Original Investigation

Analgesia After Open Abdominal Surgery in the Setting of Enhanced Recovery Surgery
A Systematic Review and Meta-analysis

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IMPORTANCE The optimal analgesic technique following open abdominal surgery within an enhanced recovery protocol remains controversial. Thoracic epidural is often recommended; however, its role is increasingly being challenged and alternative techniques are being suggested as suitable replacements.

OBJECTIVE To determine by meta-analysis whether epidurals are superior to alternative analgesic techniques following open abdominal surgery within an enhanced recovery setting in terms of postoperative morbidity and other markers of recovery.

DATA SOURCES A literature search was performed of EMBASE, Medline, PubMed, and the Cochrane databases from 1966 through May 2013.

STUDY SELECTION All randomized clinical trials comparing epidurals with an alternative analgesic technique following open abdominal surgery within an enhanced recovery protocol were included.

DATA EXTRACTION AND SYNTHESIS All studies were assessed by 2 independent reviewers. Study quality was assessed using the Cochrane bias assessment tool and the Jadad and Chalmers modified bias risk assessment tools. Dichotomous data were analyzed by random or fixed-effects odds ratios. Qualitative analysis was performed where appropriate

RESULTS Seven trials with a total of 378 patients were identified. No significant difference in complication rate was detected between epidurals and alternative analgesic methods (odds ratio, 1.14; 95% CI, 0.49-2.64; $P = .76$). Subgroup analysis showed fewer complications in the patient-controlled analgesia group compared with epidural analgesia (odds ratio, 1.97; 95% CI, 1.10-3.53; $P = .02$). Following qualitative assessment, epidural analgesia was associated with faster return of gut function and reduced pain scores; however, no difference was observed in length of stay.

CONCLUSIONS AND RELEVANCE Epidurals may be associated with superior pain control but this does not translate into improved recovery or reduced morbidity when compared with alternative analgesic techniques when used within an enhanced recovery protocol.

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Enhanced recovery after surgery (ERAS) protocols have become increasingly popular over the past decade. Randomized clinical trials, and subsequently meta-analyses, have demonstrated their success in a number of fields of surgery in terms of reduction in mortality, morbidity, and hospital length of stay (LOS).[1]

Enhanced recovery protocols are multifaceted clinical pathways that consist of preoperative, perioperative, and postoperative components of care aimed at expediting recovery, attenuating the stress response to surgery, and promoting patient motivation.[2] A key constituent of ERAS care is perioperative and postoperative analgesia. Poorly controlled pain is associated with poor mobility, prolonged hospital stay, and increased complication rates.[3]

The optimum modality for postoperative analgesia remains under debate. Thoracic epidural analgesia is often advocated as the gold-standard analgesic technique for ERAS care.[4-6] However, high failure rates,[7] epidural hematoma risk,[8] increased hypotension, and excessive intravenous fluid administration[9] associated with epidural use have highlighted the need to consider alternative techniques, and the role of routine epidural within ERAS has been questioned.[10]

Increasing research has focused on alternative methods of analgesia including continuous wound infiltration (CWI), intrathecal analgesia, and nerve blocks. These methods have been shown to be effective analgesics when compared with placebo and epidural analgesia.[11-14]

Therefore, this study reviewed the literature pertaining to all analgesic techniques in the setting of an enhanced recovery protocol following all open abdominal surgery to establish the effect of analgesic modality on recovery.

Methods

This study was conducted according to the PRISMA guidelines for meta-analysis conduct.[15] The protocol was registered prospectively on the PROSPERO database for meta-analyses (registration No. CRD42013004496). A literature search was performed independently by 2 researchers of EMBASE, Medline, PubMed, and the Cochrane databases in May 2013.

The databases were searched from 1966 through 2013 with the following terms: *enhanced recovery*, *fast track*, *ERAS* and *abdominal surgery*, *general surgery*, *vascular surgery*, *urology*, *gynaecology*, *upper abdominal surgery*, *upper GI surgery*, *oesophagogastric*, *colorectal*, *lower GI*, *pancreas*, *liver*, *hepatobiliary*, *hpb*, *laparotomy*, *subcostal* and *pain relief*, *analgesia*, *IV morphine*, *opiates*, *opioids*, *patient controlled analgesia*, *PCA*, *epidural*, *regional anaesthesia*, *neuraxial blockade*, *wound catheter*, *on-q*, *wound infiltration*, *spinal*, *intrathecal*, *transversus abdominis*, and *tap block*.

All abstracts were reviewed for relevance. Relevant full-text articles were subsequently reviewed.

Inclusion and Exclusion Criteria

All randomized clinical trials were included that compared epidurals with an alternative form of analgesia within a specified enhanced recovery protocol. It was required that the protocol be clearly stated and for it to contain at least 4 items of care considered to be contributory to an enhanced recovery program.[16] The inclusion criteria for the comparator group included all other types of analgesia.

The exclusion criteria included laparoscopic surgery, nonrandomized trials, children aged 16 years and younger, nonstandard intergroup care pathway, and nonabdominal surgery.

Quality Review and Data Extraction

All studies included in the final analysis were assessed by 2 independent reviewers. Study quality was assessed using the Cochrane bias assessment tool and the Jadad and Chalmers modified bias-risk assessment tools.[17,18]

Data were extracted directly from the articles or, if this was not possible, the authors were contacted using the published correspondence details. If no response was obtained, a follow-up email or telephone call was conducted.

Primary and Secondary Outcomes

The primary outcome was occurrence of any complication occurring within 30 days postoperatively. All reported complication types were included. Adverse effects, such as pruritus and nausea, were not included but hypotension was.

The following markers of satisfactory recovery were assessed as secondary outcomes: LOS; time to the achievement of functional recovery; time to independent mobility; resumption of diet; and time until first bowel motion/flatus. Numerical pain scores (0-100 mm, 100 being worst pain imaginable) were also assessed. Subgroup analysis was performed according to the analgesic modality and for distinct systematic complications: pulmonary, cardiovascular, and ileus.

Statistical Analysis

The meta-analysis was performed using a review manager (RevMan version 5.2; The Nordic Cochrane Centre). Dichotomous data were analyzed by random or fixed-effects odds ratios (ORs). Heterogeneity was assessed by using I^2 and χ^2 and adjudged to be significant if I^2 was greater than 50% and/or $P < .05$. Statistical significance was set at $P < .05$. When continuous quantitative data were not distributed normally, meta-analysis was not performed and a qualitative assessment was used.

Results

Study Characteristics

Details of the literature search are outlined in the PRISMA diagram shown in **Figure 1**. Seven randomized clinical trials, with a total of 378 patients, met the inclusion criteria for the meta-analysis (**Table 1**).[19-25] All trials were assessed for bias risk (**Table 2**).

The details of the trial settings and analgesic techniques used are summarized in Table 1. Four studies compared epidural with patient-controlled systemic opiates (PCA).[19-22] Three studies compared epidurals with CWI.[23-25] All study patients were adults and had American Society of Anesthesiologists scores less than 4. The study dates were from 2001

to 2013. Patients were excluded for morbid obesity, chronic analgesic use, and contraindications to either epidural or the alternative method of analgesia. The components of each enhanced recovery program used are shown in the eTable in the Supplement.

Categorical data were extracted from the articles directly for the meta-analysis. Continuous data were reported as being nonparametric in multiple instances and so transformation of the original data would be required to allow a meta-analysis to be performed. Therefore, all authors were contacted to obtain the original data set. However, 3 of the authors[19,20,25] were noncontactable and 2 of the authors[21,22] reported that the data were no longer available. Therefore, where nonparametric data were reported, it was elected to take a qualitative approach to the analysis.

Composite Outcome of Occurrence of Any Complication Within 30 Days Postoperatively

All 7 studies[19-25] reported complication rates, giving a total of 378 patients. There was significant heterogeneity between these studies (I^2 = 65%; P < .001). There was no significant difference in the incidence of all complications between epidural analgesia and the alternative analgesic modalities (OR, 1.14; 95% CI, 0.49-2.64; P = .76) (**Figure 2**). Subgroup analysis showed fewer complications in the PCA group compared with the epidural analgesia group (I^2 = 67%; OR, 1.97; 95% CI, 1.10-3.53; P = .02).[19-22] Subgroup analysis comparing CWI with epidurals[23-25] showed no significant difference between these 2 modalities (I^2 = 60%; OR, 0.61; 95% CI, 0.19-1.95; P = .41).

Individual Complication Type

No significant difference in the incidence of pulmonary complications (I^2 = 0%; OR, 1.92; 95% CI, 0.64-5.77; P = .25),[19,20,23-25] cardiac complications (I^2 = 0%; OR, 0.83; 95% CI, 0.32-2.18; P = .70),[23,24] or ileus (I^2 = 0%; OR, 0.75; 95% CI, 0.27-2.06; P = .57)[19,20,22,23] was detected between the 2 comparator groups. Furthermore, no differences in the occurrence of venous thromboembolism (I^2 = 3%; OR, 0.95; 95% CI, 0.13-6.87; P = .96), anastomotic leak (I^2 = 0%; OR, 1.06; 95% CI, 0.19-6.04; P = .95), or confusion (I^2 = 0%; OR, 1.80; 95% CI, 0.41-7.96; P = .44) were observed.

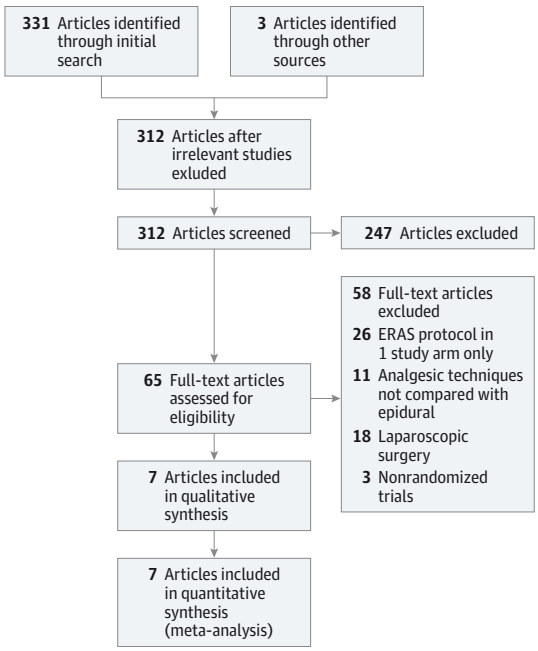
Qualitative Analysis

Given the likelihood of a skewed distribution of data presented and the absence of complete raw data sets on which to perform log transformation of data, a qualitative assessment was performed for the following outcomes.

Length of Stay and Functional Recovery

Of the 7 studies that assessed LOS,[19-25] only Jouve et al[25] showed a significant difference between the modalities (epidural: median, 4 days; interquartile range, 3.8-5.0 days; CWI: median, 5.8 days; interquartile range, 4.5-7.0 days; P = .006). Of the 3 studies that specifically reported on time to fulfil discharge criteria rather than length of hospital stay,[19,20,23] 2 studies[19,20] reported significantly shorter times in the epidural groups and 1 study[23] reported a significantly shorter time to recovery in the nonepidural (CWI) group.

Figure 1. PRISMA Diagram of Epidural and Alternative Analgesic Technique Studies



Gut Function

Four studies[19-21,25] measured time to passage of flatus. Three of these[19,21,25] showed a significantly reduced time to pass flatus in patients receiving epidural and Carli et al[20] showed that a greater proportion of patients (66%) in the epidural group had passed flatus by 48 hours compared with 27% in the PCA group (P < .01).

Six of the studies assessed time to passage of stool. Four of these[19-21,25] showed a significantly reduced time to passage of stool for the epidural group. The remaining 2 studies[22,24] did not show a significant difference in time.

Only 1 study[24] assessed time to first fluid intake postoperatively and this was significantly faster for the nonepidural (CWI) group (mean [SD], 1.768 [1.26] hours vs 1.24 [0.475] hours; P = .04).

Two studies assessed time to first solid food.[24,25] Renghi et al[24] showed no significant difference and Jouve et al[25] showed a faster time in the epidural group. Two of the studies[19,20] assessed calorie and protein intake but did not find a significant difference in the groups when multiple comparisons were taken into consideration.

Pain Scores

All 7 studies assessed pain scores.[19-25] All but Renghi et al[24] and Zutshi et al[22] reported reduced pain scores in the epidural group compared with the alternative method at 24 hours at rest. Lower pain scores were also reported in the epidural groups at 24 hours on movement, 48 hours at rest, and 48 hours on movement in all but 1 study.[24]

Ambulation

Five of the 7 studies assessed postoperative mobility.[19-21,23,24] There was heterogeneity in the particular aspect of mobility

Table 1. Study Characteristics

Source	Type of Study	Operation	No. of Patients (Epidural/ Alternative)	Epidural Content	Protocol	Continuous Infusion, Yes/No	Length of Time In Situ	Alternative	Protocol
Carli et al,[19] 2001	RCT	Open colorectal surgery	21/21	Bupivacaine, 0.1%, and fentanyl, 2 μg/mL	4-14 mL/h	Yes, plus bolus as required	Up to 4 d	IV PCA morphine	Dose administered until VAS score <50 achieved; up to 4 d
Carli et al,[20] 2002	RCT	Open colorectal surgery	32/32	Bupivicaine, 0.1%, and fentanyl, 2 μg/mL	4-15 mL/h	Yes	Up to 4 d	IV PCA morphine	1-2 mg every 5 min; continued until POD 3-4
Steinberg et al,[21] 2002	RCT	Open colon surgery	20/21	Ropivacaine, 2 mg/mL, and fentanyl, 2 μg/mL at 8 mL/h	8 mL/h	Yes	Until adequate pain control with oral analgesics was met (or a maximum of 6 d)	IV PCA morphine	2-3 mg every 3-5 min until verbal pain score below 50/100 achieved; continued until adequate pain control with oral analgesics was met (or a maximum of 6 d)
Zutshi et al,[22] 2005	RCT	Open intestinal surgery	30/31	Bupivacaine and fentanyl; concentration NS	NS	Yes, with supplemental 2-4 mL patient-controlled bolus (15-min lockout)	Until morning or second postoperative day	IV PCA morphine	NS: 48 h
Revie et al,[23] 2012	RCT	Open hepatic surgery	31/33	Bupivacaine, 0.1%, and fentanyl, 2 μg/mL	7-10 mL/h	Yes	48 h	CWI and IV PCA morphine	Levobupivacaine, 0.375%, 4 mL/h, in transversus abdominis plane and postrectus sheath with 20-mL block of bupivacaine, 0.25%, for 48 h
Renghi et al,[24] 2013	RCT	Abdominal aortic surgery	29/30	Levobupivacaine, 0.25%	4 mL/h	Yes	48 h	CWI	Preoperative fascial 20 mL; levobupivacaine, 0.5%, followed by subfascial and subcutaneous double limbed catheter with levobupivacaine, 0.25%, infusion for 48 h
Jouve et al,[25] 2013	RCT	Open colorectal surgery	24/26	Ropivacaine, 0.2%, and sufentanil, 0.25 μg/mL	5 mL/h and 5-mL bolus at 15-min lockout	Yes	48 h	CWI, IV PCA morphine, and droperidol	Ropivacaine, 0.2%, 10 mL, then 10-mL/h infusion between closed parietal peritoneum and transversalis fascia for 48 h

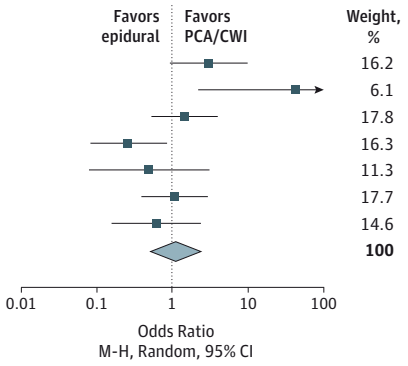
Abbreviations: CWI, continuous wound infiltration; IV, intravenous; NS, not specified; PCA, patient-controlled analgesia; POD, postoperative day; RCT, randomized clinical trial; VAS, visual analogue scale.

Table 2. Bias-Risk Assessment

Source	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Blinding of Outcome Assessments (Detection Bias)	Incomplete Outcomes Data (Attrition Bias)	Selective Reporting (Reporting Bias)	Other Bias	Jadad and Chalmers
Carli et al,[19] 2001	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk	10
Carli et al,[20] 2002	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk	Low risk	9
Steinberg et al,[21] 2002	Unclear risk	Unclear risk	High risk	High risk	High risk	Low risk	High risk	10
Zutshi et al,[22] 2005	Unclear risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	11
Revie et al,[23] 2012	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	High risk	13
Renghi et al,[24] 2013	Low risk	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	15
Jouve et al,[25] 2013	Low risk	Low risk	Unclear risk	High risk	Low risk	Low risk	High risk	15

Figure 2. Forest Plot Showing All Complications Within 30 Days of Surgery in Epidural and Nonepidural Groups

Study	Epidural Events	Epidural Total	PCA/CWI Events	PCA/CWI Total	Odds Ratio M-H, Random, 95% CI	Weight, %
Zutshi et al,[22] 2005	12	28	6	31	3.13 (0.98-10.01)	16.2
Steinberg et al,[21] 2002	10	20	0	21	43.00 (2.29-806.44)	6.1
Revie et al,[23] 2012	18	31	16	33	1.47 (0.55-3.95)	17.8
Renghi et al,[24] 2013	15	29	24	30	0.27 (0.08-0.85)	16.3
Jouve et al,[25] 2013	2	24	4	26	0.50 (0.08-3.02)	11.3
Carli et al,[20] 2002	14	32	13	31	1.08 (0.40-2.92)	17.7
Carli et al,[19] 2001	5	21	7	21	0.63 (0.16-2.42)	14.6
Total		**185**		**193**	**1.14 (0.49-2.64)**	**100**
Total events	76		70			
Heterogeneity: Tau^2=0.77; χ^2_6=16.94 (P<.001); I^2=65%						
Test for overall effect: z=0.31 (P=.76)						



CWI indicates continuous wound infiltration; M-H, Mantel-Haenszel; PCA, patient-controlled analgesia.

that was assessed, with time to standing,[21,24] number of steps taken,[23] and time spent mobilizing[19,20] all being assessed. However, none of the studies reported a significant difference in any of the assessments apart from Revie et al[23] who described a greater number of steps being taken by the nonepidural (CWI) group compared with the epidural group.

Discussion

This systematic review and meta-analysis represents a comparison between epidurals and alternative analgesic regimens within the context of enhanced recovery protocols following major open abdominal surgery. We found no advantage for the use of epidurals over any other form of analgesic regimen in terms of overall complication rate, systemic complication rate, and length of hospital stay. Epidurals were superior in terms of pain scores and return of gut function but not rates of ileus. However, trials of this type were limited in number and size.

It is acknowledged that the small numbers included in the current review do not eliminate a type II error. However, of the 7 trials reporting complication rates, only Steinberg et al[21] reported any significant difference, namely increased hypotension rates in the epidural group. Moreover, subgroup analysis showed significantly fewer complications when PCA alone was compared with epidurals. These results suggest that the potential effect of the combined postoperative recovery components has a greater effect on recovery than the individual analgesic technique used.

The use of epidurals has been advocated when providing an enhanced recovery protocol and being responsible for minimizing morbidity following major abdominal surgery.[4-6] The analysis presented here is in conflict with the large body of evidence that is often used as proof supporting the recommendations of epidurals within enhanced recovery protocols. This includes the large meta-analyses from Rodgers et al,[26] Beattie et al,[27] and Ballantyne et al[28] that showed reductions in mortality and morbidity in patients receiving epidurals compared with postoperative systemic morphine.

However, these meta-analyses include data from 1998 and earlier and trials of thoracic, vascular, and orthopedic procedures that are not all directly applicable to open abdominal surgery. Similarly, the postoperative recoveries from the included trials within these reviews did not use current multimodal enhanced recovery protocols where included care components of early mobilization,[29] minimization of intravenous fluid administration,[30] deep vein thrombosis prophylaxis,[31] and early enteral feeding[32] have all been shown to be associated with improved postoperative outcomes and are routinely incorporated into ERAS protocols.

However, this review did illustrate the greater pain scores achieved by epidurals over the alternative techniques when providing pain relief. Epidurals have consistently been shown by current evidence to deliver good pain relief compared with intravenous PCA[33] and comparable or better pain relief vs CWI.[12]

However, in the context of enhanced recovery protocols where complications and LOS are key outcomes, merely looking at pain scores and opiate consumption does not provide all the information that is required by the clinician to make a sound choice. It is well documented that inadequate pain control results in increased postoperative complications, prolonged LOS, and reduced mobility.[3] However, the results of this review show inferior analgesic capabilities of the alternative methods compared with epidurals but this did not translate into prolonged LOS or higher morbidity rates. Therefore, it is important to distinguish between inadequate pain relief and pain scores that are statistically inferior to an alternative within a trial. Providing pain scores are mild, statistically significant differences in pain scores do not necessarily translate into a clinical hindrance to prompt recovery within an enhanced recovery protocol. Therefore, assessment of functional outcomes provides more informative results.

This review showed a faster time to the return of bowel functioning with epidurals; however, no difference in ileus rates was observed. Traditionally, epidurals are associated with a faster postoperative return of gut function and reduced ileus[33] owing to their morphine-sparing qualities. However, again, this evidence is from studies not using enhanced recovery proto-

cols where ileus-avoiding practice, such as fluid overload avoidance[34] and bowel stimulation, is advocated.[35]

On a cautionary note, our analysis has shown that despite the increased presence of nausea and vomiting, as well as prolonged time for bowel function to return, this did not impact on hospital LOS or rates of ileus. Only 3 of the trials commented on readmission rates. Enhanced recovery protocols can result in higher readmission rates[36] and this must always be considered when judging the success of a protocol.

Length of stay was also not affected by analgesic type. Marret et al[37] performed a meta-analysis comparing outcomes between patients receiving epidurals or intravenous PCA morphine for undergoing colorectal surgery and concluded that, overall, epidural was associated with reduced LOS. However, a subgroup analysis concluded that the LOS in patients involved in a postoperative rehabilitation program was not improved by epidural use. This again supports the supposition that it is the multimodal components of enhanced recovery protocols combined that have the effect on recovery rather than one isolated factor.

However, it is increasingly recognized that LOS is multifactorial and not a clean assessment of a patient's recovery,[38] and functional recovery is advocated as a more accurate measure of recovery.[16] Only 3 of the trials assessed this outcome,[19,20,23] and future studies assessing the success of enhanced recovery should base their primary outcomes on the achievement of functional recovery.

None of the studies assessed the effect of each modality on the ability to attenuate the stress and inflammatory response to surgery. Enhanced recovery protocols are focused on this component and epidurals have been shown to be beneficial in the reduction in the stress response.[39,40] In the likely outcome that epidurals and alternate techniques demonstrate equipoise in a number of key areas of recovery, it may be that this is a major factor in determining the efficacy of either modality, should a difference be reliably demonstrated.

The drawbacks to this study were as follows. First, the inclusion of 3 different operation types and, therefore, the comparison of 3 different incisions and recovery pathways, weakened the effects of the comparison, although they do all reflect open abdominal surgery, the principles of recovery from which are broadly comparable. Second, the inclusion of all forms of alternatives to epidurals again reflects a lack of homogeneity and ability to compare trials. However, ultimately, the nonepidural groups consisted of either systemic opiate or wound catheter with systemic opiate. Also, the epidural protocols used by the trials varied. However, the aim of the analysis was to assess the importance of epidurals in general within enhanced recovery protocols and so a lack of superiority over an alternative type of analgesic technique allows us to consider that epidurals are no longer a routine choice in enhanced recovery protocols for open abdominal surgery. Third, one feature of our literature search was the paucity of randomized clinical trials comparing 2 analgesic modalities within the context of an enhanced recovery setting. This had potential implications on the power of the analysis to detect significant differences in outcomes and exclude a type II error, particularly in specific complication rates. However, the current review represents the best available evidence and highlights a significant implication for future research.

Conclusions

Current evidence comparing analgesic techniques within an ERAS protocol is limited. However, when considering an analgesic technique following open abdominal surgery within an enhanced recovery protocol, in contrast to previous research, no obvious advantage is illustrated by the current evidence base when using an epidural in terms of complication rate and LOS. Further research is mandated to confirm the optimum analgesic technique in this setting.

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Study concept and design: Hughes, Ventham, McNally, Wigmore.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Hughes, Ventham, Wigmore.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Hughes, Ventham, Harrison.
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Study supervision: McNally, Wigmore.

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