery and aortic surgery. In the studies shown in the upper part of the table, well-defined diagnostic procedures were applied to diagnose thromboembolic complications in all patients included in each study. When both fibrinogen scan and phlebography were used to diagnose peripheral thrombosis, the incidence of thrombosis diagnosed by fibrinogen scan was assessed. In the studies shown in the lower part of the table, no specific diagnostic procedures were mentioned or systematically performed in order to diagnose thromboembolic complications. In studies marked [a], the thromboembolic complications were non-symptomatic, or the clinical symptoms (if any) were not described. Number of clinically significant thromboses are shown within parentheses. We counted the number of patients with thromboembolic complications whenever the information was obtainable. However, as several of the above-mentioned complications may have occurred in the same patient and as most of the studies only counted the number of complications, some patients may have been counted twice. In studies marked [b], it was unclear whether all patients underwent these diagnostic procedures. Thromboembolic prophylactic treatment was mentioned inconsistently in the various studies and is not available for comparison

Reference	Intra-operative epidural technique	Postoperative epidural analgesia	Thromboembolic complications	
			Epidural analgesia	Systemic analgesia
Lower extremity surgery: systematically performed diagnostic procedures				
55	LA	LA[a]	5/15	11/15
30	LA	LA	2/17 (0/17)	11/21 (6/21)
54	LA	LA[a]	12/30	23/30
53	LA	LA[a]	21/48	38/46
21	LA	LA[a]	11/26	12/25
37	None	LA	3/17 (0/17)	13/22 (2/22)
15	LA	OP	4/49 (4/49)	22/51 (22/51)
Total lower extremity surgery	58 of 202 patients	130 of 210 patients	(28.7%, 22.5–35.0%)	(62.0%, 55.3–68.5%)
Abdominal procedures: systematically performed diagnostic procedures				
31	LA	LA	4/58 (0/60)	5/40 (2/40)
32	LA	MX[a]	10/29	9/28
28	LA	MX[a b]	2/30	7/40
52	LA	LA/OP[a]	8/21	9/24
62	LA	OP	0/15 (0/15)	3/15 (0/15)
Total abdominal surgery	24 of 153 patients	33 of 147 patients	(15.7%, 9.9–21.4%)	(22.4%, 15.7–29.2%)
Abdominal procedures: no systematically performed diagnostic procedures				
17	LA	LA	0/15	0/18
11	LA	LA	0/57	1/59
66	LA	LA	2/45	0/45
17	LA	MX	0/15	0/18
76	LA	MX	1/40	9/40
13	LA	MX	0/21	1/21
17	LA	OP	0/18	0/18
Thoracic surgery: no systematically performed diagnostic procedures				
49	LA	LA	0/10	0/10
49	MX	MX	0/11	0/10
49	OP	OP	0/12	0/10
Total			3 of 244 patients (1.3%, 0–2.6%)	11 of 193 patients (5.7%, 2.4–9.0%)

plications by phlebography or iodine–fibrinogen scans, found a non-significant reduction (from 22.4% to 15.7%) when systemic opioid analgesia was compared with epidural analgesic regimens. In three of these five studies[28 31 32] an epidural local anaesthetic regimen was used. Furthermore, in six randomized, controlled trials with no specific criteria for diagnosis of thromboembolic complications in major abdominal and thoracic surgery (Table 4), there was no significant difference in the incidence of thromboembolic complications (epidural analgesia 1.3%, systemic analgesia 5.7%). The discrepancy between the findings for abdominal surgery and those for lower body procedures in thromboembolic complications, with or without epidural analgesia, may be explained by the smaller effect on lower extremity blood flow, blood loss and coagulation and fibrinolysis with thoracic epidural analgesia.[40] It should be emphasized that in only one[13] of the abdominal studies was there specific emphasis on active mobilization facilitated by the improved analgesia provided by the epidural technique.

In conclusion, continuous epidural local anaesthetic reduces the risk of thromboembolic complications after lower body procedures (as observed with single-dose regional anaesthesia with local anaesthetics), whereas no significant positive effects have been observed with continuous thoracic epidural local anaesthetics after major abdominal procedures.

Gastrointestinal complications (paralytic ileus)

Postoperative paralytic ileus (PI) may last for days and prolong hospitalization and convalescence.[34] The main pathogenic factor of PI is activation of inhibitory splanchnic reflexes, which are subject to modification by thoracic

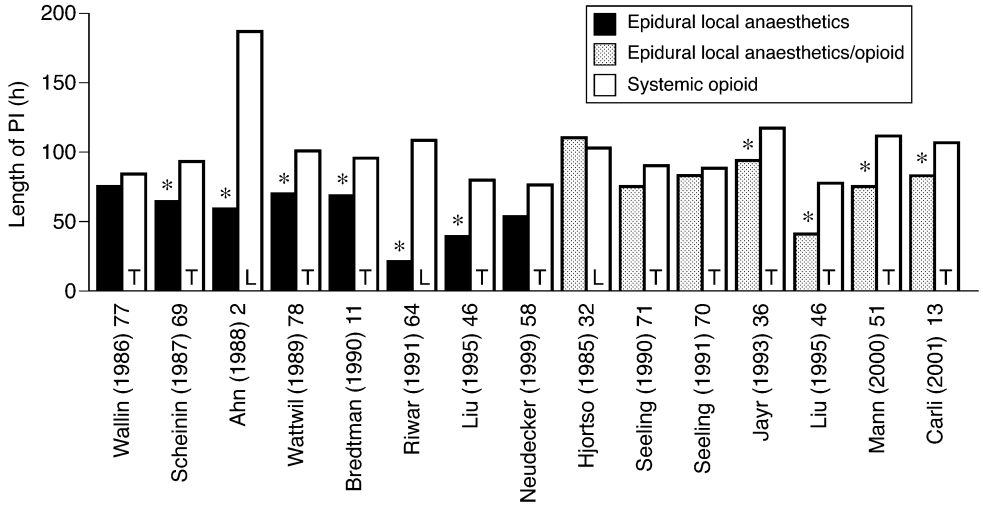

Fig 1 Effects of postoperative epidural local anaesthetic or local anaesthetic–opioid mixtures on duration of postoperative ileus (PI) in abdominal procedures. Indicators of PI are ranked in descending order (bowel movements>flatus) if more than one indicator was assessed in a study. T= thoracic epidural; L=lumbar epidural.

epidural local anaesthetics.[34 48] Accordingly, six of eight randomized clinical trials demonstrated that continuous thoracic epidural local anaesthetics reduced PI (Fig. 1).[2 11 46 58 64 69 77 78] In the two negative studies,[58 77] lack of effect was probably due to their small size, too short duration of block (24 h), or low epidural catheter insertion. In two of the three studies with inappropriate use of lumbar epidural analgesia for abdominal surgery,[2 32 64] a significant reduction in postoperative ileus was nevertheless demonstrated. When epidural local anaesthetic–opioid mixtures were compared with systemic opioid analgesia, an ileus-reducing effect was also seen in four of seven studies (Fig. 1).[13 32 36 46 51 70 71] In contrast, randomized studies have not demonstrated any reduction in ileus with an epidural opioid technique.[34]

In summary, postoperative continuous thoracic epidural local anaesthetic techniques significantly reduce PI. This effect may have major clinical implications, as it may allow early enteral nutrition, which has been demonstrated to reduce postoperative morbidity.[39] However, with a few exceptions,[13 46 58] the ileus-reducing effect of epidural local anaesthetics was not utilized to allow early oral nutrition or mobilization in these studies. There has been discussion about whether the increased gastrointestinal motility associated with epidural local anaesthetics may pose a risk to the integrity of an intestinal anastomosis. However, no risk has been demonstrated in an analysis of anastomotic dehiscence after colonic surgery using data from all published randomized studies.[33]

Postoperative cognitive dysfunction

Postoperative cognitive dysfunction occurs in up to 20% of patients after major non-cardiac surgery and may persist in about 10% of patients 3 months after surgery.[57] The pathogenesis of postoperative cognitive dysfunction is unclear and probably multifactorial, including postoperative hypoxaemia, sleep disturbances and the use of opioids and tranquillizers. In a meta-analysis of all randomized studies comparing regional anaesthesia with general anaesthesia, no effect was found on postoperative cognitive dysfunction.[65] However, most of the studies used single-dose regional anaesthesia.

Five randomized, controlled clinical trials have examined the role of continuous postoperative epidural analgesia versus systemic opioid-based analgesia.[3 51 63 72 81] In all these studies, epidural analgesia was administered intraoperatively as an adjunct to general anaesthesia. In the largest study, in 262 patients undergoing knee surgery,[81] postoperative analgesia was not adequately standardized or described, which prevented further analysis. However, no differences were demonstrated between epidural analgesia and systemic analgesia. After prostatectomy[3] and hip surgery,[63] continuous epidural analgesia with local anaesthetic had no effect on cognitive dysfunction. Furthermore, in 51 patients undergoing knee replacement surgery, no difference in the incidence of acute delirium was found between the group receiving epidural local anaesthetic–-opioid mixture and the systemic opioid group.[72] In contrast, a recent study investigating epidural low-dose bupivacaine–morphine demonstrated improved postoperative cognitive function, measured in a limited number of assessments in elderly patients after major abdominal surgery.[51]

In conclusion, the effect of postoperative continuous epidural analgesic on cognitive dysfunction is unclear. Further studies are required that also control for other pathogenic factors, such as concomitant medication, sleep disturbances and early mobilization.

Mobilization and hospital stay

The effects of epidural analgesia on postoperative mobilization have been investigated only sporadically, usually with a negative result. In one study, epidural opioid analgesia improved mobilization in obese patients undergoing gastroplasty.[62] The data from the use of continuous epidural local anaesthetic techniques in major orthopaedic procedures are controversial. Although one study demonstrated limited improvement in rehabilitation after knee replacement, hospital stay was not improved.[80] However, postoperative analgesia was not standardized in this study, although most patients randomized to epidural anaesthesia also received postoperative epidural analgesia. In one study,[12] the stay in the rehabilitation centre was reduced after continuous epidural analgesia, but the length of stay was substantial (about 40 days in total), which is different from common practice in most studies. In another study in knee and hip surgery, no difference was found in hours of daily mobilization between epidural local anaesthetic–opioid mixture and systemic opioid.[56] Furthermore, low-dose local anaesthetic–opioid epidural analgesia did not result in any improvement in rehabilitation measures in 51 patients scheduled for knee replacement surgery.[72]

The effect of epidural analgesic techniques on postoperative hospital stay, as a general indication of morbidity and mobilization is shown in Table 5. It appears that the improved pain relief given by epidural analgesic techniques (local anaesthetics, local anaesthetic–opioid mixtures, opioids alone) has no significant effect on hospital stay. These findings differ from the demonstrated positive effects in some procedures on paralytic ileus, pulmonary, cardiac and thromboembolic outcome after the use of epidural analgesia. However, as discussed below, it should be emphasized that hospital stay may be a poor outcome measure as it depends on many factors other than pain relief (e.g. use of drains, catheters, traditions, restrictions, reimbursement policy). The effect of improved pain relief by epidural analgesia may be obtunded by such factors.[39] This is supported by the finding that discharge criteria were obtained earlier in patients receiving epidural analgesia[46] but were not translated into a shorter hospital stay. Also, other studies have shown a discrepancy between achievement of discharge criteria and actual hospital stay.[47 82] Therefore, in order to demonstrate a potential reduction in hospital stay by the more costly continuous epidural analgesic techniques, the improved pain relief has to be integrated into a multimodal rehabilitation programme.[39]

Table 5 Effects of epidural analgesia on hospital stay in days. Lower extremity surgery includes vascular surgery, hip surgery and knee surgery. Major abdominal surgery includes colorectal surgery, major upper abdominal procedures, gynaecological surgery and intra-abdominal vascular surgery. Major thoracic surgery includes all major non-cardiac thoracic procedures. LA=epidural local anaesthetic; MX=epidural low-dose local anaesthetic–opioid; OP=epidural opioid. Studies in which several types of epidural analgesia were evaluated (against the same control group) are marked [a]. In one study [b], surgery consisted of a mixture of aortic surgery and lower extremity vascular surgery. In one study [c], hospital stay was reported separately for the two subgroups of the study: knee (first line) and hip surgery (second line). *P<0.05 in the individual study

Reference	Epidural analgesia			Systemic analgesia
	LA	MX	OP	
Lower extremity procedures and prostatectomy				
60	4, 7			8, 9
82	19			22
56		12[c]		13
56		9[c]		9
15			9	10
Major abdominal surgery				
Epidural local anaesthetics or local anaesthetic–opioid mixture				
60	4.8			5, 8
78	7.7			7.4
11	19.9			18.9
64	13.5			14.5
19	16			16
46	4.2[a]			5,1
58	10			8
71		19		18
76		10.7[b]		11.7
70		19		19
36		18		16
46		8.3[a]		5.1
9		16.3		13.9
51		10.5		11.5
13		8.5		7.3
Total LA/MX vs systemic analgesia		12.4 days		12.4 days
Epidural opioid				
62			7.1*	9.0
83			11.4*	15.8
46			5.4[a]	5.1
Major thoracic surgery				
4		9.5		11.1
73			9.9	9.6
24			11.1[a] * (thoracic group)	15.6
24			14.4[a] * (lumbar group)	15.6
74			15.5	17.1

Integration of postoperative pain relief and rehabilitation

In recent years, postoperative pain treatment has been optimized, especially after introduction of acute pain services. Furthermore, extensive data have demonstrated beneficial physiological effects of efficient analgesia on several organ systems. It is therefore surprising and somewhat disappointing that the overall effect of pain-relieving techniques on postoperative morbidity has so far been rather small or non-demonstrable by statistical analysis. There are several explanations for this. First, most studies have been small, with insignificant power (small number of patients and outcome) to demonstrate advantageous effects. Secondly, it is unlikely that a unimodal treatment (effective pain relief) for a complex problem such as perioperative morbidity will provide major improvements in outcome. Instead, a multimodal effort has been proposed to include effective control of postoperative pain, thereby allowing early mobilization and enforcement of an

early oral feeding programme, together with the stress-reducing effect of regional anaesthetic techniques.[39] Also, improved information for the patient well in advance of surgery is necessary.

Although the concept of multimodal postoperative rehabilitation seems rational and simple, progress has been slow.[39 41] The most plausible explanation is that a successful multimodal rehabilitation programme requires the reorganization of peri-operative care, with increased collaboration between the patient, anaesthetist (acute pain service), surgical nurse and surgeon. Furthermore, major efforts must be made for educational programmes, with emphasis on peri-operative pathophysiology, as well as a revision of traditional postoperative care programmes with drains, gastrointestinal tubes, catheters, restrictions, etc. So far, preliminary experience from a variety of surgical procedures has shown such a collaborative effort to be extremely successful in reducing hospital stay and morbidity.[7 39 41] To improve the rate of progress and to quantify the potential advantageous effects of analgesic techniques on postoperative outcome, a detailed analysis must be made of the various factors that may limit early recovery after each individual procedure, and be responsible for hospitalization on a given day. A key factor in the success of a multimodal rehabilitation programme is the development of daily nurse care programmes with an emphasis on rehabilitation[7] and the expansion of the traditional acute pain service into a collaborative effort in functional recovery.

In summary, postoperative pain relief continues to demand our attention, but further progress is needed if we are to optimize functional (dynamic) pain relief and to demonstrate clinically significant advantages of pain relief for surgical outcome. The concept of a multimodal postoperative rehabilitation programme in which pain relief is a key factor is a major task for the future. However, such efforts will undoubtedly lead to major improvements in outcome, provided that perioperative care is adjusted to derive the benefits of the physiological effects of good pain relief.

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