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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 retrobupic 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.[1] 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[2–4] but has not been consistently shown to do so after upper abdominal surgery,[5 6] even with high epidural blocks.[7]

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.[8] 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.[9 10] Furthermore, inflammatory cytokines have been shown to induce fatigue[11] and 'sickness behaviour' in humans after operation, thereby significantly decreasing well-being after major surgery.[12 13] 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.[14] Although many previous studies have examined the anti-inflammatory effects of epidural anaesthesia perioperatively, the results are not consistent or reproducible. Possible reasons for this inconsistency could include varying study design, study population, and surgical procedures.[15–17]

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.[18]

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