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ORIGINAL ARTICLE

Impact of analgesic modality on stress response following laparoscopic colorectal surgery: a post-hoc analysis of a randomised controlled trial

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Abstract
Background Epidural analgesia is perceived to modulate the stress response after open surgery. This study aimed to explore the feasibility and impact of measuring the stress response attenuation by post-operative analgesic modalities following laparoscopic colorectal surgery within an enhanced recovery after surgery (ERAS) protocol.
Methods Data were collected as part of a double-blinded randomised controlled pilot trial at two UK sites. Patients undergoing elective laparoscopic colorectal resection were randomised to receive either thoracic epidural analgesia (TEA) or continuous local anaesthetic infusion to the extraction site via wound infusion catheter (WIC) post-operatively. The aim of this study was to measure the stress response to the analgesic modality by measuring peripheral venous blood samples analysed for serum concentrations of insulin, cortisol, epinephrine and interleukin-6 at induction of anaesthesia, at 3, 6, 12 and 24 h after the start of operation. Secondary endpoints included mean pain score in the first 48 h, length of hospital stay, post-operative complications and 30-day re-admission rates.
Results There was a difference between the TEA and WIC groups that varies across time. In the TEA group, there was significant but transient reduced level of serum epinephrine and a higher level of insulin at 3 and 6 h. In the WIC, there was a significant reduction of interleukin-6 values, especially at 12 h. There was no significant difference observed in the other endpoints.
Conclusions There is a significant transient attenuating effect of TEA on stress response following laparoscopic colorectal surgery and within ERAS as expressed by serum epinephrine and insulin levels. Continuous wound infusion with local anaesthetic, however, attenuates cytokine response as expressed by interleukin-6.

Keywords Colorectal surgery · Epidural analgesia · Laparoscopy · Physiological stress response

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Introduction

The stress response to surgery initiates a cascade of neuroendocrine, metabolic and inflammatory responses that result in protein catabolism, increased cardiovascular demands, impaired pulmonary function and the potential to develop paralytic ileus [1–5].

Two major innovations that have been introduced to colorectal surgery over the past two decades aim to attenuate the surgical stress response: enhanced recovery after surgery (ERAS) programmes and laparoscopic surgery. Evidence robustly confirms that both innovations reduce stress response resulting in improving clinical endpoints such as a reduced length of hospital stay and improved short-term post-operative outcomes [6–11].

One of the mechanisms of reducing the stress response in ERAS has been attributed to the use of thoracic epidural analgesia (TEA) [12]. By attenuating the stress response, epidural anaesthesia may contribute to a reduction in post-

operative pain and an altered immunological response to surgery that may produce additional benefits [13–18]. It is widely perceived that epidural analgesia alters the stress response after open surgery reducing cardiovascular and infectious complications [19, 20]. These findings, however, were mostly made in the context of using epidural analgesia in open surgery, and it is unclear whether all aspects of the ERAS programme were fully implemented in these studies.

Alternatives to epidural analgesia are available which may be equally effective for providing post-operative pain management and have a fewer risks with equivalent analgesic properties [21]. The use of wound infusion catheters (WIC) as an alternative or adjunct has been investigated finding it to be an effective approach to post-operative pain control reducing morphine consumption and accelerating post-operative recovery [22–25]. The true impact of epidural analgesia upon the stress response with laparoscopy within a fully implemented ERAS programme has yet to be evaluated. A feasibility trial was undertaken to evaluate whether a main trial of epidural versus WIC was feasible [26].

The aim of this study was to explore the feasibility and impact of measuring the stress response attenuation by epidural analgesia following laparoscopic colorectal resection within an ERAS programme.

Materials and methods

Study design and population

Data were collected within the "EWIC" (Epidural vs. WIC) blinded pilot randomised controlled trial (RCT) comparing TEA and continuous wound infusion of local anaesthetic for post-operative analgesia following laparoscopic colorectal surgery [26]. The current study was nested within this population but specifically designed to investigate the stress response to analgesic modalities. Patients were recruited between April 2010 and May 2011 from two UK centres: Yeovil District Hospital and St Mark's Hospital, London. Patients undergoing elective laparoscopic resection for benign or malignant tumours of the colon or upper rectum were randomised to receive either TEA or continuous wound infusion via a WIC for 48 h within an ERAS protocol. The trial methodology has been described in detail in the original trial publication [26].

The anaesthetic protocol including analgesic modalities dictated that after induction of general anaesthesia, patients allocated to receive TEA had an epidural catheter inserted in the T9–10 or T10–11 interspace using the standard technique. After a test dose of 2 ml of 5 mg/ml (0.5 %) levobupivacaine (Chirocaine; Abbott Laboratories, Maidenhead, UK), a total dose of 1 ml/10 kg of 5 mg/ml levobupivacaine was given. Cardiovascular parameters were monitored and managed in the usual way. After 1 h, an infusion of 1.25 mg/ml (0.125 %) levobupivacaine with 2 mcg/ml of Fentanyl (Auden McKenzie (Pharma Division) Ltd, Ruislip, UK) was started at a rate of 4 mls/h. Additional boluses of epidural solution were given as judged necessary by the anaesthetist. Post-operatively the epidural analgesia was monitored by the pain team and aimed for a flow rate between 4 and 8 ml/h to achieve adequate analgesic coverage of the operative site, maintaining a dermatomal level below T4.

The wound infusion protocol required that at the end of the procedure, the peritoneum was closed and the WIC (ON-Q® PainBuster®, B-Braun, Melsungen AG, Hospital Care, 34209 Melsungen, Germany) inserted into the pre-peritoneal space using an introducer needle, according to manufacturer guidelines. The abdominal wall was closed in a standard manner, and the catheter then flushed with saline to check patency. A bolus of 20 ml local anaesthetic was administered prior to the catheter being attached to the ON-Q pump provided by pharmacy, and unclamped before the patient left theatre.

During the formal trial consenting process, patients were asked whether they would consent to blood tests to evaluate biochemical markers of the stress response after surgery.

The trial was approved by the UK South West 2 Research Ethics Committee (ref 09/H0206/66) and was locally approved by recruiting centres.

Randomisation and blinding

Patients were randomised in parallel to receive post-operative analgesia by either TEA or WIC for the first 48 h after their surgery (Fig. 1). Pharmacy staff in each centre determined allocation using a pre-prepared randomisation schedule using permuted blocks of variable size, and the anaesthetic department was informed by email.

To facilitate blinding of the study, details of treatment allocation were not revealed to the patient, research nurse, research fellow or surgeon. To achieve double blinding, "double dummy" administration technique was used. Analysis of the blood samples for stress response measurement in this study was performed in a blinded fashion. The anaesthetist and ward nursing staff were aware of allocation to ensure appropriate and safe administration of drugs and monitoring of TEA. The elastomeric pumps for the wound infusion were prepared with either levobupivacaine (Chirocaine; Abbott Laboratories, Maidenhead,

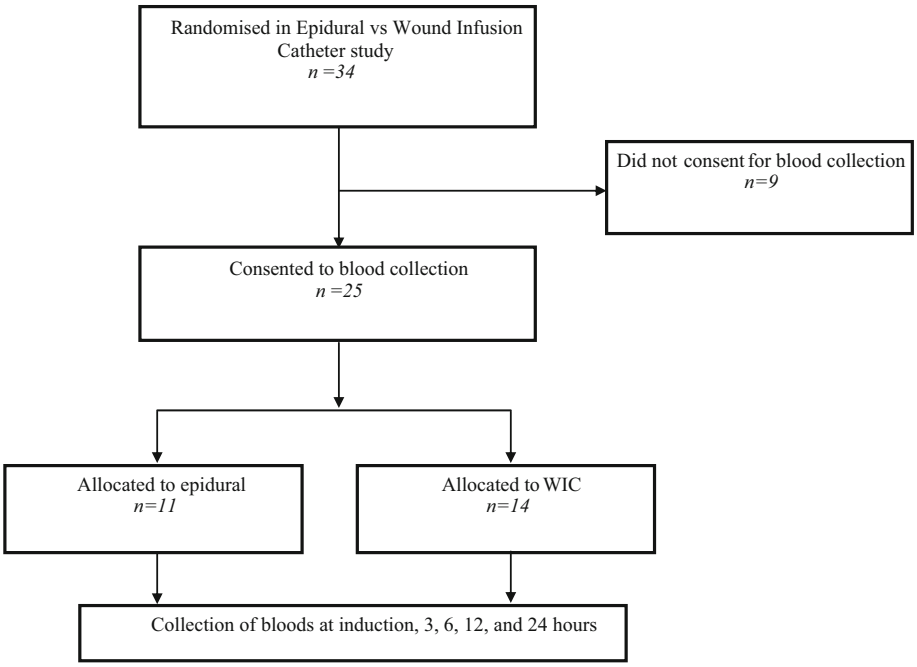

Fig. 1 Consort diagram showing enrolment of patients into stress response study

UK) local anaesthetic or saline placebo, as appropriate, on the morning of surgery.

Study procedures

Standardised anaesthetic and operative protocols were followed, which were both described in detail previously [26]. Both groups were treated according to a standardised ERAS protocol [27] and were routinely reviewed by the pain team during their post-operative stay.

Blood sample collection and biochemical assays

Peripheral venous blood samples were taken prior to induction of anaesthesia (baseline) and then at 3, 6, 12 and 24 h after the start of operation, defined as knife-to-skin time. These assessed the cascade of neuroendocrine, metabolic and inflammatory response after surgery testing serum insulin, cortisol, epinephrine and interleukin-6. Samples were obtained by an anaesthetist or research fellow using a vacutainer needle system (BD Vacutainer System; Beckton, Dickinson and Company, Oxford, UK) or a 20-ml syringe and needle. Epinephrine samples were collected in Lithium Heparin vacutainer tubes; 2 ml of plasma was separated into labelled daughter tubes within 1 h of collection and frozen at −20 °C. Cortisol samples were allowed to clot in an SST tube prior to centrifugation; 1 ml of serum was separated into labelled daughter tubes within 1 h of collection and frozen at −20 °C. Samples for insulin and interleukin-6 were both collected in separate Lithium Heparin vacutainer tubes; 0.5 ml of plasma was separated into labelled daughter tubes within 1 h of collection and frozen at −20 °C.

The samples were transported immediately to the laboratory for separation and freezing and prepared within an hour, according to the trial protocol.

Samples were handled at the research site according to protocol requirements and stored at −20 or −70 °C. Samples were transported in batches to Epsom and St. Helier University Hospital (Epsom, UK) where they were tested for serum concentration of epinephrine, cortisol, insulin and interleukin-6. A standard testing method was used, and the machine was calibrated according to the required standards. Normal values for the machines used were provided by Epsom and St. Helier University Hospital laboratory.

Outcome measures

The primary outcome of this study was to assess the serum stress response markers from the blood samples; other outcome measures included the mean pain score for the first 2 days post-operatively as measured by Memorial Pain Assessment Card [28]; amount of rescue analgesia as measured by equivalent to intravenous morphine in case of failure of TEA or WIC; length of hospital stay; and complications and 30-day readmission rate.

Sample size and statistical analyses

Formal power calculation was not undertaken as the original study was designed to investigate the feasibility of a

larger trial comparing analgesic modalities. However, measuring stress response was an additional variable and was not reported on in the main study. All data were analysed on an intention to treat basis.

Data were analysed using Stata version 12. The overall stress response for each serum marker was first summarised by calculating the "area under the curve" formed by plotting the relevant values across time (baseline, 3, 6, 12 and 24 h) using the trapezoidal rule; hence, this area under the curve (AUC) can be considered a weighted average of values across time. The AUC was compared between the TEA and WIC groups using analysis of covariance, adjusting for baseline value. This comparison assesses whether the two groups differ in overall stress response, but there is also a possibility of differential effects at different time points. To assess this possibility, mixed-effects linear models were fitted with the patient as a random effect. There was no suggestion of any consistent pattern across time (such as linear growth), so time point was fitted as a categorical (factor) fixed effect, as was group (TEA/WIC). Likelihood ratio tests were used to compare models with and without an interaction term for group by time, to test for the possibility of differential effects (TEA vs. WIC) across time. Since three of the four serum markers did produce statistically significant interaction terms, individual ANCOVAs were fitted at each time point (adjusting for baseline) to compare TEA and WIC. All natural data displayed positive skewness and were logged before analysis; hence, geometric means and SDs are reported and comparisons between TEA and WIC are reported as ratios with 95 % confidence intervals.

Funding source for the study

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Results

Twenty-five (73 %) of the patients recruited into the EWIC study gave their consent for blood testing to measure stress response (14 WIC vs. 11 TEA). Figure 1 describes the trial using a CONSORT diagram. Baseline characteristics were similar in both groups for age, body mass index, American Society of Anaesthesiologists Score, World Health Organisation performance status and tumour site (Table 1). Twenty-two patients completed their operations laparoscopically. Two in the epidural group were converted to open and one in the WIC group.

A total of 402 blood samples were collected across the four points of time (3, 6, 12 and 24 h). Ninety-eight samples were not collected (19 %), most of which were at the 3-h time point. Every effort was made to schedule the operations first on the morning lists. However, sometimes the order of the list changed to accommodate emergency surgery. The mean timing of blood sample collection was as follows: pre-operatively at 8.47 am; 3 h at 13.25 pm; 6 h at 15.44 pm; 12 h at 21.59 pm; and 24 h at 10.10 am the following day.

The results of the stress response blood assays for both arms of the trial are demonstrated in Fig. 2a–d. In terms of overall stress response as summarised by the AUC, interleukin-6 was the only marker to produce a statistically significant difference between TEA and WIC, with the WIC group experiencing approximately half the value of the TEA group (Table 2).

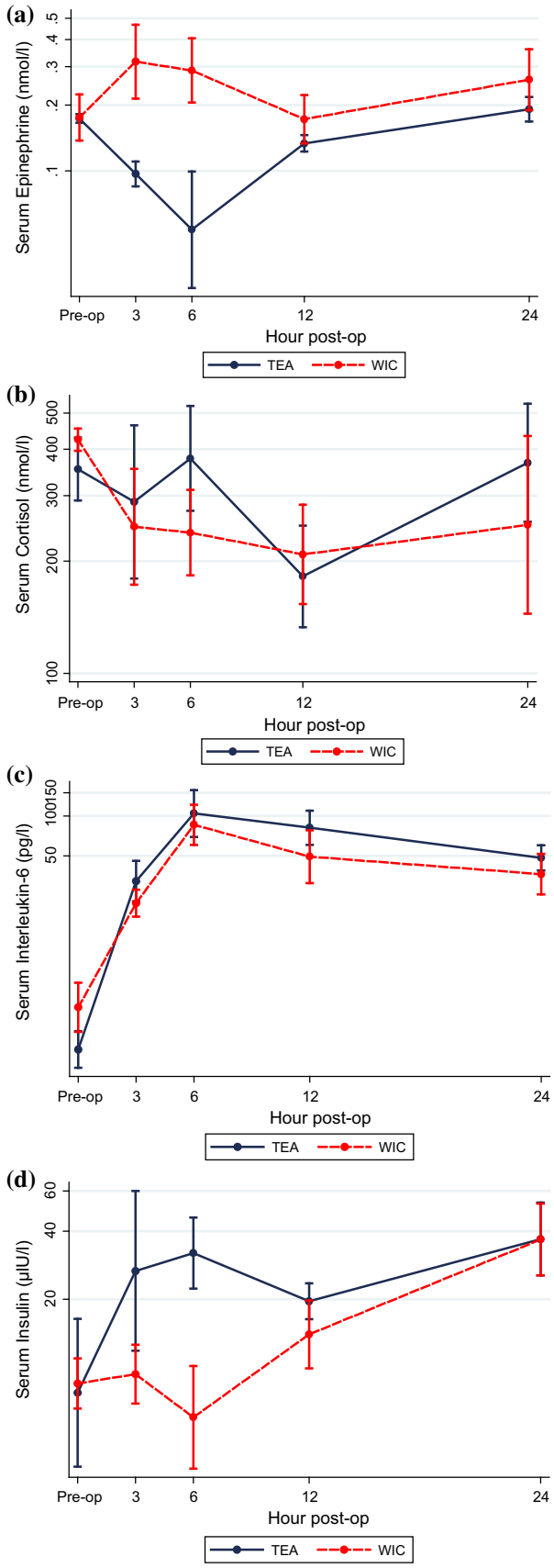
Fitting the mixed-effects models revealed statistically significant interactions between group (TEA/WIC) and time point for epinephrine, insulin and interleukin-6, but not for cortisol. This suggests that the difference between the two groups varies across time. Accordingly, individual ANCOVAs were run at each time point to provide estimates at each time point (Table 3). These results suggest that, compared to the TEA group, the WIC group has: higher epinephrine values at 3 and (especially) 6 h; lower insulin values at 3 and (especially) 6 h; and lower interleukin-6 values at 12 h.

Data on other endpoints are summarised in Table 4 including mean pain score in the first 48 h post-operatively,

Table 1 Patients' baseline characteristics

	WIC ($n = 14$)	TEA ($n = 11$)
Males	9 (64 %)	6 (54 %)
Age (years), mean (SD)	68 (12.3)	74 (7.9)
BMI (m^2/kg), mean (SD)	26.6 (3.6)	27.6 (5.0)
Current smoker	3 (21 %)	2 (18 %)
Current alcohol drinker	10 (71 %)	9 (82 %)
WHO performance status >0	4 (31 %)	5 (45 %)
ASA grade >1	9 (64 %)	9 (82 %)
Tumour site		
Caecum	4 (29 %)	2 (18 %)
Right hemi-colon	3 (21 %)	5 (45 %)
Left hemi-colon	2 (14 %)	1 (9 %)
Sigmoid colon	5 (36 %)	3 (27 %)

BMI body mass index, *ASA* American Society of Anesthesiologists, *WHO* World Health Organization



◀**Fig. 2** Serum concentrations of **a** epinephrine; **b** cortisol; **c** interleukin-6; and **d** insulin. Points are geometric means, and *error bars* represent ±1 standard error. *Note* *y*-axes on logarithmic scale

length of hospital stay, post-operative complications and 30 day re-admission rates. Mean analgesic use (equivalent to mg intravenous morphine) was 12 mg in the wound infusion arm and 9 mg in the epidural arm. Patient-controlled analgesia (PCA) was required in two patients (one in each arm). There were six complications (19 %) affecting 5 patients with 3 complications in each trial arm. Both groups followed successfully the enhanced recovery programme and adhered with post-operative elements including mobilisation and early feeding. Median length of stay was 4 days for both groups (range 2–13 days TEA and 2–35 days WIC) with two patients being readmitted (one in each arm). No suspected unexpected serious adverse reactions or serious adverse reactions have been reported during this trial. There were no in-hospital deaths.

Discussion

It is widely perceived that epidural analgesia alters the stress response after open surgery and in consequence reduces cardiovascular and infectious complications [19, 20]. Following the wide spread adoption of laparoscopic techniques in colorectal surgery, the routine use of TEA after laparoscopic techniques has been questioned by single-centre studies that have found alternative methods of analgesia to be equally effective when compared to TEA [21, 29].

The current study explored the neuroendocrine, metabolic and inflammatory response after laparoscopic surgery comparing two pain relief modalities within an RCT. We found that epidural analgesia attenuated the stress response as expressed by lower epinephrine level and higher insulin response at 3 and 6 h compared to WIC. This observation may be explained by the ability of the sympathetic nerve block induced by epidural anaesthesia to reduce the surgical stress response, including reductions in plasma catecholamine. Notably, the transient nature of the attenuating stress response on epinephrine and the lack of effect on the cortisol level may be explained by the already attenuating effect of stress response by using the combination of laparoscopic techniques and ERAS.

We have also found that cytokine response as measured by interleukin-6 was more attenuated by WIC in particular at 12 h. A previous publication [30] has shown the attenuating effects of epidural analgesia on the level of interleukin-6, which is contrary to our findings, demonstrating lowering effect of interleukin-6, by WIC.

Table 2 Standardised "area under the curve" of values of each stress response marker

	TEA, AUC geometric mean (SD)	WIC, AUC geometric mean (SD)	Adjusted ratio[a] (95 % confidence interval)	*p* value
Epinephrine	0.20 (1.63)	0.24 (1.74)	1.30 (0.87–1.94)	0.18
Cortisol	315 (2.78)	280 (2.07)	0.72 (0.36–1.44)	0.34
Insulin	19.4 (2.34)	25.0 (2.38)	1.16 (0.57–2.38)	0.67
Interleukin-6	56.4 (3.53)	34.4 (2.51)	0.45 (0.22–0.91)	0.03

AUC area under the curve, *TEA* thoracic epidural anaesthesia, *WIC* wound infusion catheter, *SD* standard deviation

[a] WIC relative to TEA, adjusted for pre-operative value using analysis of covariance on logged values, back-transformed

Table 3 Value of each stress response marker at each time point

	TEA, geometric mean (SD)	WIC, geometric mean (SD)	Adjusted ratio* (95 % confidence interval)
Epinephrine			
Pre-op	0.19 (1.72)	0.17 (1.70)	
3 h	0.14 (2.37)	0.31 (2.61)	2.27 (0.93–5.52)
6 h	0.11 (4.39)	0.26 (2.32)	3.17 (1.11–9.06)
12 h	0.19 (1.51)	0.19 (1.89)	1.14 (0.66–1.98)
24 h	0.21 (1.37)	0.24 (2.03)	1.19 (0.68–2.11)
		p value for interaction[#] = 0.032	
Cortisol			
Pre-op	304 (1.64)	357 (1.41)	
3 h	251 (2.66)	248 (2.46)	0.61 (0.26–1.42)
6 h	295 (3.33)	318 (2.56)	0.71 (0.28–1.85)
12 h	224 (4.11)	175 (2.60)	0.59 (0.19–1.87)
24 h	437 (1.86)	185 (4.35)	0.39 (0.12–1.28)
		p value for interaction[#] = 0.41	
Insulin			
Pre-op	5.03 (3.20)	6.73 (2.40)	
3 h	15.9 (3.61)	11.3 (2.53)	0.59 (0.17–2.05)
6 h	17.7 (2.70)	9.51 (3.81)	0.39 (0.13–1.15)
12 h	13.3 (1.98)	17.3 (2.19)	1.19 (0.61–2.31)
24 h	33.1 (1.93)	46.3 (2.91)	1.33 (0.56–3.18)
		p value for interaction[#] = 0.042	
Interleukin-6			
Pre-op	1.75 (1.91)	2.28 (2.70)	
3 h	26.7 (1.76)	19.9 (1.99)	0.71 (0.32–1.57)
6 h	75.4 (2.50)	72.8 (2.87)	0.59 (0.29–1.23)
12 h	94.0 (3.28)	42.1 (3.61)	0.28 (0.12–0.66)
24 h	52.7 (3.79)	40.6 (2.74)	0.51 (0.19–1.32)
		p value for interaction[#] = 0.046	

TEA thoracic epidural anaesthesia, *WIC* wound infusion catheter, *SD* standard deviation

[#] *p* value based on likelihood ratio test for interaction between intervention effect (infusion vs. epidural) and time effect (hour post-op), derived from mixed-effects model

[a] WIC relative to TEA, adjusted for pre-operative value using Analysis of Covariance on logged values, back-transformed

One possible explanation is that interleukin-6 is produced at the site of the surgical wound, where it subsequently enters systemic circulation and it is likely that the continuous wound infusion of local anaesthetic inhibits the release of interleukin-6 in a more pronounced manner than the effect of epidural. Although the pathways of the production and transport of interleukin-6 to the bloodstream have not been completely documented, the effect of serum

Table 4 Outcome measures for both epidural and WIC arms

Outcome measure	TEA	WIC
Pain assessment score mean (SD)		
Day 1 post	2.4 (2.0)	2.6 (2.2)
Day 2 post	3.2 (3.1)	2.4 (2.9)
Mean rescue analgesia		
Equivalent to mg iv morphine	9	12
Gastrointestinal (total number of cases)		
Rectal bleeding	0	1
Post-operative ileus	1	1
Anastomotic leak	1	1
Skin/subcutaneous tissues		
Necrotising fasciitis	1	0
Re-admission	1	1

TEA thoracic epidural anaesthesia, *WIC* wound infusion catheter, *SD* standard deviation

interleukin-6 on the immune system is well documented for its effects on immunosuppression and pain modulation [31] and this may account for the central analgesic effect of WIC. It has been previously reported that there is a correlation between surgical severity and tissue injury and the effect of interleukin-6 which can predict the occurrence of hyperalgesia [32, 33]. Further investigations are required to determine the exact mechanism of action of local anaesthetic infusion on interleukin-6 transport into the bloodstream and the potential regulators of this pathway, which may serve as targets for future drug development.

To our knowledge, this small randomised trial is the first to investigate the stress response of epidural analgesia and WIC following laparoscopic colorectal resection and within an ERAS programme. A recently published randomised control trial comparing epidural to PCA found that epidural analgesia negatively impacted recovery as measured by clinical outcomes, but neuroendocrine stress response was not reported [34]. In addition the LAFA trial measured, the neuroendocrine stress response following laparoscopic surgery compared to open surgery but did not address the impact of the analgesic modality [35].

Studying the impact of analgesic modalities upon stress response within the setting of enhanced recovery and laparoscopic surgery is novel. In this study, the outcome assessors and patients were blinded, which is important to minimise bias. A recently published study showed that there was a significant survival benefit in patients who received epidural analgesia after colorectal cancer surgery [36]. However, the survival benefit with epidural analgesia was greater in patients who had greater medical morbidity, and given the apparent transient nature of the stress response following this minimally invasive surgery, the impact upon stress response may not be the most important factor to be considered when selecting analgesic modality. Future research in this field may, therefore, elect to focus on investigating clinical outcomes through control of dynamic pain rather than attempts to attenuate the stress response. Another recent double-blinded RCT [37] assessing the impact of intravenous infusion of lignocaine on perioperative stress response showed that lignocaine attenuates the operative stress response which was translated into reducing post-operative ileus.

There were, however, limitations to this project. This was an exploratory study with a modest number of patients. No formal power calculation was made as there is no prior evidence to guide what mean or standard deviation to expect for each arm within laparoscopic surgery and enhanced recovery. However, based on the finding of this study, the mean pain score for WIC on post-operative day 1 was 26 mm with a standard deviation of 22 mm. To detect a difference between individual trial arms of 10 mm, with 90 % power at the 5 % significance level, 102 patients would be needed in each trial arm. Additionally, due to the logistics of blood collection in the immediate recovery period, there was some missing data, mostly at the 3-h time point, highlighting the difficulty of collecting samples for research early in the post-operative period. However, there was good-quality data collection at multiple points later in the post-operative period. Also, due to the small size of this study, correlation with clinical outcomes was not feasible, although the length of stay and complication rates did not differ between the two groups. Nevertheless, the data are useful exploratory results that justify and guide further larger studies to investigate the trends which were identified in this study and could include further measurements of stress response at 36 and 48 h.

Conclusions

This exploratory study has confirmed that stress response measurement is feasible within a RCT comparing analgesic modalities. There is a significant transient attenuating effect of epidural analgesia on stress response following laparoscopic colorectal surgery and within ERAS as expressed by serum epinephrine and insulin levels. Continuous wound infusion with local anaesthetics, however, attenuates cytokine response as expressed by interleukin-6. Larger studies are required to investigate these findings further.

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Conflict of interest None.

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