Original Article

Suppression of perioperative stress response in elective abdominal surgery: A randomized comparison between dexmedetomidine and epidural block

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Abstract

Background and Aims: Stress response after surgery induces local and systemic inflammation which may be detrimental if it goes unchecked. Blockade of afferent neurons or inhibition of hypothalamic function may mitigate the stress response.
Material and Methods: A total of 50 consenting adult ASA I/II patients undergoing elective abdominal surgery were randomized to receive either dexmedetomidine (**Group D**) or epidural bupivacaine (**Group E**) in addition to balanced general anesthesia. Laparoscopic surgery, contraindications to epidural administration, history of psychiatric disorders, obesity (BMI >30 kg/m^2), on beta blockers or continuous steroid therapy for >5 days over last 1 year, and known case of endocrine abnormalities or malignancy were excluded. Serum cortisol, blood glucose, and blood urea were estimated. Hemodynamic parameters, total dose of dexmedetomidine, bupivacaine, emergence characteristics, and analgesic consumption over 24 h postoperatively were recorded. Statistical comparisons were done using Student's *t*-test, repeated measure analysis of variance followed by Dunnett's test, generalized linear model and Chi-square/Fisher's exact test. A P value <0.05 was considered significant.
Results: Serum cortisol levels were significantly lower in group E than group D 24 h after surgery ($P = 0.029$). Intraoperative and postoperative glucose level was lower in group E compared with group D. Time to request of first rescue analgesic was longer in group E than group D ($P = 0.040$). There was no significant difference between the number of doses of paracetamol required in the postoperative period ($P = 0.198$).
Conclusion: Epidural bupivacaine was more effective than intravenous dexmedetomidine for suppression of neuroendocrine and metabolic response to surgery. Dexmedetomidine provided better hemodynamic stability at the time of noxious stimuli and postoperatively.

Keywords: Anesthesia technique, cortisol, dexmedetomidine, stress response, surgery

Introduction

Surgical procedures evoke a variety of stress response.[1,2] While minor stressors induce a transient local inflammatory response that may be pro-healing,[3] major stressors may lead to potentially detrimental systemic inflammation.

Stress response is mediated by corticotropin (ACTH), which in turn stimulates the adrenal cortex and increases cortisol secretion. Cortisol promotes protein breakdown and gluconeogenesis.[1] The stimulation of sympatho-adrenal-medullary axis results in increased secretion of epinephrine and norepinephrine.[1,3] Stress response mediated effects include increased myocardial contractility, oxygen demand, coronary and cerebral vasodilatation, sodium and water retention, hypercoagulability, fibrinolysis, immunosuppression, wound infections, hyperglycemia, and reduced urinary output.[1,3-5] The adversely

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effected patient-related outcomes include delayed surgical wound healing and mobilization, and increased length of hospital stay.[3] Surgical stress is, therefore, undesirable and should be curbed.[1,3]

Several perioperative factors contribute toward surgical stress, and their modification may aid in modulating stress response. Minimally invasive rather than open surgical techniques, optimum perioperative analgesia, hormonal treatments, and regulation of nutrition are some of the effective interventions to attenuate stress response.[1,3,6]

Epidural block, due to its excellent analgesic property, reduces afferent input from operative site to central nervous system and hypothalamo-pituitary axis, thus suppresses the stress response and facilitates early postoperative physiotherapy and rehabilitation.[7,8]

Dexmedetomidine, an $\alpha 2$ agonist, by virtue of reducing central sympathetic outflow,[9,10] effectively suppresses hemodynamic responses to noxious stimuli.[11,12] Dexmedetomidine was earlier noted to reduce surgical stress by reducing serum cortisol, thereby enhancing postoperative recovery.[13]

It appears that owing to its centrally mediated mechanism of action, dexmedetomidine may be better than epidural block for suppressing perioperative stress response. However, a previous study reported similar efficacy of dexmedetomidine and epidural block for intraoperative stress response suppression.[2] There was no mention of postoperative markers in this study. This is despite the likelihood that in clinical practice, once an epidural catheterization is performed, it will be used to provide postoperative analgesia as well. And depending on this extended use of epidural block in postoperative period, the stress response may vary in postoperative period also.

Against the above background, we aimed to evaluate and compare intraoperative use of dexmedetomidine along with general anesthesia, versus epidural block extended onto postoperative period along with general anesthesia, on markers of neuroendocrine and metabolic stress response during intraoperative as well as postoperative period following elective abdominal surgeries.

The primary outcome variable was serum cortisol level and secondary ones included blood glucose, blood urea, as well as hemodynamic stability.

Material and Methods

This prospective, randomized, comparative study was registered with Clinical Trial Registry of India – Indian Council of Medical Research prior to patient enrollment (Registration number CTRI/2018/11/016289). The procedures followed were in accordance with the ethical standards of the Institutional Ethics Committee-Human Research and with the Helsinki Declaration of 1975, as revised in 2000 (approved in the meeting held on 26.10.2018; Chairperson: Prof. Nalin Mehta). The study was conducted between December 2018 and March 2020.

A total of 50 patients with American Society of Anesthesiologists physical status I or II aged between 18 and 60 years and scheduled for elective abdominal surgery under general anesthesia were included. A written and informed consent was taken from each participant before enrollment. Patients undergoing laparoscopic abdominal surgery, with obesity (BMI >30 kg/m^2), contraindications to epidural administration viz., infection at local site, INR >1.5 or hemodynamic instability, those receiving continuous steroid therapy for >5 days during last 1 year or beta blockers, history of allergy to therapeutic drugs used in the study, and those with any known endocrine abnormalities as well as present or past malignancy were excluded from the study.

Patients were randomly allocated to one of the following two groups according to a computer-generated random number table. Patients of group D received intraoperative dexmedetomidine infusion and those in group E received epidural infusion of bupivacaine intraoperatively followed by boluses postoperatively.

For patients of group D, a loading dose of dexmedetomidine (0.6 μg/kg i.v.) was administered over 10 min before induction; followed by 0.4 μg/kg/h i.v. For group E patients, the epidural catheter was inserted at T9-T10 or T10-T11 intervertebral level in the midline with patients in the sitting position, using loss of resistance to air technique for identifying the epidural space. The catheter was threaded 4 to 5 cm inside epidural space and a test dose of 3 ml (2% lignocaine with 1:200000 adrenaline) was injected after confirming absence of blood and cerebrospinal fluid through it. This was followed by a 5-ml bolus to confirm onset of block, and then an infusion (5 ml/h) of plain bupivacaine (0.25%) using a syringe pump. After the last skin suture was placed, the respective infusion of dexmedetomidine (group D) or epidural bupivacaine (group E) was discontinued. The test interventions were carried out after establishing the monitoring and intravenous access in operating room.

In the operating room, monitoring was instituted for all patients including pulse oximetry, lead II electrocardiography, end-tidal capnography, and non-invasive oscillometric blood pressure measurements. Intravenous access was established and balanced salt solution infusion was initiated. The technique of general anesthesia was standardized for patients of either group. Anesthesia was induced using titrated doses of propofol (1%) after injecting fentanyl (1 μg/kg). Vecuronium (0.1 mg/kg) was administered to facilitate muscle relaxation and endotracheal intubation. Anesthesia was maintained with 33% O_2 in N_2O and isoflurane at 1 ± 0.2 minimum alveolar concentration, along with intermittent top-ups of vecuronium administered for continued muscle relaxation. Intraoperative analgesia was supplemented with fentanyl (1 μg/kg) if required. Bradycardia (heart rate <50 beats/min) was managed with atropine 0.6 mg and hypotension (mean arterial pressure <60 mmHg) using mephentermine 6 mg Neuromuscular blockade was reversed with neostigmine (0.05–0.08 mg/kg) and glycopyrrolate (0.008–0.01 mg/kg).

At the time of emergence, the level of sedation-agitation was evaluated using the Riker sedation agitation scale[14] (1: unarousable; 2: very sedated; 3: sedated; 4: calm and cooperative; 5: agitated; 6: very agitated; 7: dangerous agitation). A score of ≥5 was defined as emergence agitation. For postoperative analgesia, evaluated over first 24 h postoperatively, the therapeutic protocol varied between both groups due to presence of epidural catheter in group E. For group D patients, infiltration at the surgical site skin incision was done with 0.25% bupivacaine (8–10 ml) at the end of surgery, prior to reversal. Postoperative pain was measured on a 10-cm Visual Analog Scale (VAS) where "0" denoted no pain and "10" denoted worst pain. At VAS >3, patients of group D received tramadol 1 mg/kg i.v. and those in group E received an epidural bolus of 0.25% bupivacaine (5–8 ml). Subsequent dose of tramadol or epidural bupivacaine was given in respective group keeping a dosing interval of at least 6 h. Paracetamol (1 gm i.v.) was given as a rescue analgesic whenever required in either group.

Venous blood sample was withdrawn prior to induction and institution of the test intervention (baseline, T0), 30 min after surgical incision (T1), at the time of extubation (T2), 2 h post-extubation (T3), and 24 h post-surgery (T4).

Serum cortisol was measured at all the above mentioned time points (T0 to T4) using commercially available kits based on the Enzyme-Linked Immuno-Sorbent Assay (ELISA) technique (DRG® Cortisol ELISA kit, DRG Instruments GmBH, Germany; range: 0–800 ng/ml). Blood glucose estimation was carried out using a bed side-glucometer at all the five time points described above (T0 to T4). Blood urea levels were estimated at T0 and T4 time-points using the institutional biochemistry laboratory facility.

Heart rate and mean arterial pressure were recorded just prior to induction (baseline: T0), just before and immediately after tracheal intubation, at the time of surgical incision, every 10 min subsequently till skin closure, at the time of extubation, and every 30 min postoperatively till 120 min. In addition, heart rate and mean arterial pressure were also noted at the end of loading dose of dexmedetomidine (0.6 μg/kg i.v.) in group D and epidural bolus of bupivacaine (5 ml) in group E.

Incidence of emergence-agitation as assessed by Riker's sedation-agitation score, dose of propofol required for induction, total dose of intraoperative fentanyl, time to request for first dose of analgesic, 24 h consumption of tramadol (group D only), 24 h epidural bupivacaine consumption in the postoperative period (group E only), and number of doses of paracetamol requested within 24 h postoperative period for both groups were also recorded.

Statistical analysis

As per the reported variability of 6.0 μg/dl (60 ng/ml) for serum cortisol associated with use of dexmedetomidine[15] and 8.1 μg/dl (i.e., 81 ng/ml) with epidural analgesia[16] to estimate a mean difference of 6.0 μg/dl (60 ng/ml) in serum cortisol at 24th postoperative hour, a sample of 22 cases in each group was required at $\alpha = 5\%$ and power = 80%. To account for a 10% failure rate with epidural catheter insertion, 25 cases were included in each group.

Data entry was done in spreadsheet and statistical analysis was done using IBM SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, N.Y., USA). Unpaired student t-test was applied for comparing one-time measured normally distributed quantitative data. Non-normally distributed data were analyzed using Mann–Whitney U-test. Comparison of serum cortisol, blood glucose, urea, and postoperative hemodynamic parameters were done using repeated measure analysis of variance (ANOVA). Since the duration of surgical procedures was variable, the number of patients with available values of repeated hemodynamic parameters also differed at various time points in the intraoperative period. Linear mixed model was applied for heart rate and mean arterial pressure, the best covariance structure was determined on the basis of Akaike's information criterion (AIC). Heterogeneous first order autoregression found the minimum AIC, and estimated marginal mean (standard error) of respective variables at different time points was reported after considering covariance structure. Qualitative parameters were compared using Chi-square/Fisher's exact test. A P value < 0.05 was considered significant.

Results

The CONSORT patient enrollment flow chart is depicted in Figure 1. A total of 59 adult patients were assessed for eligibility and finally data from 49 were analyzed. The demographic profile of the participants and the type of surgical procedures are shown in Table 1. The levels of biochemical markers for stress response are shown in Table 2.

The primary outcome measure viz, the serum cortisol level was significantly lower for group E than group D at the 24th postoperative hour (T4) but it was not significantly different at any of the other time points including the baseline [Table 2]. Blood glucose values were significantly lower for group E as compared with group D at T1, T2, and T4; with borderline significance at T3, despite being similar at baseline [Table 2]. Blood urea levels was not significantly different between the groups at either time point, that is, baseline and 24 h after surgery [Table 2].

The hemodynamic stability was also assessed to reflect the stress response. Figure 2 shows the estimated marginal means of heart rate during the intraoperative period. The heart rate for group D was consistently lower than in group E throughout the intraoperative period. Significantly lower heart rate values were observed in group D than group E after loading drug ($P = 0.001$), after intubation ($P = 0.017$), at 90 min ($P = 0.014$), 120 min ($P = 0.032$), 150 min ($P = 0.007$), after skin closure ($P = 0.011$), and at the time of extubation ($P = 0.015$).

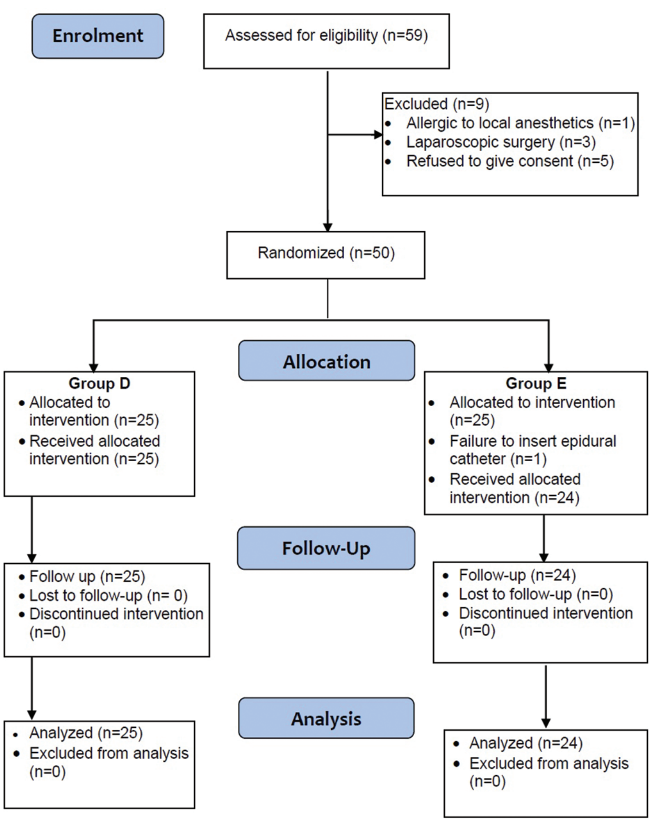

Figure 1: CONSORT Flow Diagram

The estimated marginal mean of mean arterial pressure during intraoperative period is shown in Figure 3. The estimated mean of mean arterial pressure between groups was not significantly different at any time point ($P > 0.05$).

Both hemodynamic parameters showed similar trend during the observed postoperative period. While the mean heart rate was significantly lower for group D than group E ($P = 0.018$), the mean arterial pressure was non-significantly different between the groups ($P = 0.314$). None of the study patients

Table 1: Comparison of demographic parameters and type of surgical procedure

Parameter	Group D (n=25)	Group E (n=24)
Age* (years)	40.7±11.4	38.3±8.2
Height* (cm)	154.3±6.1	157.0±5.1
Weight* (kg)	58.2±11.2	57.1±8.3
Body mass index (kg/m²)*	24.4±4.2	23.1±2.7
ASAphysical status † (I: II)	22:3	24:0
Gender† (Male: Female)	22:3	21:3
Upper abdominal surgeries (Incision above umbilicus)‡		
Open cholecystectomy	13 (52)	09 (37.5)
Abdominal rectopexy	00 (0)	01 (4.16)
Lower abdominal surgeries (Incision below umbilicus)‡		
Total abdominal hysterectomy	09 (36)	09 (37.5)
Benign ovarian cystectomy	00 (0)	03 (12.5)
Abdominal myomectomy	02 (8)	01 (4.16)
Laparotomy for benign colonic stricture	00 (0)	01 (4.16)
Tubal recanalization	01 (4)	00 (0)

**values are expressed as mean±SD; †values are expressed as ratio; ‡values are expressed as number (percentage)*

Table 2: Comparison of various biochemical markers for stress response

Time point	Group D (n=25)	Group E (n=24)	P
Serum cortisol (ng/ml)			
T0	188.9±73.0	180.3±69.8	0.678
T1	312.2±97.8	262.4±90.3	0.070
T2	327.3±127.7	331.7±150.6	0.914
T3	364.6±128.5	402.4±158.7	0.363
T4	245.3±92.5	186.1±90.8	0.029
Blood glucose (mg/dl)			
T0	101.6±8.9	102.0±8.9	0.877
T1	131.2±25.4	115.5±19.0	0.019
T2	136.0±21.1	121.1±19.1	0.012
T3	136.7±19.4	126.7±15.8	0.054
T4	131.6±18.0	121.7±15.3	0.044
Blood urea (mg/dl)			
T0	22.2±5.7	20.3±4.98	0.212
T4	27.9±6.2	25.96±5.8	

T0: baseline; T1: 30 min after surgical incision, T2: at the time of extubation, T3: 2 h after extubation; T4: 24 h after surgery; All values are expressed as mean±SD; P<0.05 significant

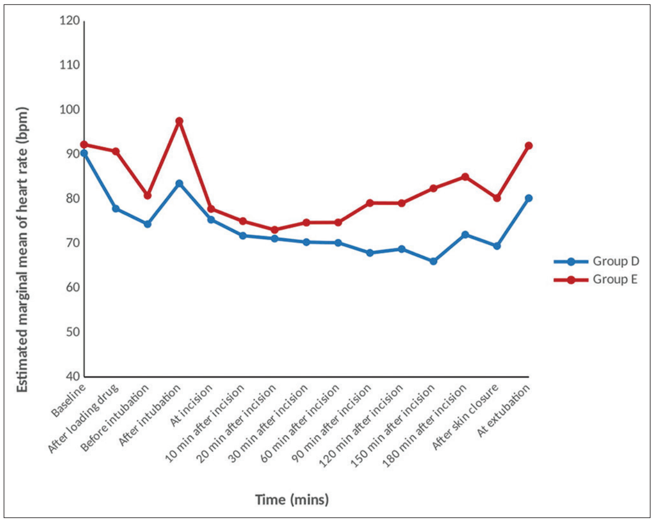

Figure 2: Estimated marginal mean of heart rate in the intraoperative period

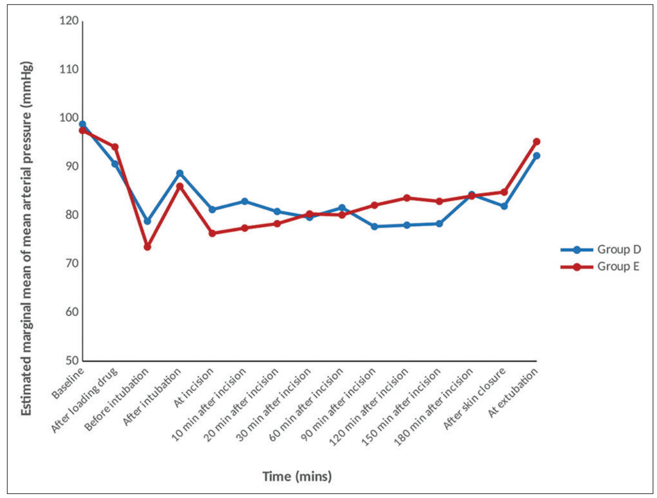

Figure 3: Estimated marginal mean of mean arterial pressure in the intraoperative period

had emergence-agitation as per the Riker's sedation agitation scale. In group D, 18 (72%) patients were sedated (score 3) as compared with 4 (16.7%) in group E; while 18 (75%) patients in group E were calm and co-operative (score 4) compared with 6 (24%) in group D. Table 3 shows other ancillary observations. The dose of propofol required for induction, total dose of intraoperative fentanyl, and number of doses of paracetamol requested within 24 h were not significantly different between the two groups. The time to request of first dose of analgesic was significantly shorter in group D compared with group E ($P = 0.040$).

Table 3: Ancillary observations

Variable	Group D (n=25)	Group E (n=24)	P
Propofol* (mg)	100.0±30.4	115.8±26.2	0.057
Fentanyl* (μg)	64.1±17.5	61.2±16.3	0.550
Time to request of 1st dose of analgesic* (min)	42.2±16.8	55.0±24.9	0.040
Number of doses of tramadol in 24 h*	2.4±0.6	--------	--------
Number of doses of bupivacaine in 24 h*	--------	2.3±0.5	--------
Number of doses of paracetamol in 24 h†	3 [3-4]	3 [2-3.5]	0.198

**values are expressed as mean±SD; †values are expressed as median [IQR]; P<0.05 significant*

Discussion

This study was designed to compare stress response evoked by abdominal surgery conducted under general anesthesia with one of the adjunctive two regimes: intraoperative infusion of dexmedetomidine or a perioperative epidural blockade.

The salient findings included a significantly lower serum cortisol level at 24th postoperative hour after surgery ($P = 0.029$) as well as blood glucose during intraoperative as well as postoperative period for those receiving the perioperative epidural blockade as compared with intraoperative dexmedetomidine infusion. Although epidural regimen exhibited significantly higher heart rates as compared with the intraoperative dexmedetomidine infusion one at the time of noxious stimuli (viz., intubation and extubation as well as during postoperative period), the mean arterial pressure was not significantly different. Neither was there any significant difference in the blood urea level at 24th h postoperatively ($P = 0.212$).

Epidural analgesia combined with general anesthesia has been shown to have a favorable effect compared with general anesthesia alone on the serum cortisol level measured at 2nd and 24th postoperative hour in patients undergoing hip and knee surgery.[16] Lower serum cortisol levels in the early postoperative period have been reported in patients undergoing radical prostatectomy receiving thoracic epidural based analgesia compared with those who received systemic opioid based analgesia.[17] In our study, 24th h postoperative serum cortisol levels were significantly lower in the epidural block group compared with the dexmedetomidine group. However, at 2nd postoperative hour, the serum cortisol was comparable in both our groups, a finding consistent with earlier evidence where dexmedetomidine was compared with epidural.[2] However, they did not study the cortisol level at 24th postoperative hour. Cortisol increases intraoperatively due to surgical stimulation owing to the increased circulating ACTH.[1,3-5] Epidural block, by virtue of producing extensive afferent blockade, is known to suppress the rise in serum cortisol level.[1,4,5,18] Although the normal concentration of serum cortisol is around 50 to 150 ng/ml, the baseline (pre-induction) level in our study was 188.9 ± 73.0 ng/ml and 180.3 ± 69.8 ng/ml for those receiving the dexmedetomidine and epidural intervention, respectively. The higher values observed may be a result of the varied mental/emotional stress that patients experience in the perioperative period.

We found that perioperative epidural block regime was better than intraoperative dexmedetomidine regime in controlling the rise in blood glucose during intraoperative period as well as at 24th postoperative hour. The increase in blood glucose observed perioperatively is due to increased hepatic glycogenolysis, gluconeogenesis, and insulin resistance.[1,3,6,19] When compared with placebo, dexmedetomidine[15,19-21] and epidural analgesia both reduce the surge in blood glucose.[22,23] However, there is lack of comparative data between dexmedetomidine and epidural analgesia on perioperative glycemic response.

Both the regimes had similar effect on the blood urea. As per some previous reports, protein degradation and urinary excretion of nitrogenous products may remain elevated for up to 4 to 5 days post-surgery.[1,3-5]

Heart rate was lower in dexmedetomidine-treated group. This may be attributed to its inhibitory effect on hypothalamus and a consequent reduction in central sympathetic outflow.[9,10,24] The postoperative effect may be explained on the basis of context-sensitive half-life which ranges from 4 min after a 10 min infusion to as long as 250 min after an 8-h infusion.[24] Since our patients received dexmedetomidine infusion for around 2 to 3 h (mean duration of anesthesia was 145.5 ± 43.6 min), the effect may have persisted into the early postoperative period.

Emergence agitation was not seen in any patient in the study. Dexmedetomidine group patients were more sedated compared with patients who received epidural block likely due to its action on locus ceruleus through α-2A-AR receptor.[24] Similar findings have been reported by Kim *et al*.[25] Li *et al*.[2] also reported that dexmedetomidine prevented emergence agitation. A larger number of patients in the epidural group were calm at the emergence. The time to request of first analgesic was longer in the epidural group compared with the dexmedetomidine group because neuraxial local anesthetic produces afferent neuronal blockade, which is more profound and lasts longer than the analgesic effect produced by dexmedetomidine by its action on spinal cord through α-2A-AR receptor.

To the best of our knowledge, there is only one previous study which has compared the intraoperative stress response produced by dexmedetomidine and epidural block when given as an add-on to total intravenous anesthesia in terms of cortisol, epinephrine, norepinephrine, and cytokines. Our study compared perioperative stress response evoked by two regimes in addition to general anesthesia: intraoperative dexmedetomidine infusion versus perioperative epidural bupivacaine. We evaluated stress levels in terms of serum cortisol, blood glucose, and urea; both intraoperatively and postoperatively at 2nd and 24th postoperative hour.

Our study has certain limitations that need addressal. First, it was not blinded as the performance of a sham epidural block/catheterization in the dexmedetomidine group was considered avoidable due to the obvious patient concerns and feasibility. Second, we were unable to extend the epidural infusion for the postoperative period due to resource-limitations and hence the findings would be valid with postoperative bolus dosing only. However, intermittent epidural boluses programmed for pain relief are acceptable for postoperative pain control and have been noted to be associated with lesser local anesthetic consumption compared with continuous epidural infusion.[26] Third, our findings apply to a mixed surgical population undergoing upper or lower abdominal surgery, while the stress response may vary depending upon the site and extent of the surgical incision. Both groups however exhibited a similar distribution of upper abdominal and lower abdominal procedures.

Based on our observations, we conclude that a perioperative epidural block appears to be favorable over an intraoperative dexmedetomidine infusion for suppressing the neuroendocrine and metabolic response to surgical stress in patients undergoing abdominal surgery under general anesthesia. Dexmedetomidine does however provide better hemodynamic stability in terms of heart rate at the time of noxious stimuli in intraoperative period as well as postoperative period.

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Conflicts of interest

There are no conflicts of interest.

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