Recent Advances in Postoperative Pain Therapy for Thoracic Surgery

Torsten Loop · Stephen Harris · Alexander Grimm

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Abstract The efficient and potent treatment of pain accompanied with thoracic surgery is fundamental and beneficial for patients, since severe postoperative pulmonary complications and the incidence of chronic pain will be reduced. In this systematic review evidence-based strategies in preventing and treating pain after thoracic surgery will be discussed.

Keywords Analgesia · Thoracic surgery · Thoracotomy · Epidural

Introduction

Post-thoracotomy pain is frequent and associated with considerable complications [1, 2]. Severe postoperative pain in general impairs postoperative patient mobilization, increases perioperative morbidity, and potentially triggers a chronic pain syndrome with an incidence, dependent on the analgesic regimen, ranging from 21 to 61 % [3–5]. Post-thoracotomy pain in particular will adversely affect pulmonary function by impairing deep breathing and effective coughing, resulting in retention of secretions, atelectasis, and pneumonia [6]. Despite these findings, the impact and the functional relevance of aggressive, optimized analgesia on patient outcome remain unclear [7•].

However, various studies support the evidence that effective, perioperative analgesia reduces postoperative pulmonary complications [6]. Multiple systemic and

regional analgesic techniques (i.e., intercostal nerve block, thoracic paravertebral block, interpleural block, epidural blocks with local anesthetics with and without opioids) effectively control post-thoracotomy pain [7•]. Thoracic epidural analgesia (TEA) is commonly considered the “gold standard” for postoperative pain treatment after thoracotomy, but this method is not suitable for all patients and may be associated with numerous risks (e.g., dural perforation, spinal cord damage by formation of hematoma, infection and abscess, hypotension, urine retention) [7•, 8•, 9]. Alternatively, thoracic paravertebral nerve block (TPVB) produces unilateral analgesia over several thoracic segments and has been shown to provide effective post-thoracotomy pain control [7•, 8•, 10•, 11–13]. TPVB was as effective as TEA in controlling post-thoracotomy pain and associated with fewer hemodynamic side effects [8•, 13].

The aim of this systematic review is to evaluate available evidence-based studies comparing various regional and systemic analgesic techniques for the management of post-thoracotomy pain.

Methods

A systematic literature search was performed utilizing PubMed (www.ncbi.nlm.nih.gov/pubmed) to formulate evidence-based recommendations for pain management specific for thoracic surgery (see Fig. 1). Between 1966 and 2013, the following search terms were included: pain, analgesia, anesthesia, anesthetic, epidural, neuraxial, spinal, caudal, intrathecal, paravertebral block, intrapleural block, intercostal block, and procedures such as lobectomy, pneumonectomy, thoracic surgery, thoracotomy, and post-thoracotomy. Study inclusion criteria of the Cochrane Collaboration (www.cochrane.de) were used. Two hundred

T. Loop (✉) · S. Harris · A. Grimm
Department of Anesthesiology and Critical Care Medicine,
University Medical Center, Freiburg, Hugstetter Strasse 55,
79106 Freiburg, Germany
e-mail: torsten.loop@uniklinik-freiburg.de

Fig. 1 Flow chart of the systematic literature research

thirty-three clinical studies were identified and analyzed for this review.

Systematic reviews seek to collect all evidence that fits pre-specified eligibility criteria in order to address a specific research question and aim to minimize bias by using explicit, systematic methods. Recommendations for an intervention (i.e., analgesic therapy) are classified by the balance of risk versus benefit of the service and the level of evidence on which this information is based. A ‘level A’ recommendation means good scientific evidence, suggesting that the benefits of the clinical intervention substantially outweigh potential risks. In contrast, ‘level D’ means that scientific evidence is lacking, of poor quality, or conflicting, such that the risk/benefit balance cannot be assessed. These facts result in a ranking system classifying the recommendations in I (evidence from meta-analysis of randomized controlled trials) to V (evidence from a panel of experts) (see Table 1; www.cebm.net).

Only studies with the highest quality (level A) criteria were included, and recommendations are formulated in italic type.

Analgesic Strategies and Concepts

Despite various definitions and controversial debates, the effective and optimal perioperative analgesic strategy leading to reductions in pain and/or analgesic use after thoracic surgery is a preemptive and multimodal approach [4, 14–17].

Systemic Analgesia

Non-opioids and opioids are the classic drugs in pain therapy and are a valid alternative or supplement to regional procedures with local anesthetics for a patient controlled analgesia. Pain relief with opioids in thoracic surgery patients may be associated with a higher incidence of postoperative pulmonary complications, such as

pneumonia or respiratory depression [18]. Nevertheless, opioids are an integral part of a multimodal approach and management of acute perioperative pain associated with thoracic surgery [7•, 19, 20].

Non-opioids such as selective and traditional non-steroid anti-inflammatory drugs (sNSAID or tNSAID) reduce the demand for opioids and the incidence of postoperative pulmonary complications [21, 22]. The application and dosage of NSAIDs must strictly follow the recommendations, because the analgesic effect is limited, and higher doses may induce cardiac, renal, hemostatic, and gastrointestinal side effects [23]. The perioperative use of acetaminophen during major surgery is able to reduce the opioid demand, even if thoracotomy-specific evidence is still lacking [24–31]. Perioperative analgesic therapy with sNSAIDs remains controversial [32, 33]. Data obtained from a clinical study in thoracic surgery patients revealed improved analgesia without increased cardiovascular risk after parecoxib, valdecoxib, or celecoxib application compared to control patients [33, 34]. The application of sNSAIDs targeting analgesia in thoracic surgery patients must be judged according to the individual risk profile of the patient [35].

Potentially, the risk of complications is less with acetaminophen medication (20 of 100 million applications) compared to acetylsalicylic acid (aspirin) (185 of 100 million applications) or diclofenac (592 of 100 million applications) [36].

It should be mentioned that the anti-proliferative and anti-inflammatory effects of NSAIDs reduce the efficacy of surgical pleurodesis [37]. Postoperatively, thoracotomy-associated ipsilateral shoulder pain can be effectively treated with NSAIDs [38, 39].

Based on meta-analysis and analogous to data from other major surgeries, the intraoperative use of ketamine may have an additional analgesic effect, independent of the opioid and ketamine dosage used and time of application [40–42].

Based on systematic meta-analysis and level A studies, a multimodal approach of analgesia concerning the systemic

Table 1 Levels of evidence (www.cebm.net)

Level 1A	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	1a SR (with homogeneity*) of RCTs SR (with homogeneity*) of inception cohort studies; CDRT validated in different populations SR (with homogeneity*) of Level 1 diagnostic studies; CDRT with 1b studies from different clinical centres SR (with homogeneity*) of prospective cohort studies SR (with homogeneity*) of Level 1 economic studies
Level 1b	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual RCT (with narrow Confidence Interval†) Individual inception cohort study with > 80% follow-up; CDRT validated in single population Validating** cohort study with good††† reference standards; or CDRT tested within one clinical centre Prospective cohort study with good follow-up**** Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
Level 1c	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	All or none§ All or none case series Absolute SpPins and SnNouts†† All or none case-series Absolute better-value or worse-value analyses ††††
Level 2a	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	SR (with homogeneity*) of cohort studies SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs SR (with homogeneity*) of Level >2 diagnostic studies SR (with homogeneity*) of 2b and better studies SR (with homogeneity*) of Level >2 economic studies
Level 2b	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual cohort study (including low quality RCT; e.g., <80% followup) Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDRT or validated on split sample §§§ only Exploratory** cohort study with good††† reference standards; CDRT after derivation, or validated only on split-sample§§§ or databases Retrospective cohort study, or poor follow-up Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
Level 2c	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	"Outcomes" Research; Ecological studies "Outcomes" Research Ecological studies Audit or outcomes research
Level 3a	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	SR (with homogeneity*) of case-control studies SR (with homogeneity*) of 3b and better studies SR (with homogeneity*) of 3b and better studies SR (with homogeneity*) of 3b And better studies
Level 3b	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Individual Case-Control Study Non-consecutive study; or without consistently applied reference standards Non-consecutive cohort study, or very limited population Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses Incorporating clinically sensible variations.
Level 4	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Case-series (and poor quality cohort and casecontrol studies§§) Case-series (and poor quality prognostic cohort studies***) Case-control study, poor or nonindependent reference standard Case-series or superseded reference standards Analysis with no sensitivity analysis
Level 5	Therapy/Prevention, Aetiology/Harm Prognosis Diagnosis Differential diag/symptom prevalence Economic and decision analyses	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles" Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

For definitions of terms used, see the glossary at www.cebm.net/?o=1116. From OCEBM Levels of Evidence Working Group*. "The Oxford Levels of Evidence 2." Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>. *OCEBM Levels of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard, and Mary Hodgkinson

application of non-opioids (i.e., NSAIDs) in combination with regional neuroaxial analgesia (i.e., TEA, PVB) improves analgesia and pain relief after open thoracic surgery [7•, 43–45] (grade A).

Regional Analgesia

Thoracic Epidural Analgesia

TEA is currently considered the 'gold standard' regarding analgesia for open thoracic surgery [46, 47]. A recommendation with the highest level of evidence was

implemented in the guidelines for the treatment of acute perioperative and post-traumatic pain published by the German task force of scientific medical societies (AWMF registry no. 041/001; www.awmf.de). TEA is indicated for middle and major thoracic surgery and should, assuming no contraindications, be initiated preoperatively at thoracic segments Th₄–Th₇ [48, 49•]. Typically, a combination of local anesthetics (bupivacaine or ropivacaine) with a lipophilic opioid (fentanyl or sufentanil) should be used pre- and intraoperatively [2, 7•, 50, 51]. The combination resulted in both dose reduction and fewer side effects. Which concentration and dose of local anesthetic and

opioid are optimal? The effectiveness of epidural application of bupivacaine 0.1 % combined with fentanyl 5 µg/ml has been proved to be effective in pain relief [52]. The established combination of ropivacaine supplemented with sufentanil should be used in a 0.2 % concentration plus 0.5–0.75 µg/ml opioid, respectively [49, 53–56]. The epidural application of hydrophilic opioids such as morphine cannot be recommended because of its poor controllability [57]. The postoperative duration of TEA therapy will take 3–4 days and can be terminated after removal of the thoracic drains. Postoperatively, epidural infusion of low-dose local anesthetic (bupivacaine 0.5–1 mg/ml or ropivacaine 1–2 mg/ml) should be combined with a lipophilic opioid (5 µg/ml fentanyl or 0.5 µg/ml sufentanil).

TEA: Clinical Outcome and Side Effects

Although TEA offers substantial advantages such as lower incidence of complications compared to systemic analgesia with parenteral opioids, its effect on outcome is still unclear [20, 58, 59, 60].

A retrospective analysis of 1,200 patients demonstrated a reduction of mortality and complications for TEA when pulmonary risk factors were present (i.e., chronic obstructive pulmonary disease) [61]. A prospective, randomized, clinical trial showed a lower rate of postoperative pulmonary complications (6.6 vs. 35 %) in 60 thoracic surgery patients with a ‘fast-track’ concept (with TEA) compared to conventional management [6]. Subgroup analysis demonstrated a greater benefit for patients with pulmonary comorbidity [6]. Regarding technical, medical, or other reasons, thoracic epidural catheter placement may possibly be unsuccessful or associated with complications such as hypotension and/or urinary retention [62]. Even though severe complications are rare with TEA treatment, it is not without controversy because the potential, serious

consequences for the patients are fatal. The overall incidence of complications due to TEA is 3.1 % (estimated in 4,185 patients) [63]. In 1.1 % of the patients, placing the TEA catheter was not technically possible. Dura perforation, radicular pain, and nerve injury emerged in 0.7 % [63]. The risk of spinal compression due to epidural hematoma or intraspinal abscess formation was 0.02 % (1:4,741) or 0.014 % (1:7,142), respectively [64]. Horlocker et al. [65–68] published the incidence of epidural hematoma after implementation or removal of TEA catheters with a calculated risk at 1:150,000, which may be increased in patients with impaired blood clotting or medication with anticoagulants up to 1:3,000. The prevalence of epidural abscess formation seems very low despite bacterial colonization of the catheter [69, 70]. Epidural medication-associated side effects such as nausea, vomitus, pruritus, hypotension, urinary retention, and sedation are frequent [71].

Beyond the analgesic effect, TEA features several physiological effects on the cardiorespiratory and gastrointestinal tract, which may have a beneficial effect on rehabilitation after thoracic surgery due to the modulation of the neuroendocrine and stress response [72]. Positive biological effects include improvement of left ventricular function, reduction of cardiovascular complications, enhanced bowel function, favorable properties on blood clotting, and postoperative immune function and inflammation [72]. Perioperative TEA increases respiratory minute and tidal volume, lowers pulmonary vascular resistance, and reduces the incidence of atelectasis and pneumonia [73].

Based on a multitude of grade-I studies and one systematic meta-analysis (see Table 2), we can recommend TEA as the first choice for analgesia during thoracic surgery with high pain intensity (evidence level A). TEA should be started before the skin incision (evidence level A), and a local anesthetic with or without a lipophilic opioid should be continuously infused (evidence level A).

Table 2 TEA and thoracic surgery

Author	Number of patients	Therapy	Control	Analgesia
Senard et al. [33]	N = 40	TEA + celecoxib	TEA	Therapy group +
Ali et al. [74]	N = 60	TEA	i.v. Opioid (PCA)	TEA group ++
Mendola et al. [75]	N = 150	TEA	Various LA concentrations	All concentrations effective
De Cosmo et al. [56]	N = 54	TEA with R	TEA with B	Both effective
Behera et al. [76]	N = 30	TEA	i.v. Opioid	TEA group ++
Weber et al. [77]	N = 40	TEA	i.v. Opioid (PCA)	TEA group ++
De Cosmo et al. [78]	N = 72	TEA (B 0.126 %)	TEA (B 0.06 %)	TEA B 0.125 % ++
Bauer et al. [79]	N = 68	TEA	i.v. Opioid (PCA)	TEA group ++
Tuncel et al. [54]	N = 62	TEA + sufentanil	TEA	TEA + sufentanil ++
Wu et al. [46]	10 studies	TEA	i.v. Opioid (PCA)	TEA group ++

TEA thoracic epidural analgesia, PCA patient-controlled analgesia, LA local anesthetics, R ropivacaine, B bupivacaine

Fig. 2 Photographs of thoracic paravertebral blockade in a patient. Place the patient in the sitting position. Widely prepare and drape the targeted thoracic segments using sterile technique

Thoracic Paravertebral Analgesia

An alternative method of pain control that has gained increasing popularity is TPVB, pioneered by Hugo Sellheim in 1905. As with TEA, local anesthetics are injected into a pain-conducting anatomic region, the thoracic paravertebral space, directly or continuously through a catheter. The local anesthetic is injected close to the thoracic vertebra close to the spinal nerves emerging from the intervertebral foramina. The vertical diffusion lateral to the vertebral column results in ipsilateral somatic and sympathetic nerve block in multiple thoracic dermatomes [12, 80•, 81, 82]. To perform this technique, the needle (18-G Tuohy) is walked off the superior edge of the transverse process 2.5 cm lateral to the Proc. spinosus and advanced slowly until loss of resistance to saline is observed (see Fig. 2). Advancement of the needle into the paravertebral space above the transverse process makes introduction of the catheter easier as compared to inferior placement because the needle/catheter angle is less steep. The catheter is introduced through the needle and advanced approximately 3 cm into the paravertebral space. After gentle aspiration, a test dose of 3 ml of local anesthetic with or without adrenalin is administered. Thoracic paravertebral blockade (TPVB) is induced with a bolus dose followed by continuous paravertebral application of local anesthetics [82]. In patients with a body mass index 25 or above, the distance between the skin and paravertebral space varies considerably [83]. Unfortunately, the catheter placement in these cases resulted in frequent misplacement into the epidural space or toward the prevertebral region [84]. Following a nerve-stimulated or ultrasound-guided approach to position the catheter in the paravertebral space may be an alternative and can be accomplished by the classic method (i.e., parallel to the spinal processes), an intercostal approach, or a proximal lateral approach (i.e., perpendicular to the spinal processes; see Fig. 2) [84, 85•, 86]. The number of segments to be anesthetized correlates in a linear approximation to the volume of infused local anesthetics and maximal dose adapted to bodyweight [87].

For example, blocking segments Th₃–Th₇ (necessary for thoracotomy), 30 ml local anesthetic is required for an 80-kg patient at height [87].

Thoracic paravertebral nerve block (TPVB) produces unilateral analgesia over several thoracic segments and has been shown to provide effective post-thoracotomy pain control [7•, 8•, 10•, 11–13]. Compared to TEA, significant value and final conclusions related to analgesia after thoracic surgery are not stated clearly [8•, 13, 88]. A meta-analysis from Davies et al. [13] compared TEA and TPVB on the basis of ten randomized, non-blinded studies including 520 patients. The limitations of this study are the differences in doses and combination of infused drugs, TPVB technique, method of postoperative analgesia, and primary endpoint for TEA and TPVB. In four of ten studies (254 patients), a combination of local anesthetics and opioids was infused in the TEA group, in the TPVB group only one study (50 patients) [13]. This favors the quality of TEA-based analgesia. The meta-analysis-based calculation could not demonstrate a significant advantage. Furthermore, TPVB was associated with a lower failure rate and lower incidence of pulmonary complications apart from other side effects (nausea, vomitus, hypotension, urinary retention) [13]. Another meta-analysis included 20 studies with 800 patients demonstrating that TPVB provided better analgesia than TEA when higher doses of local anesthetics (>1 g bupivacaine/24 h) were used preoperatively and infused continuously afterwards [89]. A prospective cohort study in 312 patients after pneumonectomy demonstrated a higher incidence of postoperative complications in TEA [8] (Table 3; Fig. 3).

Based on a multitude of grade-I studies, the TPVB can be recommended as an alternative to TEA for thoracic surgery with expected high levels of pain intensity (evidence level A).

Intrathecal Opioids

The effectiveness of a single injection of an opioid into the subarachnoid space is a long-established but infrequently used analgesic technique in thoracic surgery [92–94].

Table 3 Comparison of TPVB and TEA [7•, 10•, 11, 13, 83, 85•, 86, 87, 89–91]

	TPVB	TEA
Blockade	unilateral	bilateral
Quality of analgesia	++	++
Hemodynamic stability	+	–
Success rate	>90 %	>90 %
Indication range	++	+
Complication rate	2.6–5 %	<0.1 %

Predominantly, subarachnoidal formulated morphine (100–1,000 µg) and sufentanil (<25 µg) have been used for this purpose [94]. To date, a low number of studies published an effective pain relief during thoracic surgery but

often lacked an evidence-based design [92, 95]. A study in cardiac surgery patients demonstrated effective analgesia after subarachnoidal application of morphine 7 µg/kg [96]. An intrathecal combination of morphine (200 µg) and sufentanil (20 µg) induced sudden analgesia for 24 h [93]. The incidence of postoperative respiratory complications may increase dose dependently, requiring a sufficient and prolonged monitoring [94, 97, 98].

Based on the various findings, a prospective randomized clinical study compares TEA with the combination of TPVB and intrathecal opioids for postoperative pain control in patients undergoing open lung resection [99]. The TEA provided statistically better acute pain relief after open thoracotomy than a combination of TPVB and intrathecal opioid administration. However, as the

Fig. 3 Pain algorithm for thoracic surgery (modified from www.postoppain.org)

differences in pain scores between the groups were small and of questionable clinical relevance, the results indicate that combined TPV and intrathecal opioid administration is a satisfactory alternative for post-thoracotomy pain relief [99].

Based on these grade-II studies with a low number of included patients, only level C evidence can be recommended for the intrathecal application of opioids for pain relief during thoracic surgery.

Intercostal Nerve Blockade

Intercostal nerve blockade can be performed preoperatively percutaneously from outside the chest or intraoperatively by the surgeon under direct vision from inside the chest before thoracotomy closure or even postoperatively. The blocks are administered just below a rib in the region of the intercostal bundle, carefully avoiding intravascular injection. It is important for the efficacy to perform the nerve blockade dorsally to the mid-axillary line to include the proximal skin branch of the intercostal nerve. Injection of local anesthetic should be performed on multiple intercostal nerves (3–5 ml each) with a thin needle (22 G or 25 G) [100]. The use of ropivacaine with or without adrenaline offers advantages because of its lower toxicity [101]. The intercostal nerve blockade offers sufficient analgesia during video-assisted thoracoscopy [100]. The pre-, intra-, and postoperative intercostal block with bupivacaine reduces the morphine demand by 20 % but produces no comparable postoperative pain relief like TEA [102–107].

Based on the data of these grade-II studies, the perioperative intercostal nerve blockade seems significantly less effective compared to TEA in thoracic surgery but may be reconsidered in the event of contraindications to neuroaxial regional analgesia (evidence level C) [7••].

Conclusions

Post-thoracotomy pain in particular will adversely affect pulmonary function by impairing deep breathing and effective coughing, resulting in retention of secretions, atelectasis, and pneumonia. Furthermore, pain accompanying thoracic surgery without a substantial decrease postoperatively may persist for months or years (i.e., chronic or long-term pain syndrome) [1]. Analgesia in thoracic surgery should be multimodal. This systematic review comes to the conclusion and recommendation that the use of either TEA or TPVB provides effective analgesia for thoracic surgery. TPVB reduces the incidence of pulmonary complications and hypotension. TEA is superior to intrathecal and intercostal techniques.

Key Messages

- Effective and optimal analgesia for major thoracic surgery should be multimodal.
- Based on grade-I studies, the level A recommendation favors a combination of systemic non-opioids and opioids with a central regional technique for pain relief during thoracic surgery.
- Opioid-based parenteral analgesia increases postoperative complications.
- Thoracic epidural analgesia is the ‘gold standard’ for analgesia in patients undergoing major open thoracic surgical procedures.
- The epidural infusion of local anesthetics should start preoperatively and be maintained continuously with or without a lipophilic opioid.
- Thoracic epidural analgesia has a lower postoperative complication rate compared to systemic parenteral opioid-based analgesia.
- Thoracic epidural analgesia provides several positive physiologic effects on the cardiorespiratory system and gastrointestinal tract, which may have a beneficial effect on postoperative rehabilitation due to the modulation of the neuroendocrine and stress response.
- Multiple segmental TPVB is an effective analgesic concept for major thoracic surgery.
- TPVB can be recommended as an alternative technique for pain relief in thoracic surgery.
- The application of intrathecal opioids or intercostal nerve blockade for thoracic analgesia can only be recommended at a lower level of evidence.

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Compliance with Ethics Guidelines

Conflict of Interest Torsten Loop, Stephen Harris, and Alexander Grimm declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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