Effect of Preperitoneal Versus Epidural Analgesia on Postoperative Inflammatory Response and Pain Following Radical Cystectomy: A Prospective, Randomized Trial

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Objectives: Continuous wound infiltration of local anesthetics has been proposed as an alternative to epidural analgesia during abdominal surgery. Cytokines have a major role in inflammatory changes caused by surgery. This study aimed to compare the effects of continuous preperitoneal versus epidural analgesia on inflammatory cytokines postoperatively.

Materials and Methods: Forty patients scheduled for radical cystectomy were included in this observer-blinded, randomized trial; patients were randomly assigned into 2 groups to receive; continuous preperitoneal wound infiltration (PPB) or epidural analgesia (EDB). Serum levels of interleukins (IL1β, IL6, IL10, and tumor necrosis factor α) were measured at baseline (before induction of anesthesia), preinfusion (before the start of local anesthetic infusion), 6 and 24 hours postoperatively. Visual Analog Scale at rest/movement (VAS-R/M), time to the first request of analgesia, total morphine consumption, sedation score, hemodynamics, and side effects were observed 24 hours postoperatively.

Results: There was a significant reduction in IL_6, $IL_{1\beta}$ and increase in IL_{10} in PPB compared with EDB at 6 and 24 hours postoperatively and compared with preinfusion levels ($P \leq 0.001$). In EDB, a significant increase in $IL_{1\beta}$, IL_{10}, and tumor necrosis factor α at 6 hours compared with preinfusion levels ($P \leq 0.002$). VAS-R/M was significantly decreased at 2, 4, 6, 8, and 12 hours in EDB compared with PPB ($P \leq 0.014$), with no significant difference in the mean time to the first request of analgesia and total morphine consumption between the 2 groups.

Conclusion: Continuous preperitoneal analgesia better attenuated postoperative inflammatory response and provided a comparable overall analgesia to that with continuous epidural analgesia following radical cystectomy.

Key Words: epidural, preperitoneal infusion, postoperative inflammatory response

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Prevention of postoperative pain is essential for the recovery of surgical patients. Epidural analgesia is currently the international standard for perioperative pain management in abdominal surgery.[1] Thoracic epidural analgesia has a well-known effect on neurohormonal response. Attenuation of the stress response by postoperative epidural analgesia has shown several benefits such as lower pain scores and less immunologic alterations.[2] A neuroendocrine response blunted by epidural anesthesia could affect postoperative immune function because the immune and nervous systems bidirectionally communicate and influence each other.[3]

The excellent analgesic effect of epidural analgesia is clearly established, but there are several potential disadvantages, for example; preoperative hypotension, the risk of serious neurological complications (epidural hematoma and abscess), and need for preoperative placement in awake patients.[4,5]

Continuous wound infusion (CWI) with local anesthetics (LAs) at the end of surgery has been suggested as an alternative for epidural analgesia after laparotomy.[6] This is based on the recognition of the important role played by parietal nociceptive afferents in the overall pain induced by surgery. Regional anesthesia has the advantage of preventing noxious stimuli from reaching the central nervous system and therefore can attenuate the surgical stress response.[7] Surgical stress causes variable effects on hemodynamic and immunologic responses.[8]

The use of this technique has shown an efficiency in postoperative analgesia and recovery after colorectal surgery with the use of a multiholed wound catheter placed at the preperitoneal space (ie, between the parietal peritoneum and the abdominal fascia layers) and CWI analgesia.[9–11]

Cytokines are intracellular regulatory proteins acting through specific receptors and have a major role in the immune response, hematopoiesis and inflammatory changes caused by surgery or infection.[12]

The aim of this study was to compare the effect of continuous preperitoneal wound infiltration versus continuous epidural analgesia on postoperative inflammatory response and analgesia after open radical cystectomy.

MATERIALS AND METHODS

This randomized, comparative, observer-blinded trial was conducted after approval from the ethics committee of South Egypt Cancer Institute—Assiut University (Ethical committee approval no. 369) and was registered at www.ClinicalTrial.gov with identifier No: NCT03002909. After obtaining a signed, written, informed consent, patients with ASA status I-II, aged 18 to 65 years, with stage II and III bladder cancer who are scheduled for open radical cystectomy through a longitudinal, midline, infraumbilical, ≈20-cm long skin incision with

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neobladder reconstruction, were included in this study. Patients with general contraindications for the epidural blockade, the recent history of chemotherapy, radiotherapy, chronic opioid use, liver or renal impairment, known allergy for any of the study medications, coagulopathies and those with surgical wound length or orientation changed from the standard one mentioned previously were excluded.

Preoperatively, patients were taught how to use the Visual Analog Scale (VAS), scored from 0 to 10 (where 0 = no pain and 10 = worst pain imaginable) in order to evaluate the intensity of their pain and how to use patient-controlled analgesia.

Patients in all groups received preemptive conscious sedation by IV administration of 2-mg midazolam. Routine monitoring including; ECG, noninvasive blood pressure, pulse oximetry, and capnography was attached. Patients were randomly assigned using sealed envelopes into one of 2 groups (20 patients each); to receive postoperatively either: Continuous wound (preperitoneal) infiltration (PPB) group Or, continuous epidural analgesia in (EDB) group.

In the epidural group (EDB), a 16-G Touhy epidural needle (B/Braun Melsungen AG, D-34209 Melsungen, Germany) was inserted preoperatively while awake to avoid possible neural injury.[13] Thoracic epidural catheter insertion was performed by an expert anesthetist under sterile conditions through T9-T10 interspace through a paramedian approach using the "loss-of-resistance" technique and the catheter was advanced 4-cm cephalad beyond the point of epidural entry with a negative aspiration test for both blood and cerebrospinal fluid. A test dose of 3 mL of 1.5% preservative-free lidocaine with 1:200.000 epinephrine was administered in the catheter to exclude intravascular and/or intrathecal catheter insertion.

In all patients, general anesthesia was induced with intravenous fentanyl 1 μg/kg, thiopental 5 mg/kg, endotracheal intubation was facilitated with rocuronium 0.6 mg/kg, anesthesia was maintained with inhalational anesthetic isoflurane 1.5 to 1.7 MAC in 50% oxygen/air mixture and rocuronium 0.15 mg/kg bolus given every 30 minutes.

In the preperitoneal group (PPB), towards the end of surgery, a multiholed 15-cm Baxter PAINfusor catheter (MD-ON-050, Baxter International Inc., UK) was placed in the preperitoneal space (the subfascial space between the peritoneum and posterior fascia) under direct vision and tunneled via the rectus sheath to the skin, rolled out and exiting laterally and stabilized with an adhesive tape on skin. A bolus of 20 mL bupivacaine 0.25% was injected in the preperitoneal catheter and 14 mL of bupivacaine 0.25% in the epidural catheter at the end of surgery (at wound closure) and before patient extubation. Continuous infusion was started by connecting patients' catheters in both groups to a prefilled, electronic, infusion pump containing a solution of bupivacaine 0.25% at an infusion rate per hour that is half of the previous dose, that is, preperitoneal infusion rate of 10 mL/h and an epidural infusion rate of 7 mL/h. Patients were extubated after giving adequate reversal of skeletal muscle relaxant with the duration of surgery and that of anesthesia recorded.

Postoperatively, all patients were admitted to post-anesthesia care unit with the patients' heart rate, mean arterial blood pressure, respiratory rate, and oxygen saturation monitored and recorded, the presence and the severity of pain at rest and movement (coughing) was assessed using a 10-cm VAS, sedation was assessed using sedation score (awake and alert = 0, quietly awake = 1, asleep but easily aroused = 2, deeply asleep = 3). Assessment time points were immediately (baseline), 2, 4, 8, 12, 18, and 24 hours postoperatively. The occurrence of side effects of the studied drugs was observed and recorded for 24 hours postoperatively.

Rescue analgesia was allowed if the continuous bupivacaine infusion was inadequate (VAS $\geq$ 3) With an initial morphine IV patient-controlled analgesia bolus of 0.1 mg/kg once pain was expressed by the patient or if the VAS was $\geq$ 3 followed by 1-mg bolus with a lockout period of 15 minutes with no background infusion allowed.

Patient satisfaction at the time of discharge from post-anesthesia care unit was assessed by a scale of 4 points where: 1 = unsatisfactory, 2 = regular, 3 = satisfactory, and 4 = excellent.

Clinical assessment for vital signs, analgesia, side effects, patients' satisfaction, and also blood sampling was performed by an observer who was blinded to group assignment.

A 2-mL venous blood sample was obtained from each patient to measure plasma $IL_{1\beta}$, IL_6, IL_{10}, and tumor necrosis factor α (TNF_α) levels to assess inflammatory response before induction of anesthesia as a baseline for further comparisons. Another 2-mL blood sample was obtained immediately before giving the bolus injection in either the epidural or preperitoneal catheters. The last 2 venous blood samples (2 mL each) were obtained at 6 and 24 hours postoperatively.

Blood samples taken were collected in plasma tubes containing EDTA, centrifuged and stored at 20°C for assessment of plasma concentrations of $IL_{1\beta}$, IL_6, IL_{10} and TNF_α to assess level of inflammatory cytokines; all of the samples were analyzed at the same time with the same assay reagents by the same physician who was blinded to group assignment.

Our primary outcome measure was the postoperative change in the level of interleukin (IL) 6. Secondary outcome measures were the postoperative change in the levels of other measured cytokines, the mean change in VAS scores (at rest and on movement), total postoperative opioid consumption, time to the first request of rescue analgesia, patient satisfaction and the incidence of side effects or complications.

Hypotension is defined as a 15% decrease in systolic blood pressure from baseline. Bradycardia is defined as a heart rate slower than 50 beats per minute or a decrease in heart rate of $\geq$ 20% from baseline, whichever occurs first. Hypotension was treated with an IV bolus of ephidrine 0.1 mg/kg and normal saline 5 mL/kg; these doses were repeated as required. Bradycardia was treated with IV atropine 0.01 mg/kg. Postoperative nausea and/or vomiting was treated with 8-mg ondansetron and if not corrected; 10-mg metoclopramide was used.

Statistical Analysis

Our sample size calculations were based on data from previous literature on changes on the levels of IL6.[14] To detect a minimal difference of 1 SD in the IL6 levels in between, and within the study groups, it was calculated that 18 patients per group were required for the study to have a power of 80% and a type I error of 0.05, using a confidence interval (CI) of 95%.

To compensate for dropouts, we recruited 20 patients in each group to account for random errors and additional comparisons.

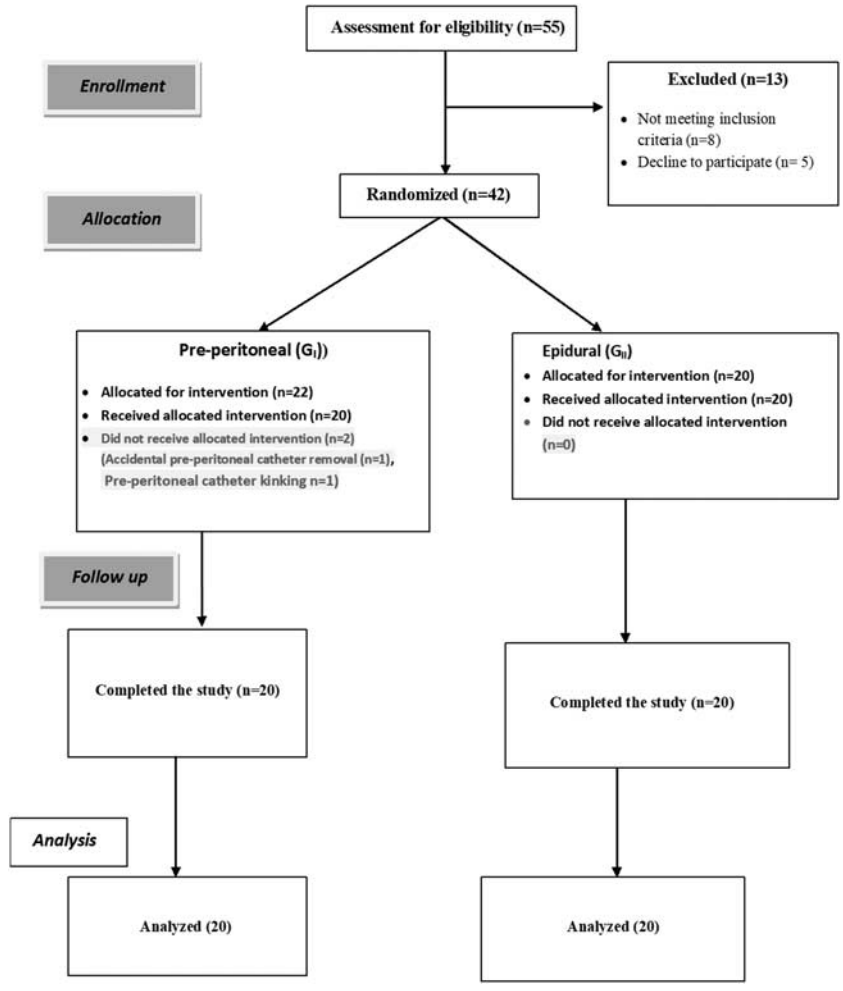

FIGURE 1. Flow chart of cases through the study.

Data entry and analysis were performed using Statistical Package for Social Science (SPSS) version 19. Data were presented as number, percentage, mean, and SD. χ^2 test was used to compare between qualitative variables. Kolmogorov-Smirnov normality test was used to test the distribution of quantitative variables to select accordingly the type of statistical testing to use. Independent sample *t* test was used for normally distributed and Mann-Whitney test was used for non-normally distributed quantitative variables between the 2 studied groups. The paired sample *t* test was used to compare between before and after follow-up in the same group. Differences were considered to be significant at $P < 0.05$.

RESULTS

Forty patients were enrolled in this study in order to investigate the analgesic efficacy of continuous preperitoneal wound infiltration (PPB) versus epidural analgesia (EDB) and the effect on the inflammatory cytokines response. Participants' flow through the study is illustrated in (Fig. 1). Looking into patients' demographic data (age, sex, weight, and ASA class) and clinical data (length of incision and surgery and anesthesia durations), there was no significant difference between the 2 groups ($P > 0.05$) (Table 1).

Examination of IL_6 level revealed there was no significant differences at the baseline and preinfusion levels between the 2 groups but there was a significant difference in (PPB) compared with (EDB) at 6 and 24 hours postoperatively ($P < 0.001$).

TABLE 1. Demographic and Operative Data of the Groups

	PPB (N = 20)	EDB (N = 20)	*P*
Age (y)	45 ± 8	47 ± 8	0.273
Sex			0.527
Male	11 (55)	9 (45)	
Female	9 (45)	11 (55)	
Weight (kg)	76 ± 9	75 ± 7	0.454
Length of incision (cm)	16 ± 3	16 ± 3	0.775
Duration of surgery (min)	145 ± 18	147 ± 14	0.463
Duration of anesthesia (min)	154 ± 15	156 ± 13	0.455
ASA score			0.197
ASA I	10 (50)	14 (70)	
ASA II	10 (50)	6 (30)	

Data are presented as mean ± SD and number (percentage).
ASA indicates American Society of Anesthesiologist; EDB, epidural group; PPB, preperitoneal group.

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TABLE 2. Mean Changes in the Level of Interleukins (pg/mL) ($IL_{1\beta}$, IL6, IL10, and TNF_{α}) During the 24 hours Postoperatively

	Preperitoneal Group (PPB) (N = 20)	Epidural Group (EDB) (N = 20)	P^1
$IL_{1\beta}$			
At baseline	1.4 ± 0.2	1.3 ± 0.2	0.081
Preinfusion	1.6 ± 0.4	1.6 ± 0.5	0.630
After 6 h	1.4 ± 0.3	2.6 ± 0.9	0.000*
P^2	0.124	0.000*	
After 24 h	1.3 ± 0.2	2.1 ± 0.5	0.000*
P^3	0.015*	0.000*	
IL6			
At baseline	20.2 ± 8.7	21.7 ± 8.2	0.715
Preinfusion	188.8 ± 63.5	220.9 ± 62	0.152
After 6 h	97 ± 33.4	227 ± 61	0.000*
P^2	0.000*	0.338	
After 24 h	84.8 ± 25.7	224.5 ± 58	0.000*
P^3	0.000*	0.599	
IL10			
At baseline	14.8 ± 9	16.9 ± 8	0.534
Preinfusion	30.5 ± 16.5	38.6 ± 22.6	0.218
After 6 h	178 ± 59	116.8 ± 26.3	0.000*
P^2	0.000*	0.000*	
After 24 h	148 ± 55.3	33.4 ± 13	0.000*
P^3	0.000*	0.443	
TNF_{α}			
At baseline	6.5 ± 1.3	6.2 ± 2.8	0.646
Preinfusion	28.2 ± 12.6	32.7 ± 8.3	0.433
After 6 h	38.4 ± 9.6	48.7 ± 15.5	0.042*
P^2	0.007*	0.001*	
After 24 h	38.1 ± 9.6	36.5 ± 6.6	0.745
P^3	0.909	0.007*	

Data are presented as mean ± SD.

*P-value <0.05.

[1]P-value obtained by comparing preperitoneal (PPB) to epidural (EDB) group.

[2]P-value obtained by comparing level of interleukins at 6 hours to the preinfusion level in the same group.

[3]P-value obtained by comparing level of interleukins at 24 hours to the preinfusion level in the same group.

IL indicates interleukin; TNF_{α}, tumor necrosis factor.

Moreover, there was a significant difference only in (PPB) at 6 and 24 hours compared with the preinfusion levels ($P < 0.001$) (Table 2) (Fig. 2). As regards changes in the $IL_{1\beta}$ level; there was no significant difference at the baseline and preinfusion levels between the 2 groups but there was a significant difference in (PPB) compared with (EDB) at 6 and 24 hours postoperatively ($P < 0.001$). Comparing postinfusion to preinfusion levels within each group, there was a significant decrease at 24 hours in (PPB) and a significant increase at 6 and 24 hours levels in (EDB) (Table 2) (Fig. 3).

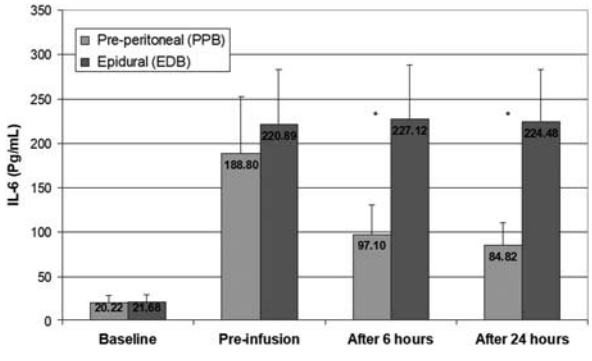

FIGURE 2. Mean changes in serum level of interleukin 6 (IL6) (pg/mL) in the 24 hours postoperatively. Data are presented as mean and SD; Whiskers represent SD. After 6 or 24 hours indicates 6 and 24 hours after beginning local anesthetics infusion postoperatively; baseline, before induction of anesthesia; EDB, epidural group; PPB, preperitoneal group; preinfusion, immediately before local anesthetics infusion in either the epidural or preperitoneal catheters. *$P < 0.05$.

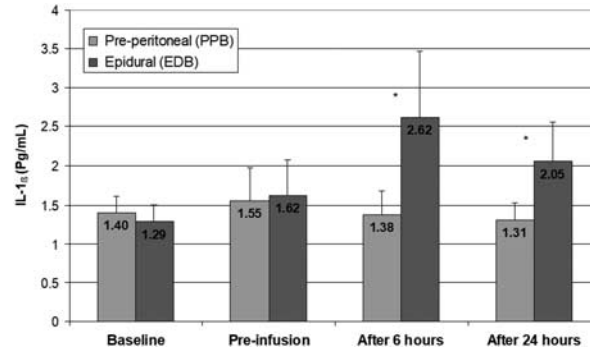

FIGURE 3. Mean changes in serum level of interleukin 1β (IL1β) (pg/mL) in the 24 hours postoperatively. Data are presented as mean and SD; Whiskers represent SD. After 6 or 24 hours indicates 6 and 24 hours after beginning local anesthetics infusion postoperatively; baseline, before induction of anesthesia; EDB, epidural group; PPB, preperitoneal group; preinfusion, immediately before local anesthetics infusion in either the epidural or preperitoneal catheters. *$P < 0.05$.

No significant differences were observed in IL10 between the 2 groups at the baseline and preinfusion levels, but there was a significant increase in (PPB) compared with (EDB) ($P < 0.001$) at 6 and 24 hours, also there was a significant increase in IL10 levels at 6 and 24 hours and at 6 hours within PPB and EDB groups, respectively compared with the preinfusion levels ($P < 0.001$) (Table 2) (Fig. 4). As regards TNF_{α} there was no significant difference at the baseline and the preinfusion levels between groups but there was a significant decrease at 6 hours in PPB compared with EDB ($P = 0.042$), and when comparing levels at 6 hour to the preinfusion level; there was a significant increase in PPB ($P = 0.006$), and at 6 and 24 hours in EDB ($P = 0.007$) (Table 2) (Fig. 5).

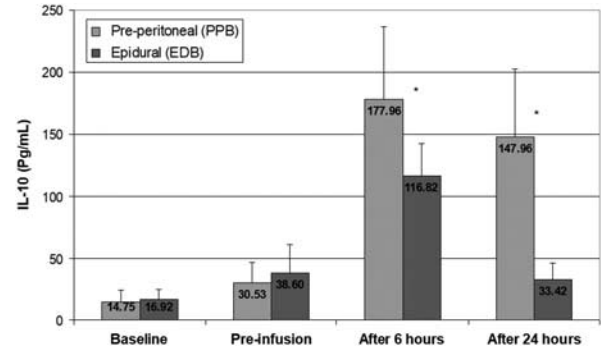

FIGURE 4. Mean changes in serum level of interleukin 10 (IL10) (pg/mL) in the 24 hours postoperatively. Data are presented as mean and SD; Whiskers represent SD. After 6 or 24 hours indicates 6 and 24 hours after beginning local anesthetics infusion postoperatively; baseline, before induction of anesthesia; EDB, epidural group; IL10, interleukin 10; PPB, preperitoneal group; preinfusion, immediately before local anesthetics infusion in either the epidural or preperitoneal catheters. *$P < 0.05$.

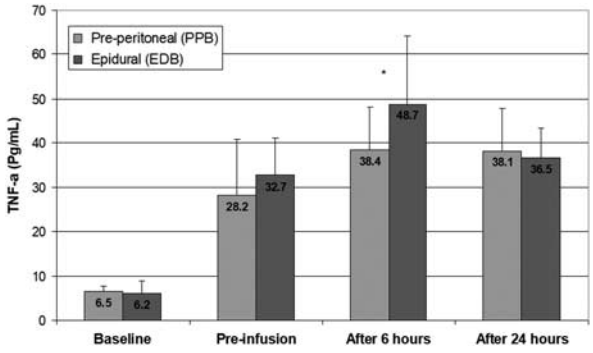

FIGURE 5. Mean changes in serum level of tumor necrosis factor (TNF_α) (pg/mL) in the 24 hours postoperatively. Data are presented as mean and SD; Whiskers represent SD. After 6 or 24 hours indicates 6 and 24 hours after beginning local anesthetics infusion postoperatively; baseline, before induction of anesthesia; EDB, epidural group; PPB, preperitoneal group; pre-infusion, immediately before local anesthetics infusion in either the epidural or preperitoneal catheters. *$P < 0.05$.

There were statistically significant differences in VAS score at rest and movement between the 2 studied groups at 2, 4, 6, 8, and 12 hours ($P \leq 0.014$) postoperatively (Figs. 6, 7). Only 7 patients in PPB (35%) and 6 in EDB (30%) ($P = 0.736$) groups requested supplementary analgesia with the mean time to the first request of supplementary analgesia of 20.86 (95% CI, 19.31-22.41 h) and 19.50 (95% CI, 15.37-23.63 h) in (PPB) and (EDB), respectively ($P = 0.736$). The mean total morphine consumption was 7.29 (95% CI, 6.41-8.17 mg) and 7.50 (95% CI, 6.93-8.08 mg) ($P = 0.812$) in PPB and EDB, respectively. A number of 6 patients (30.0%) had a "satisfied" satisfaction score in both GI and EDB; 14 patients (70.0%) had an "excellent" score in both groups PPB and EDB (Table 3).

As regards postoperative hemodynamic variables, a statistically significant decrease in the mean arterial blood pressure was observed at 2, 4, and 6 hours and an increase in the heart rate at 2 and 4 hours postoperatively in EDB compared with PPB ($P \leq 0.031$). No significant differences in the respiratory rate and oxygen saturation between the 2 groups were observed. No significant difference was observed between the 2 groups in the sedation score ($P > 0.05$).

In the EDB group, 2 patients (10%) had nausea and vomiting, only 1 patient (5%) developed hypotension and 1 patient (5%) developed sedation with no other side effects observed. no significant differences were observed between the 2 groups.

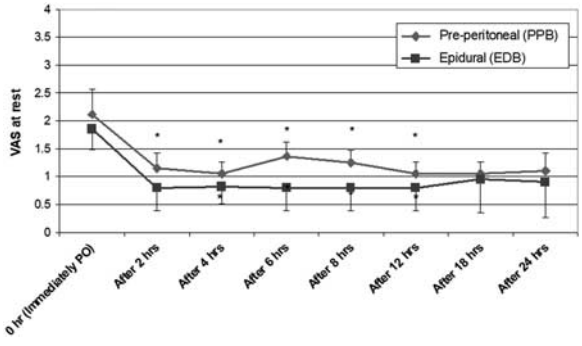

FIGURE 6. Visual Analog Scale at rest (VAS-R) in the 24 hours postoperatively. Mean VAS-R scores for pain intensity at rest at different times postoperatively. Data are presented as mean and SD; Whiskers represent SD. EDB indicates epidural group; PPB, preperitoneal group; PO, postoperative. *$P < 0.05$.

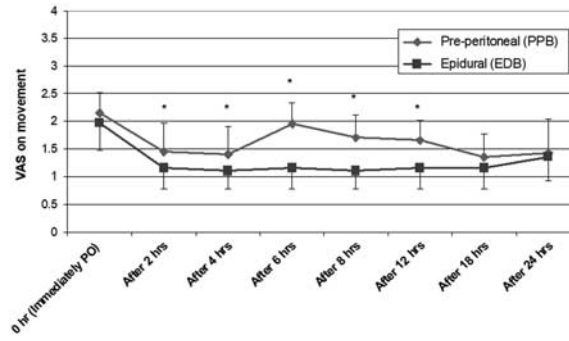

FIGURE 7. Visual Analog Scale at movement (VAS-M) in the 24 hours postoperatively. Mean VAS-M for pain intensity at movement (on coughing) at different times postoperatively. Data are presented as mean and SD; Whiskers represent SD. EDB indicates epidural group; PPB, preperitoneal group; PO, postoperative. *$P < 0.05$.

DISCUSSION

Continuous wound infusion (CWI) of LAs through a fenestrated catheter placed by the surgeon at the site of the wound incision has been proven to improve postoperative analgesia in several types of surgery. Use of CWI with a LA has proven efficacy for postoperative pain relief with a very low toxicity and failure rate in many fields of surgery. LAs prevent and alleviate postoperative pain by reversibly blocking the conduction of nerve nociceptive impulses responsible for the sensation of pain.[15]

A large body of literature suggests that LAs exert a significant anti-inflammatory effect when administered systemically.[16] LAs have been found to inhibit immune

TABLE 3. Number of Patients who Received Supplementary Analgesia and Mean Time of First Request of Supplementary Analgesia (h) and Total Amount of Postoperative Morphine Consumption (mg) After Local Anesthetic Infusion in the 24 Hours Postoperatively

	PPB (N = 20)	EDB (N = 20)	*P*
No. patients who requested for supplementary analgesia in the first 24 h postoperatively			0.736
Yes	7 (35)	6 (30)	
No	13 (65)	14 (70)	
First request (h)	20.86 (19.31-22.41)	19.50 (15.37-23.63)	0.664
Total morphine dose (mg)	7.29 (6.41-8.17)	7.50 (6.93-8.08)	0.812
Patient satisfaction			1.000
Unsatisfactory	0	0 (0)	
Regular	0	0 (0)	
Satisfactory	6 (30)	6 (30)	
Excellent	14 (70)	14 (70)	

Data are presented as mean (95% CI) and number (percentage).
CI indicates confidence interval; EDB, epidural group; PPB; preperitoneal group.

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function and the migration of granulocytes to inflamed tissue, thereby attenuating the release of proinflammatory mediators such as IL1, IL8, and TNF.[17,18]

However, little is known about the effects of LAs when administered locally rather than systemically. Local administration may result in effects quite different from those observed after systemic administration because resident cells such as keratinocytes are critically involved in local inflammatory processes after tissue injury.[19,20]

In our study, we compared the analgesic efficacy of continuous preperitoneal wound infiltration to epidural analgesia and its effect on inflammatory cytokines in patients for whom open radical cystectomy was conducted. We found that there was a reduction in $IL_{1\beta}$, IL_6, and TNF_α in the preperitoneal group compared with epidural group and a significant reduction within the same group when comparing the postinfusion to the preinfusion levels. At the same time there was a significant increase in the level of IL_{10} in the preperitoneal group compared with epidural group and within the same group when comparing the postinfusion to the preinfusion levels, with a satisfactory analgesic profile and hemodynamic stability in the preperitoneal group compared with the epidural group without significant side effects.

Continuous preperitoneal wound infiltration is easy to implement and seems to be devoid of possible serious side effects or complications of neuroaxial blocks, making specific supervision unnecessary. In our study, continuous preperitoneal analgesia decreased pain intensity and reduced total dose of rescue morphine with its systemic side effects, and it was associated with more attenuation in the postoperative inflammatory response. It could, therefore, be considered as one of the interesting alternatives to epidural analgesia especially in this specific group of immunocompromised cancer patients.

The findings of our study with regard to postoperative analgesia were in line with the results of a study by Mungroop et al[21] who found that continuous wound infiltration was noninferior to epidural analgesia for patients undergoing hepato-pancreato-biliary surgery. Moreover, Beaussier et al[9] concluded that continuous preperitoneal infiltration of 0.2% ropivacaine at 10 mL/h during 48 hours was an effective method to relieve pain after open colorectal surgery as it reduced morphine consumption and accelerated the postoperative recovery. Ozer et al[22] reported that preperitoneal catheter analgesia is an effective analgesic method when applied and used properly. Moreover, Bertoglio et al[23] concluded that preperitoneal continuous wound infusion with ropivacaine after open colorectal cancer surgery provided effective postoperative pain relief not inferior to continuous epidural infusion analgesia.

Two main groups of cytokines are present; proinflammatory cytokines (eg, TNF_α and IL_6) and anti-inflammatory cytokines (eg, IL_{10}).[14] The balance between proinflammatory and anti-inflammatory cytokines limit the spread of infection, tissue injury, and promote tissue healing and repair by their local and systemic effects.[24] A study by Baker and colleagues determined that proinflammatory cytokine levels can be used as a surrogate marker of local and systemic inflammatory responses following major elective colorectal surgery and showed that the intraperitoneal drainage fluid, analyzed for local wound healing, reflected the microenvironment from which it was collected. After trauma, cytokines are primarily synthesized and released at the site of injury before they are released systemically.[25]

We were specifically interested in studying the role of IL_6, TNF_α, and IL_{10} during surgical trauma. IL_6 has been shown to be a sensitive marker of inflammation and increases after surgeries, both locally as well as in the plasma. IL_6 is secreted by T cells and macrophages and stimulates the immune response after trauma or following tissue damage.[26,27]

In our study, there was a significant increase in the level of IL_6 which peaked in the preinfusion sample and started to decrease after 6 hours in the preperitoneal group. After 24 hours it reached a lower level but still higher than baseline levels. These changes were significantly lower than in the epidural group which indeed means more attenuation to the inflammatory response thus might be explained by the proximity of preperitoneal catheter to the surgical site, and thus, blockade of cytokines from its original site of release to the systemic circulation. This was in agreement with results of Kuchalik et al[28] who found a modest preventive effect of local infiltration of anesthesia on early postoperative inflammation by a lower IL_6 concentration at 4 hours as well as lower CRP concentration 3 days more than femoral nerve block after total hip arthroplasty. The longer duration of cytokine response attenuation in our study could be explained by continuous infiltration all over the 24 hours postoperatively instead of single-shot injection.

IL_6 is primarily responsible for the hepatic response, resulting in the synthesis of acute phase proteins and C-reactive protein, activation of immunosuppressive cytokines such as IL_{10}, and hematopoiesis.[29] IL_{10} is a powerful anti-inflammatory cytokine that downregulates the expression of Th1 cytokines. IL_{10} is capable of inhibiting the synthesis of proinflammatory cytokines like TNF_α, IL_6, IL_8, and $IL_{1\beta}$[30] and also provides protection from ischemia and reperfusion injury.[31] It also displays a potent ability to suppress the antigen-presentation capacity of antigen-presenting cells; however, it is also stimulatory toward certain T cells and mast cells and stimulates B-cell maturation and antibody production.[32] In our study, there was a significant increase in IL_{10} in the epidural and preperitoneal groups at 6 hours postoperatively but it was more in the preperitoneal group which may indicate more protection against inflammation and, on the contrary to the epidural group, this rise persisted in the preperitoneal group for up to 24 hours postoperatively. Our findings are in accordance with Xu et al[14] who demonstrated that the combination of thoracic epidural anesthesia and propofol causes a reduction in IL_6 levels, and an increase in IL_{10} compared witho general anesthesia in cancer colon patients and may influence cancer outcome. Further, our findings are agreeing with the study by Sultan[24] who reported that IL_{10} increased in the postoperative period. In addition, Amin and Salah[33] compared spinal versus general anesthesia and found a lower inflammatory response in the spinal anesthesia group. In another study, no significant differences in plasma TNF_α or IL6 were found between patients operated under general or regional anesthesia.[34]

Our study was limited by a number of factors, first: the blinding of the study, which is observer-blinded, of course, a double-blinded study would have yielded more powerful conclusions ruling out any possible bias, second: the short follow-up period (only for 24 h postoperatively) and the few number of measurements of cytokines. We recommend further double-blinded research work, with longer follow-up period and more frequent measurements of cytokines levels with the correlation between laboratory results and the overall surgical outcome.

In conclusion, continuous preperitoneal analgesia better attenuated postoperative inflammatory response and provided a comparable overall analgesia to that with continuous epidural analgesia after open radical cystectomy.

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