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Sepsis/Infection

Effect of thoracic epidural block on infection-induced inflammatory response: A randomized controlled trial☆,☆☆,★,★★,☆☆☆

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ABSTRACT

Purpose: Epidural block decreases inflammation and oxidative stress in experimental models of sepsis as well as after surgery. There is, however, no clinical evidence evaluating its effect on infection-induced inflammatory process. The present trial evaluated the effect of thoracic epidural block (TEB) on systemic inflammatory response in patients with small intestinal perforation peritonitis. Outcome measures included systemic levels of interleukin (IL)-6, IL-10, procalcitonin, and C-reactive protein and postoperative Sepsis-Related Organ Failure Assessment scores.

Material and methods: Sixty adult patients undergoing emergency abdominal laparotomy without any contraindication to TEB were randomized to receive general anesthesia alone or in combination with the TEB, which was continued for 48 hours postoperatively (n = 30 each).

Results: Use of TEB was associated with a statistically insignificant trend of preservation of anti-inflammatory response depicted by higher levels of IL-10 and lack of alteration in proinflammatory IL-6, along with appreciably lower procalcitonin levels, decreased incidence of raised C-reactive protein levels, and better postoperative SOFA score ($P > .05$). It resulted in significantly better postoperative respiratory function and faster return of bowel motility ($P < .05$). Although the sample size is too small for conclusive statement, none of the patients developed epidural abscess.

Conclusion: Thoracic epidural block showed a trend toward better preservation of anti-inflammatory response and clinical recovery that, however, failed to achieve statistical significance ($P > .05$).

1. Introduction

The use of epidural block in anesthetic practice is well established for its analgesic and nonanalgesic benefits [1].

Critically ill patients constitute a special group of patients with regard to use of epidural block. Although benefits such as analgesia, improved respiratory functions, and improved bowel motility resulting in shorter hospitalization favor its usage, presence of infection/sepsis may complicate its application [2]. This is because sepsis has traditionally been considered a contraindication for epidural blockade [3]. Recent experimental evidence, however, indicates that thoracic epidural block may confer direct benefits on progression of sepsis itself [4], by increasing perfusion of the gut [5-7] and ceratin other mechanisms as well [8-10]. Sepsis is often defined as an infection-induced host inflammatory response that is typically dysregulated and leads to organ dysfunction [11]. Consequently, the role of inflammatory mechanisms in sepsis is widely researched. It is now known that although the early hyperinflammation contributes to the organ dysfunction and early deaths, in protracted chronic cases, it is a contrasting immunosupression that drives the morbidity and mortality [12].

The effect of epidural block on inflammatory response has been an area of interest. In experimental models with sepsis/ischemia-reperfusion injury, epidural block decreased various markers of inflammation and oxidative stress [13,14]. There are suggestions of its beneficial effects on postsurgical inflammatory response also as evidenced by reduction in levels of proinflammatory mediators [15-18].

There are, however, no clinical studies evaluating effect of epidural block on infection-induced inflammatory response along with the associated organ dysfunction.

Patients of perforation peritonitis constitute the commonest surgical emergency in our part of the world, presenting with infection-induced systemic inflammation and mostly progressing to sepsis, often

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necessitating care in intensive care unit (ICU) as well. Use of thoracic epidural block is reported in this group of patients for clinical improvement in 2 trials. It resulted in improved mucosal perfusion and gut function in critically ill patients with perforation peritonitis [19], and a trend toward improved clinical outcome after abdominal laparotomy [20]. Neither of these 2 studies, however, evaluated the effect of epidural block on the inflammatory response.

Thus, we planned in the present trial to evaluate effect of thoracic epidural block on inflammatory response and associated organ dysfunction in patients with small bowel perforation peritonitis-induced systemic inflammation scheduled for emergency laparotomy. The inflammatory mediators included were proinflammatory interleukin (IL)-6, anti-inflammatory IL-10, procalcitonin, and the acute-phase reactant C-reactive protein (CRP). In addition, measures of postoperative organ function and other clinical outcomes were also evaluated.

2. Materials and methods

This randomized controlled blinded trial was undertaken after Institutional Ethical Committee approval by the Institutional Ethics Committee–Human Research, UCMS, Delhi (Secretary Prof Pramod Kumari) provided on October 26, 2012, and obtaining informed written consent from all patients.

Sixty adult patients aged between 18 and 65 years, scheduled for emergency abdominal laparotomy in view of small intestinal perforation peritonitis, and having evidence of systemic inflammatory response syndrome (SIRS) were included in the trial. The markers of SIRS were as previously defined [21].

Patients with any contraindication to epidural block such as coagulation abnormalities and mean arterial pressure less than 65 mm Hg despite adequate fluid resuscitation, or those requiring vasopressors preoperatively, refusal to undergo the procedure, skin infection at site of epidural catheter insertion, and history of sensitivity to local anesthetics or spinal disease were excluded from the trial. Patients with peritonitis due to anastomotic dehiscence or abdominal trauma were also not included.

Patients were randomized to 1 of 2 groups using computer-generated random number table (group GA: general anesthesia alone or group GT: thoracic epidural block along with general anesthesia; $n = 30$ each). Patients of group GA received general anesthesia, whereas those randomized to group GT received general anesthesia along with a thoracic epidural block that was also continued for 48 hours postoperatively to provide analgesia.

In patients randomized to group GT, epidural catheterization was performed before induction of anesthesia at vertebral level T8/9 or T9/10 via midline approach. The epidural catheter (Portex, Smith Medical International, USA) was inserted 4 to 5 cm inside the epidural space and after a test dose of 3 mL lignocaine (2%) with adrenaline (5 μg mL^{-1}) and bupivacaine (3 mL of 0.125%) along with 50 μg of fentanyl was injected through the epidural catheter. Further aliquots of bupivacaine (0.125%) were used to achieve a sensory block of at least T5-T10 as determined by complete loss to pin-prick sensation in the midline. Hypotension caused by the epidural block (>20% decrease in mean arterial pressure) was managed using intravenous fluids as well as titrated boluses of ephedrine (6 mg).

Besides the segmental thoracic epidural block performed for patients of group GT, the anesthetic and perioperative management was similar in both groups. In all patients, lead II electrocardiography, pulse oximetry, capnography, noninvasive oscillometric blood pressure, and central venous pressure (CVP) monitoring were instituted in operating room (Datex Ohmeda, Madison, Wis). For CVP monitoring, a peripherally inserted central catheter was secured. Fluid resuscitation was done using Ringer's lactate (CVP ≥ 10 cm H_2O before induction). After fluid resuscitation, heart rate, mean arterial pressure, hemoglobin oxygen saturation (Spo_2), and CVP were recorded as the baseline values.

The technique of general anesthesia also remained similar for both groups. After preoxygenation, rapid sequence intubation was done and anesthesia maintained with mixture of oxygen and nitrous oxide along with isoflurane. The fraction of inspired oxygen (Fio_2) was initiated at 0.3 and then titrated to maintain intraoperative $Spo_2 > 95\%$. Top-ups of nondepolarizing muscle relaxant were used for maintaining intraoperative muscle relaxation reversed at the end of surgery using intravenous glycopyrrolate 0.02 mg kg^{-1} along with neostigmine 0.05 mg kg^{-1} if postoperative ventilation was not indicated. Mechanical ventilation was adjusted to maintain end-tidal carbon dioxide between 35 to 40 mm Hg in both groups. If mean arterial pressure decreased to less than 65 mm Hg despite adequate CVP, noradrenaline infusion was initiated. Blood was transfused to maintain a hematocrit of at least 27%.

For group GA, intraoperative analgesia was provided by intravenous fentanyl 2 μg kg^{-1} at the time of induction followed by aliquots of 20 μg whenever required. It was provided for group GT by the epidural block along with intravenous fentanyl boluses if required. An epidural infusion of bupivacaine (0.125%) along with fentanyl (2 μg mL^{-1}) was continued for postoperative analgesia during the first 48 hours, whereas in group GA, multimodal analgesia was provided by intravenous morphine and paracetamol; titrated to a visual analog scale score lower than 4. After the first 48 hours, analgesia in both groups was provided by intravenous tramadol with/without paracetamol in the wards as per routine practice.

No attempt was made to alter perioperative supportive care, such as antibiotic administration or the surgical decisions in either group.

2.1. Outcome measures

2.1.1. Inflammatory mediators

Blood samples were collected for IL-6, IL-10, procalcitonin, and CRP determination just before anesthetic induction (baseline value), at end of surgery (only for interleukins), and on second and fourth postoperative days. The sample of blood was collected aseptically at each predefined time point and allowed to stand at room temperature for 1 hour to clot. The supernatant was removed and placed in new tube. Serum was stored at −80°C till further use. For the assay, serum was seeded on a 96-welled plate and IL-6 (Diaclone SAS, Besançon Cedex, France) and IL-10 (Diaclone SAS), and procalcitonin (Biovendor-Laboratorni medicina as, Brno, Czech Republic) measured by commercially available enzyme-linked immunosorbent assay according to the manufacturer's instruction. C-reactive protein (Tulip Diagnostics, Goa, India) levels were analyzed using a qualitative latex agglutination test. A positive agglutination identified a CRP value greater than 0.6 mg dL^{-1}. Healthy controls in the kit tested as negative (ie, < 0.6 mg dL^{-1}). Given the limited availability of procalcitonin kits, assay for procalcitonin could be done for 26 and 27 patients each of group GA and GT, respectively.

2.1.2. Postoperative organ function

The daily Sepsis-Related Organ Failure Assessment (SOFA) scores [22] calculated for first 7 postoperative days were used to derive aggregate, maximum, and delta SOFA scores. Aggregate SOFA is the sum of worst score for each organ system, whereas maximum SOFA the highest score attained over entire duration. Both aggregate and maximum SOFA scores predict cumulative organ dysfunction over the evaluated duration [23]. Delta SOFA was calculated as the difference between SOFA scores at 48 hours and the preoperative value, with a positive value, thus implying worsening of organ functions at 48 hours and a negative value, an improvement of organ functions. Delta SOFA was calculated at the end of 48 hours, as this denoted the time of cessation of the intervention, that is, thoracic epidural blockade. Postoperative worsening of individual organ function scores was also noted.

2.1.3. Other observations

The need for postoperative ventilation, ICU stay, duration of hospital stay, and occurrence of in-hospital mortality were also noted.