Thoracic epidural analgesia inhibits the neuro-hormonal but not the acute inflammatory stress response after radical retropubic prostatectomy


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Editor’s key points
- The surgical stress response may have adverse effects on postoperative recovery.
- Thoracic epidural analgesia can reduce this response, whereas systemic opioids do not.
- This study investigated neuroendocrine and inflammatory changes after radical prostatectomy.
- Epidural analgesia reduced the neuroendocrine response with no beneficial effect on the inflammatory response.

Background. Epidural anaesthesia and analgesia has been shown to suppress the neuro-hormonal stress response, but its role in the inflammatory response is unclear. The primary aim was to assess whether the choice of analgesic technique influences these processes in patients undergoing radical retropubic prostatectomy.

Methods. Twenty-six patients were randomized to Group P (systemic opioid-based analgesia) or Group E (thoracic epidural-based analgesia) perioperatively. Induction and maintenance of anaesthesia followed a standardized protocol. The following measurements were made perioperatively: plasma cortisol, glucose, insulin, C-reactive proteins, leucocyte count, plasma cytokines [interleukin (IL)-6, tumour necrosis factor (TNF)-α], and pokeweed mitogen-stimulated cytokines [interferon (IFN)-γ, IL-2, IL-12p70, IL-10, IL-4, and IL-17]. Other parameters recorded were pain, morphine consumption, and perioperative complications.

Results. Plasma concentration of cortisol and glucose were significantly higher in Group P compared with Group E at the end of surgery, the mean difference was 232 nmol litre⁻¹ (95% confidence interval (CI) 84–381) (P=0.004) and 1.6 mmol litre⁻¹ (95% CI 0.6–2.5) (P=0.003), respectively. No significant differences were seen in IL-6 and TNF-α at 24 h (P=0.953 and 0.368, respectively) and at 72 h (P=0.931 and 0.691, respectively). IL-17 was higher in Group P compared with Group E, both at 24 h (P=0.001) and 72 h (P=0.018) after operation. Pain intensity was significantly greater in Group P compared with Group E (P<0.05) up to 24 h.

Conclusions. In this small prospective randomized study, thoracic epidural analgesia reduced the early postoperative stress response but not the acute inflammatory response after radical retropubic prostatectomy, suggesting that other pathways are involved during the acute phase reaction.

Keywords: anaesthesia technique; epidural, physiological; surgery: stress response; urological

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The physical trauma of surgery induces a surgical stress response (SSR). This is the name given to the hormonal, metabolic, immunological, and inflammatory changes which follow injury or trauma in order to prevent ongoing tissue damage, destroy the infective organism, and activate the repair processes necessary to restore normal function. The early phase of this process is called acute phase response and it is characterized by a series of changes, including activation of hypothalamo–pituitary–adrenal axis with release of adrenocorticotropic hormone leading to an increase in plasma cortisol and secretion of endogenous catecholamines. Epidural anaesthesia and analgesia reduce the neuroendocrine stress response after lower abdominal surgery, thereby preventing an increase in stress markers such as cortisol, glucose, and catecholamines during surgery but has not been consistently shown to do so after upper abdominal surgery, even with high epidural blocks.

The SSR initiates a cascade of inflammatory responses mediated by several substances with cytokines playing a key role. They act as pro- and anti-inflammatory effectors by stimulating or dampening the activation of immune cells and release of more cytokines. An imbalance of this complicated network of potent mediators may result in a
hyper-inflammatory reaction: the associated paralysis of cell-mediated immunity could be responsible for the infectious complications seen in surgical patients. Furthermore, inflammatory cytokines have been shown to induce fatigue and ‘sickness behaviour’ in humans after operation, thereby significantly decreasing well-being after major surgery. Thus, epidural anaesthesia and analgesia may improve several patient-related outcomes, not just by decreasing catecholamine and cortisol responses to surgery, but also suppressing the early inflammatory response and maintaining a physiological cytokine balance during the postoperative period. Although many previous studies have examined the anti-inflammatory effects of epidural anaesthesia peripherally, the results are not consistent or reproducible. Possible reasons for this inconsistency could include varying study design, study population, and surgical procedures.

The primary aim of the present study was to assess whether the choice of pain management technique influences the SSR, including a dampening of the neuroendocrinal pathways and perioperative inflammation, in a homogenous group of patients undergoing radical retropubic prostatectomy.

Methods

The Regional Ethics Committee in Uppsala, Sweden, approved the study, before patient recruitment. It was registered in an International directory, www.ClinicalTrials.gov (Identifier: NCT01367418). Informed verbal and written consent were obtained from 26 patients (ASA physical status I–II) in the age group 50–75 yr, undergoing elective radical retropubic prostatectomy during the period September 2010–June 2011. Exclusion criteria were: chronic analgesic or corticosteroid medication, known endocrinological or immunological diseases, allergy to local anaesthetics (LA), and other contraindications for epidural catheter placement. Patients were randomly allocated to one of the two groups:

- **Group P** (patient-controlled i.v. analgesia group) had i.v. opioid-based analgesia perioperatively.
- **Group E** (patient-controlled epidural analgesia (PCEA) group) received epidural analgesia using LA during the operation and a combination of LA and opioids after operation.

Randomization and blinding

Group randomization and concealed allocation was done using cards inserted into opaque, sealed envelopes by an independent person not involved in the study. The study was only blinded to laboratory personnel involved in biochemical assays.

Anaesthesia and intraoperative analgesia

All patients received oral midazolam 0.05 mg kg$^{-1}$ 15–30 min before surgery and paracetamol 1 g was given orally every 6 h during the perioperative period.

Group E: An epidural catheter was inserted at the Th 10–12 inter-space and subsequently tested for subarachnoid or intravascular placement using 3 ml of bupivacaine 0.5% with epinephrine. A bolus dose of 2–3 ml of the same drugs was injected and loss of sensation to cold determined after 10 min. If a sensory block to Th8 dermatome was obtained, the patient was considered to be ready for induction of anaesthesia otherwise a further dose of 2–3 ml was injected epidurally. If this failed to achieve adequate block, the catheter was re-sited or the patient excluded from the study. Intraoperative analgesia was achieved using a continuous infusion of bupivacaine 0.5% at 2–4 ml h$^{-1}$ during the operation. Twenty minutes before the end of the operation, 15–20 μg sufentanil was injected epidurally for bridging.

Group P: Fentanyl 25–50 μg was administered i.v. as needed during surgery, depending on the clinical signs of adequate anaesthesia and morphine i.v. was given at the end of surgery for postoperative analgesia.

Radical retropubic prostatectomy was performed using a unilateral or bilateral nerve-sparing technique when the tumour and patient characteristics permitted.

Anaesthesia was induced in all patients with fentanyl 2 μg kg$^{-1}$ and thiopental 3–4 mg kg$^{-1}$ or propofol 1–2 mg kg$^{-1}$ i.v. Tracheal intubation was performed after muscle relaxation with rocuronium 0.6 mg kg$^{-1}$ and anaesthesia maintained with 1–3% sevoflurane in 33% oxygen in air. Mechanical ventilation was used in a low-flow system in order to maintain an end-tidal CO$_2$ of between 4.5 and 5.5 kPa. In all patients, sevoflurane concentration was adjusted in order to maintain adequate anaesthetic depth. At the end of surgery, muscle relaxation was reversed using glycopyrrolate (0.2 mg) and neostigmine (2.5 mg) i.v. Ringer acetate, 2–4 ml kg$^{-1}$ h$^{-1}$, was used to maintain basal fluid requirements, and colloids, blood, or phenylephrine infusion used to maintain a mean arterial pressure >60–65 mm Hg. Bradycardia (heart rate <45 beats min$^{-1}$) was treated with atropine 0.5 mg i.v.

Postoperative management

In the post-anaesthesia care unit (PACU), patients in Group P received a patient-controlled analgesia (PCA) pump which was programmed to give bolus dose of 1 mg morphine with a lockout time of 6 min. Patients in Group E received a PCEA device which delivered an infusion of ropivacaine 2 mg ml$^{-1}$ and sufentanil 1 μg ml$^{-1}$, 3–6 ml h$^{-1}$ with boluses of 3 ml, maximum twice per hour self-administered by the patients. All patients received morphine (1–2 mg) i.v. as rescue medication by a nurse if pain on the numeric rating scale (NRS) (0, no pain; 10, worst imaginable pain) was >3. The patients were observed in the PACU for 4 h before being transferred to the general urological ward where protocolized pain management was continued for 48 h and thereafter, a combination of paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) was given for...
pain relief. Those patients who continued to have pain despite this medication were given opiates as needed.

**Recordings**

**Anaesthetics**
The end-tidal MAC concentration of inhalation anaesthetics was recorded approximately every 15 min during surgery. The mean value of MAC during the procedure was then calculated for each patient as a summary measure.

**Pain intensity**

Pain at rest (at incision site and deep pain) and pain on coughing on arrival in the PACU, at 4, 8, 24, and 48 h were measured using the NRS.

**Analgesics**

Morphine consumption during 0–24, 24–48, and 48–72 h was recorded. Supplementary analgesics consumption was also recorded each day.

**Side-effects and complications**

All surgical and anaesthesia-related complications were recorded.

**Blood sampling**

Blood samples were collected in lithium–heparin tubes before operation, at the end of operation (2 h), at 24, and at 72 h after operation for analysis of plasma cytokines (IL-6 and TNF-α), surgical stress markers (cortisol, glucose and insulin), and plasma cytokines and cytokines from polyclonal stimulation with pokeweed mitogen as described in the Appendix. In addition, C-reactive protein (CRP) and leucocyte count were determined on postoperative days (POD) 1 and 3.

**Statistics**

This was an exploratory, pilot study and therefore no power analysis was performed to determine sample size. Patient characteristic data, anaesthetic and fluids requirements, blood loss, and end-tidal concentration of volatile agents were analysed using the unpaired two-sample t-test. Pain intensity on the NRS and morphine consumption were analysed using the Mann–Whitney U-test followed by the Bonferroni–Holm correction for repeated measurements. Some cytokines and stress markers showed a tendency towards non-normality and therefore logarithmic transformation was performed where appropriate. The general linear model was used with markers (stress hormones or cytokines) as outcome variable, group (P or E) as between-factor variable, and time (measured at the end of operation, 24 and 72 h after operation) as within-factor variable. Before operation, measured markers were considered as covariate. Post hoc tests comparing these markers between Groups P and E at 24 and 72 h after operation were also performed. The incidence of side-effects and adverse events were analysed using the χ² test. Results are presented as mean (SD) or median (range) as appropriate and significant differences were considered when the P-value was <0.05.

**Results**

In all, 30 patients were interviewed for possible recruitment into the study; of these, 26 patients had all the inclusion criteria and none of the exclusion criteria and were randomized to one of the two groups (Fig. 1). Eight patients in Group E and six in Group P did not have nerve-sparing surgery. Among the others in Group E, two patients had unilateral and two bilateral nerve-sparing surgery, while in Group P, five had unilateral and three bilateral nerve-sparing surgery. One patient, randomized to Group P, interrupted the study after 7 h because of respiratory depression, which resulted in substitution of PCA morphine with NSAIDs as the primary pain management strategy. All patients in Group E received an epidural catheter successfully and there were no complications associated with catheter insertion.

There were no differences in the patient characteristic data, ASA classification, and baseline data including arterial pressure and heart rate (Table 1). There was a significantly lower consumption of intraoperative opiates (P<0.01) and volatile agents (P<0.01) in Group E compared with Group P (Table 2). No other differences were found between the groups. The total amount of intraoperative phenylephrine administered was greater in Group E compared with Group P (P=0.03) (Table 2).

A significantly higher concentration of plasma cortisol was found in Group P compared with Group E at the end of the surgery (P=0.004) (Fig. 2A). The mean difference between groups at the end of operation was 232 nmol litre⁻¹ [95% confidence interval (CI) 84–381]. A similar trend in plasma glucose was seen and the mean difference between groups at the end of operation was 1.6 mmol litre⁻¹ [95% CI 0.6–2.5] (P=0.003) (Fig. 2A). No differences were found in the mean insulin concentration between the groups at any time points (Fig. 2C).

Plasma levels of TNF-α and IL-6 did not differ between the groups at any time point, although IL-6 did increase at 24 h post-surgery (Table 3, Fig. 3A). No differences were found between the groups in IFN-γ, IL-2, IL-12p70, IL-4, or IL-10, measured after polyclonal stimulation of whole blood with pokeweed mitogen (PWM) at any time point. In contrast, IL-17 levels after polyclonal stimulation were significantly higher in Group P at 24 h (P=0.001) and 72 h (0.018) after operation (Table 3, Fig. 3A).

CRP and leucocyte count were higher in Group P on the first and third day after operation (Table 2). However, no statistically significant differences were found between the groups.

Incision pain was significantly lower in Group E compared with Group P on arrival in the PACU (P<0.01) and during the first 8 h (P<0.05) (data not shown). Deep pain and pain on coughing were also significantly lower in Group E at 0 h (P<0.01), 4 h (P<0.01), and 8 h (P<0.01) after operation.
Patients interviewed for participation in study: n = 30

Did not fulfill inclusion or exclusion criteria: n = 4

Patients randomized into the study: n = 26

Group P: Patient-controlled morphine analgesia (PCA) n = 14

1 patient excluded after 7 h*

Patients included: n = 13

Group E: Patient-controlled epidural analgesia (PCEA) n = 12

Patients included: n = 12

* Please see text for details

Pain on coughing continued to be lower even at 24 h after operation in Group E (P = 0.042) (Fig. 4A and B). Morphine consumption in Group P and the amount of LA infused by epidural analgesia in Group E are shown in Table 2.

No significant differences in the incidence of nausea and vomiting or postoperative bleeding were found between the groups during the study time (Table 2). Two patients in Group E had postoperative adverse events; one patient had significant haematuria requiring i.v. tranexamic acid. The second patient required blood transfusion and subsequently developed bronchopneumonia that was treated with antibiotics. In both of these patients, the complications resolved.
before home discharge. One patient in Group P had respiratory depression 7 h after surgery and pain was subsequently managed with paracetamol and NSAIDs. This patient was excluded from the study after the PCA pump was stopped.

**Discussion**

The trauma of surgical procedures induces pain, changes in hormonal and autonomic nervous system activity, inflammation, and immunological suppression. In the present study, we were able to demonstrate that the cortisol concentration was lower in patients having thoracic epidural anaesthesia (TEA) compared with i.v. opioid-based anaesthesia, probably due to blocking of the neuroendocrine pathway by TEA, thus confirming previous findings in patients undergoing lower abdominal surgery.² ³ We were also able to demonstrate a lower blood glucose concentration at the end of surgery in patients having TEA. However, insulin concentration did not differ between the groups, which was similar to the finding of Hong and colleagues ² in patients also undergoing radical retropubic prostatectomy. Thus, several early neuroendocrine stress markers measured in this study showed a reduction in SSR by epidural-based analgesia compared with opioid-based i.v. analgesia.

Inflammation after surgery is a physiological response that restores the normal host function. Cytokines are

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**Table 2** Perioperative data. Time to surgery and anaesthesia, drugs, fluid requirements, peroperative bleeding, postoperative morphine and other analgesic requirements, side-effects, CRP, and leucocyte count. PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia; LA, local anaesthetic; NSAID, non-steroidal anti-inflammatory drug; CRP, C-reactive protein. All results are presented as mean (so), unless otherwise shown.

<table>
<thead>
<tr>
<th></th>
<th>Group P (PCA) (n = 14)</th>
<th>Group E (PCEA) (n = 12)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of operation (min)</td>
<td>109 (30)</td>
<td>100 (27)</td>
<td>0.453</td>
</tr>
<tr>
<td>Total dose of thiopental (mg), n=21</td>
<td>433 (122)</td>
<td>398 (114)</td>
<td>0.525</td>
</tr>
<tr>
<td>Total dose of propofol (mg), n=5</td>
<td>192 (18)</td>
<td>NA</td>
<td></td>
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<tr>
<td>Total dose of fentanyl (µg)</td>
<td>319 (65)</td>
<td>164 (23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End-tidal sevofluorane (%)</td>
<td>1.9 (0.2)</td>
<td>1.5 (0.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Total ephedrine (mg) [median (range)]</td>
<td>5 (0–20)</td>
<td>10 (0–15)</td>
<td>0.400</td>
</tr>
<tr>
<td>Total phenylephrine (µg) [median (range)]</td>
<td>0 (0–0.6)</td>
<td>0 (0–1.8)</td>
<td>0.031</td>
</tr>
<tr>
<td>Intraoperative bleeding (ml)</td>
<td>765 (449)</td>
<td>645 (527)</td>
<td>0.552</td>
</tr>
<tr>
<td>No. of patients given blood peroperatively [median (range)]</td>
<td>0 (0–2)</td>
<td>0 (0–3)</td>
<td>0.724</td>
</tr>
<tr>
<td>Fluids given peroperatively (ml)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Crystalloids</td>
<td>1219 (411)</td>
<td>1259 (226)</td>
<td>0.777</td>
</tr>
<tr>
<td>Colloids</td>
<td>857 (433)</td>
<td>963 (426)</td>
<td>0.554</td>
</tr>
<tr>
<td>PCA morphine i.v. (mg) [median (range)]</td>
<td>22 (6–56)</td>
<td>22 (0–83)</td>
<td></td>
</tr>
<tr>
<td>0–24 h</td>
<td>22 (6–56)</td>
<td>22 (0–83)</td>
<td>Not applicable</td>
</tr>
<tr>
<td>24–48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rescue morphine i.v. (mg) [median (range)]</td>
<td>10.5 (3–25)</td>
<td>0 (0–0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>0–48 h</td>
<td>10.5 (3–25)</td>
<td>0 (0–0)</td>
<td></td>
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<tr>
<td>Opioid p.o. requirements (mg) [median (range)]</td>
<td>0 (0–15)</td>
<td>0 (0–10)</td>
<td>0.346</td>
</tr>
<tr>
<td>48–72 h</td>
<td>0 (0–15)</td>
<td>0 (0–10)</td>
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<td>NSAID p.o. requirements (tab): median (range)</td>
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<tr>
<td>24–48 h</td>
<td>1 (1–2)</td>
<td>1 (1–2)</td>
<td>0.854</td>
</tr>
<tr>
<td>48–72 h</td>
<td>3 (0–4)</td>
<td>3 (2–4)</td>
<td>0.300</td>
</tr>
<tr>
<td>Total PCEA-LA consumption (ml) [median (range)]</td>
<td>Not applicable</td>
<td>77 (65–203)</td>
<td></td>
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<tr>
<td>0–24 h</td>
<td></td>
<td>77 (65–203)</td>
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<tr>
<td>24–48 h</td>
<td>84 (8–119)</td>
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<tr>
<td>Nausea or vomiting, n (%)</td>
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<tr>
<td>0–24 h</td>
<td>1 (8.3%)</td>
<td>4 (33.3%)</td>
<td>0.317</td>
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<tr>
<td>24–48 h</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>Anti-emetics given, n (%)</td>
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<tr>
<td>0–24 h</td>
<td>2 (15.4%)</td>
<td>4 (36.4%)</td>
<td>0.357</td>
</tr>
<tr>
<td>24–48 h</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<tr>
<td>CRP (mg litre⁻¹)</td>
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<tr>
<td>24 h</td>
<td>67 (25)</td>
<td>69 (36)</td>
<td>0.907</td>
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<tr>
<td>72 h</td>
<td>112 (32)</td>
<td>98 (68)</td>
<td>0.515</td>
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<tr>
<td>Leucocyte count (10⁹ litre⁻¹)</td>
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<tr>
<td>24 h</td>
<td>8.9 (2.4)</td>
<td>8.5 (2.1)</td>
<td>0.664</td>
</tr>
<tr>
<td>72 h</td>
<td>7.2 (2.9)</td>
<td>6.6 (1.4)</td>
<td>0.498</td>
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</tbody>
</table>
released mainly from immune cells, but even from damaged endothelial tissues. The systemic inflammatory reaction seen in sepsis or multiple trauma can, however, be detrimental to the host. Although this systemic inflammatory reaction has not clearly been seen after major elective surgery and a clear correlation of plasma cytokines with the magnitude of the surgical procedure has not been definitively established, post-surgical outcome has been correlated to inflammatory–immunological impairment. We measured the plasma levels of two pro-inflammatory cytokines that initiate the inflammatory acute phase response, TNF-α and IL-6, as well as a battery of cytokines mainly involved in adaptive immune responses, IFN-γ, IL-2, IL-12p70, IL-17, IL-4, and IL-10. We did not find a statistically significant difference between the groups in any of these cytokines except IL-17, which was significantly lower in the group receiving epidural analgesia both at 24 and 72 h after operation. Whether epidural-based analgesia could prevent an increase in IL-17 by reducing the quantity of inhaled volatile agent is unclear, but noteworthy. IL-17 is the primary cytokine produced by the pro-inflammatory CD4**+** T helper 17 (Th17) subset, which are mainly localized in airways and intestinal epithelial layers. They promote an acute inflammatory response by recruiting and activating neutrophils through up-regulation of IL-8 and it has been speculated in a previous study that volatile agents may influence pro-inflammatory cytokines during mechanical ventilation. IL-6 plasma concentration is higher at 24 h after operation compared with the preoperative value and is likely a response to the trauma of the surgery itself with no significant changes between the groups. Normally, the acute phase reaction subsides over 24–48 h and it is somewhat surprising that the levels of TNF-α started to increase at 72 h after operation. TNF-α has a short half-life and the peak concentration is usually seen within 2 h after trauma, preceding the IL-6 release. Therefore, it is possible that the peak in TNF-α plasma levels appeared early when we did not measure it. Thus, epidural-based analgesia did not significantly suppress the concentration of the proinflammatory plasma cytokines TNF-α and IL-6, nor prevent the release of PWM-stimulated cytokines. Our findings are similar to those of Beilin and colleagues who also found that IL-6 levels did not differ significantly in the i.v. analgesia group compared with epidural analgesia. However, in our study, mitogen-stimulated cytokines in the epidural group seem to follow a more physiological, ‘balanced’ pattern between pro- and anti-inflammatory cytokines, than those in the i.v. analgesia group, such that there was less variation and early return to preoperative values in the epidural group. Before this study, we believed that the protective effects of epidural on the stress response could be seen clearly by a blunted inflammatory response compared with that seen in the morphine group. However, this was not the case and could be explained by the relatively small change in plasma cytokine levels...
Table 3 Plasma and pokeweed mitogen-stimulated (PWM) cytokines. Data are presented as median values (range) in the different group (Groups P and E) at the end of the operation (End op), at 24 and 72 h after operation and as mean difference (95% CI) between groups at the same points times. PCA, patient-controlled analgesia; PCEA, patient-controlled epidural analgesia.

*Markers needed a logarithmic transformation for statistic analysis due to non-normal distribution. After logarithmic transformation, mean difference indicates the percentage difference between groups. If the lower limit of the confidence interval is higher than 1 for logarithmic scale or higher than 0 for absolute scale, the difference is statistically significant. NA, not applicable.

<table>
<thead>
<tr>
<th>End op</th>
<th>Group P (PCA)</th>
<th>Group E (PCEA)</th>
<th>Group P–E mean difference (95% CI)</th>
<th>P-value</th>
<th>Group P</th>
<th>Group E</th>
<th>Group P–E mean difference (95% CI)</th>
<th>P-value</th>
<th>Group P (PCA)</th>
<th>Group E (PCEA)</th>
<th>Group P–E mean difference (95% CI)</th>
<th>P-value</th>
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<td>End op</td>
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<td>24 h</td>
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<tr>
<td>IL-6 (pg ml(^{-1}))</td>
<td>4.5 (0.8–28.8)</td>
<td>3.3 (0.65–26.9)</td>
<td>1.43* (0.60–3.37)</td>
<td>0.399</td>
<td>29.1 (18.6–72.3)</td>
<td>35.7 (10.8–142)</td>
<td>0.99* (0.59–1.65)</td>
<td>0.953</td>
<td>7.8 (2.5–64.7)</td>
<td>9.5 (2.6–54.1)</td>
<td>0.97* (0.55–1.73)</td>
<td>0.931</td>
</tr>
<tr>
<td>TNF-(\alpha) (pg ml(^{-1}))</td>
<td>9.3 (2.6–12.7)</td>
<td>8.2 (2.6–12.7)</td>
<td>1.55 (0.94–4.04)</td>
<td>0.210</td>
<td>9.5 (6.1–26.9)</td>
<td>8.5 (4.2–12)</td>
<td>1.35 (–1.70 to 4.39)</td>
<td>0.368</td>
<td>11.6 (7.6–77.5)</td>
<td>9.7 (6.2–15.6)</td>
<td>1.82 (–7.57 to 11.22)</td>
<td>0.691</td>
</tr>
<tr>
<td>IFN-(\gamma) (pg ml(^{-1}))</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>8418 (2392–17 390)</td>
<td>6427 (122–20 778)</td>
<td>747 (–1472 to 2966)</td>
<td>0.491</td>
<td>8417 (1933–12 513)</td>
<td>9100 (1929–21 678)</td>
<td>1.82 (–17.41 to 12.68)</td>
<td>0.591</td>
</tr>
<tr>
<td>IL-2 (pg ml(^{-1}))</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>310 (82.6–889)</td>
<td>234 (15.6–851)</td>
<td>1.16* (0.78–1.73)</td>
<td>0.452</td>
<td>356 (141–1323)</td>
<td>459 (121–1168)</td>
<td>0.95* (0.60–1.52)</td>
<td>0.843</td>
</tr>
<tr>
<td>IL-12p70 (pg ml(^{-1}))</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>2.6 (0.34–8.1)</td>
<td>2.1 (0.5–3.4)</td>
<td>1.48* (0.83–2.65)</td>
<td>0.171</td>
<td>2.63 (0.8–17.4)</td>
<td>3.8 (0.34–5.75)</td>
<td>1.20* (0.68–2.11)</td>
<td>0.504</td>
</tr>
<tr>
<td>IL-17 (pg ml(^{-1}))</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>327 (91.4–725)</td>
<td>270 (413–490)</td>
<td>155 (67 to 242)</td>
<td>0.001</td>
<td>216 (72–569)</td>
<td>189 (68.7–375)</td>
<td>1.11 (22–201)</td>
<td>0.018</td>
</tr>
<tr>
<td>IL-4 (pg ml(^{-1}))</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>56.5 (14.5–247)</td>
<td>48.1 (2.2–114)</td>
<td>1.22* (0.92–1.64)</td>
<td>0.157</td>
<td>102 (23.9–283)</td>
<td>92 (22.6–211)</td>
<td>1.12* (0.76–1.64)</td>
<td>0.557</td>
</tr>
<tr>
<td>IL-10 (pg ml(^{-1}))</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>1129 (456–2507)</td>
<td>1218.5 (317–1855)</td>
<td>1.14* (0.81–1.59)</td>
<td>0.445</td>
<td>764 (241–1792)</td>
<td>802 (477–1105)</td>
<td>1.14* (0.84–1.54)</td>
<td>0.373</td>
</tr>
</tbody>
</table>
levels seen after operation in our study, which may in turn be
due to the low intensity of the surgical trauma after RRP.

Some in vitro studies under experimental conditions seem
to indicate a minor suppressive effect of inhalation agents on
interleukin release after mitogen stimulation, which is dose-
and exposure time-related.\(^2\) However, the specific effect of
sevofluorane seems to be less depressive when compared
with the other volatile anaesthetics,\(^2\) which may contribute
to the lack of difference in interleukin between the groups.
Our findings are important in that they suggest that TEA

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**Fig 3** Perioperative (A) plasma cytokines and (a) pokeweed mitogen-stimulated cytokines.
does not blunt the inflammatory response to surgery and that other techniques should be used if it is to be reduced more efficiently. Indeed, in a recent study, it was demonstrated that a combination of LA injected intraperitoneally and epidurally peroperatively in patients undergoing colonic surgery attenuated the neuroendocrine and also the inflammatory responses to surgery. This could be due to the known anti-inflammatory effects of LA, which may have prevented cytokine release from the site of trauma.

**Study limitations**

Some problems remain with this study. The number of patients recruited into the study was small, thus limiting our conclusions. Cytokine and other neuroendocrine assays are expensive and financial constraints did not allow us to study a larger number of patients. On the other hand, the results of the cytokine assays over time were very similar between the groups and therefore studying a greater number of patients may not provide further knowledge, specifically in patients undergoing RRP. We measured those cytokines that we believed were important in the characterization of the stress response and at specific time points after having reviewed the literature. It is possible that an exploratory analysis of other cytokines involved in surgical stress may have revealed further information. Another limitation is that the study was not blinded and therefore patient-dependent variables such as pain scores may be subject to bias. On the other hand, in double-blinded studies on patients undergoing radical retropubic prostatectomy, we have previously shown that pain is lower in patients receiving TEA. In some patients, propofol was used for induction of anaesthesia instead of thiopental. Although propofol has been shown to have minimal effects on the inflammatory response when used for maintenance of anaesthesia, single doses of propofol or thiopental used for induction of anaesthesia have not been shown to be of any consequence. Finally, NSAIDs were administered after 48 h in all patients according to hospital routines. This may have affected the inflammatory parameters measured at 72 h in all patients.

**Conclusions**

In the present study, we were able to confirm that TEA and analgesia partly blunted the early neuroendocrine response to surgery by preventing an increase in cortisol and plasma glucose and also by reducing postoperative pain significantly. However, with the exception of reduced peaks in IL-17 production after PWM stimulation in the epidural group, the pro- and anti-inflammatory cytokines in plasma and after polyclonal stimulation of peripheral blood remained similar between the groups. Taken together, these findings indicate that while neuraxial block reduces pain significantly and reduces the neuroendocrine stress response, it does not clearly prevent the inflammatory response to lower abdominal surgery. Future studies should assess other methods to further obtund the inflammatory response to surgery.

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**Declaration of interest**

None declared.

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References


Appendix

Laboratory techniques

**Plasma cytokines and stress markers:** sampled blood was centrifuged at 1000g for 5 min and the plasma aliquots were stored at −80°C until future analysis.

Pokeweed mitogen (PWM) induced cytokine production: the remaining blood was diluted 1:10 in RPMI 1604 (Gibco, Paisley, UK; Invitrogen, St Louis, MO, USA) supplemented with L-glutamine and 0.02 mg ml⁻¹ gentamicin but without
additional serum. The stimulation was performed in 12 × 75 mm polystyrene tubes to which 5 \( \mu \text{g ml}^{-1} \) PWM (Sigma-Aldrich) were added in a total volume of 500 \( \mu \text{l} \). As negative controls, cells were cultured with complete medium without addition of mitogen. All samples were cultured for 3 days in a humidified incubator (37°C, 5% CO\(_2\)). Thereafter, the samples were centrifuged at 300g for 5 min and the supernatants were collected and frozen at −80°C until further analysis.

**Luminex multiplex analysis**

The Human cytokine Milliplex\textsuperscript{TM} MAP kit was purchased from Millipore (Millipore Corporation, Billerica, MA, USA). The multiplex assays used were customized for the analysis of cytokines in plasma and supernatants following stimulation with PWM. For the analysis of plasma samples, a 2-plex (IL-6, TNF-\( \alpha \)) and for analysis of supernatants from PWM-stimulated peripheral blood lymphocytes a 6-plex (IL-2, IL-4, IL-10, IL12p70, IL-17, and IFN-\( \gamma \)) setup was used. The assays were performed in duplicates according to the manufacturers’ protocol. In brief, a serially diluted standard curve (10 000—3.2 pg ml\(^{-1}\)), two controls and all samples were added in duplicate to a filter plate along with the anti-cytokine antibody-coated polystyrene beads. The plate was incubated for 1 h at room temperature (RT). After two washes, biotinylated cytokine-specific detection antibodies were added and the plates were incubated for an additional 30 min at RT followed by a 30 min incubation with phycoerythrin-coupled streptavidin. Thereafter, the plate was washed twice and Sheath Fluid (Luminex Corporation, Austin, TX, USA) was added to the wells. The analysis of the plate was performed using a Luminex 200\textsuperscript{TM}. For calculation of cytokine concentrations, a 5-parameter logistic fit curve method was performed using the Milliplex Analyst software (Millipore).

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