Original Article

Analgesic efficacy of Clonidine as an adjuvant in ultrasound-guided rectus sheath block for midline incisional hernia repair – A randomized double-blind controlled trial

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Abstract

Background and Aims: Clonidine as an adjuvant has not been evaluated in rectus sheath block (RSB) for postoperative pain management in incisional hernia repair. The study aims to evaluate clonidine as an adjuvant in single-shot RSB along with general anesthesia (GA).

Material and Methods: This randomized, double-blind controlled study was conducted following IEC-Human approval and written informed consent from 30 patients of either sex, aged 16 to 60 years, ASA physical status I or II undergoing midline incisional hernia repair under GA. All patients received ultrasound-guided bilateral RSB following administration of GA. The subjects enrolled in the study were randomly allocated to receive either normal saline 1 mL (group B) or clonidine 1 μg/kg diluted to 1 mL with normal saline (group BC) as adjuvant along with 9 mL bupivacaine hydrochloride 0.25%. Inj. tramadol 1 mg/kg was administered for rescue analgesia. The primary outcome was the time to first request for analgesia, and secondary outcomes were total consumption of rescue analgesic over 24 h, numerical rating score (NRS), patients' satisfaction, hemodynamics, and side effects. Unpaired t-test and Chi-square test were used.

Results: On intergroup analysis, the mean time to first request for analgesia (in min) was significantly higher in group BC i.e., [9.60 (± 5.23) vs 5.33 (± 3.53); ($P < 0.034$]; whereas, the mean rescue analgesic consumption in 24 h (in mg) was higher in group B i.e., [(88.00 ± 60.97) vs (46.00 ± 48.08)]; ($P < 0.045$)]. Hemodynamic parameters i.e., mean blood pressure and heart rate were comparable between the two groups, and there were no side effects.

Conclusion: Clonidine as an adjuvant in single-shot ultasonography (USG)-guided RSB along with GA is efficacious for postoperative pain management following midline incisional hernia repair.

Keywords: Clonidine, incisional hernia, pain-postoperative, rectus sheath block

Introduction

Incisional hernia repair, due to a large skin incision, is usually associated with significant postoperative pain. The rectus sheath block (RSB) is an old technique; however, its use in clinical practice has gained new interest.[1] Rectus sheath block has been used for the midline abdominal incisions and has been considered to be an alternative where epidural block is contraindicated as it is not associated with motor blockade and keeps the patient ambulatory in the postoperative period.[2] Rectus sheath block has been very commonly used

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for postoperative pain management following umbilical hernia repair, laparoscopic cholecystectomy, and abdominal cancer surgery involving a midline incision.

Since the last decade, the advent of ultrasonography (USG) has resulted in increased safety margin and optimal block quality of RSB.[3] The addition of adjuvants further improves the quality of a regional block. Some adjuvants such as midazolam[4] and dexmedetomidine[5] have been tried in RSB. Clonidine, an imidazole derivative with selective alpha-2 adrenergic agonist action, has been shown to reduce the onset time, improve the efficacy of the block during surgery, and extend the postoperative analgesia in peripheral nerve blocks.[6] However, on extensive literature search, we could not retrieve any study evaluating the efficacy of clonidine as an adjuvant in RSB so far in adults. In addition, no study has evaluated RSB for postoperative pain management following incisional hernia repair.

Hence, the present study was conducted to evaluate the analgesic efficacy of clonidine as an adjuvant to bupivacaine in single-shot ultasonography (USG)-guided RSB for incisional hernia repair involving midline incision. The primary objective was the time to first request for analgesia, and the secondary outcomes were total consumption of rescue analgesic in 24 h, intraoperative fentanyl consumption, numerical rating score (NRS) for pain, patients' satisfaction, and side effects.

Material and Methods

The current randomized, double-blind controlled study was conducted following the Institutional Ethics Committee – Human Research (IEC-HR) approval. The patients were recruited from February 2019 till March 2020. The investigators took written informed consent from each participant. The study was prospectively registered at Clinical Trial Registry-India (http://ctri.nic.in), CTRI/2019/02/017496 on 6th February 2019

The patients of either sex, aged 16 to 60 years, of ASA physical status I or II, undergoing midline incisional hernia repair under general anesthesia (GA) were included. The patients with morbid obesity (BMI ≥35 kg/m^2), a significant history of cardiac, hepatic, or renal disease, local infection at the block or systemic infection, pre-existing coagulation disorder, or allergy to local anesthetics (LA) were excluded.

The randomization was done using a computer-generated random number table and serially-numbered sealed opaque envelopes for allocation concealment. All the patients were administered USG-guided bilateral RSB. They were randomly allocated into one of the two groups. Those in Group-B received RSB with 9 mL of bupivacaine hydrochloride 0.25% + 1 mL of saline 0.9%; whereas, the patients in Group-BC received RSB with 9 mL of bupivacaine hydrochloride 0.25% + 1 μg/kg clonidine diluted to 1 mL using saline 0.9% on either side (-). Thus, a total volume of 10 mL was used on each side, and the total dose of clonidine administered in group BC was 2 μg/kg. One-mL insulin syringe was used for preparing the test drug. The study drug solution was prepared by a person not involved in the study. Both the patient and the investigator who recorded the data were blinded to the group assignment.

In the preoperative room, the patients were instructed on how to use NRS on a scale of 0 to 10 (0 = no pain, 10 = worst pain imaginable.) Standard intraoperative monitoring included continuous electrocardiography, capnography, pulse oximetry, temperature, and intermittent non-invasive blood pressure. Following induction of GA with fentanyl 2 μg/kg and propofol 1.5–2 mg/kg IV, tracheal intubation was facilitated by the administration of vecuronium 0.1 mg/kg IV. Anesthesia was maintained with oxygen, nitrous oxide, and isoflurane.

Under GA, a single injection USG-guided RSB was performed bilaterally in all the patients using a linear ultrasound probe (5–10 MHz) In the supine position, the probe was placed transversally on the abdomen just above the umbilicus. Then, the probe was moved laterally, and rectus abdominis was scanned in the transverse plane, a 23-G needle was placed in the same plane directly under the probe at an angle of 45^o to the skin in lateral to medial orientation. The needle was then advanced through the subcutaneous tissue to pierce the anterior rectus sheath. It was then advanced further until it reached the plane between the rectus muscle and posterior rectus sheath. Then, 0.25 mL to 0.5 mL of LA was injected, it appeared as hypoechoic space if it was in correct plane and if not, then the needle was intramuscular and was advanced further [Figure 1]. Using the same technique and injectate, the RSB was performed on the opposite side. The number of attempts of needle piercing or any difficulties encountered were also noted. In the present study, we evaluated the single injection of RSB and not continuous infusion catheter. Although, the latter would have been more efficacious, but we assumed that managing two catheters would have been cumbersome and not cost-effective in our setup.

Hemodynamic parameters i.e., heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP) were recorded intraoperatively, at an interval of 5 min till the end of the surgery. Ondansetron 4 mg IV was given for postoperative nausea vomiting prophylaxis towards the end of the surgery. The neuromuscular blockade was reversed using inj. glycopyrrolate and neostigmine, and the trachea was extubated. Any episode of bradycardia (HR < 60

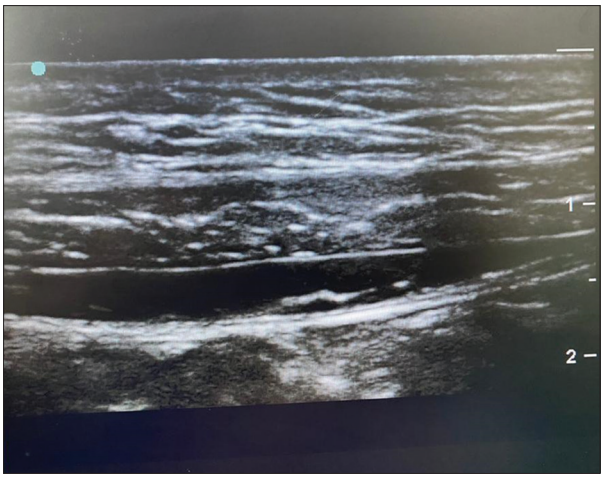

Figure 1: Hydrodissection of rectus sheath as drug deposited between the posterior layer of the rectus sheath and rectus muscle

bpm) or hypotension (SBP <20% of baseline) in the intraoperative period was recorded and treated using inj atropine 0.6 mg IV and IV fluid bolus, respectively. Any increase in HR or SBP above 20% was considered as the inadequate depth of anesthesia and managed by titrating isoflurane (end-tidal 0.7%–1%); however, if persisted, 1 mcg/kg fentanyl boluses were given. The total dose of fentanyl used in the intraoperative period was recorded.

In the postoperative period, the patient was kept under strict observation and monitoring for 6 h. Hemodynamic parameters (HR, SBP, DBP, MAP) were recorded every 30 min in the postoperative period for 6 h. NRS pain score was recorded every 30 min for the initial 2 h and then at the end of the 4th, 6th, 12thand 24th h, postoperatively. The first dose of paracetmol (1 gm) was administered towards the end of the surgical procedure. All patients received 1 g paracetamol IV every 8 h during the first 24 h after surgery. The time to first request of analgesia was defined as the time interval from completion of RSB till the first request of rescue analgesia and was recorded. Rescue analgesia was provided, if the NRS score was ≥4, using IV boluses of 1 mg/kg tramadol, with the total dose not exceeding 200 mg/day. Ondansetron 0.1 mg/kg IV was administered prior to IV tramadol. Total consumption of tramadol in 24 h was recorded.

Patients' sedation was assessed on 5-point Ramsay's sedation score.[7] The patients' satisfaction with their pain control regimen was recorded using satisfaction score (1: extremely satisfied; 2: satisfied; 3: dissatisfied; 4: extremely dissatisfied). Any adverse reactions like nausea/vomiting, dryness of mouth, hypotension, bradycardia, etc., were also recorded.

The primary outcome was the time to first request of analgesia, and secondary outcomes were NRS pain scores, total intraoperative rescue analgesic consumption, total postoperative rescue analgesic consumption in 24 h, patients' satisfaction score, adverse effects such as hypotension, bradycardia, etc., and any technical difficulties with block placement.

In the previous study by Ammar *et al.*,[4] the variation in the duration of analgesia in the bupivacaine only group in RSB was found to be 306 min [IQR: 267–332]. To estimate an increase of 10% in the duration of analgesia, at alpha 5% and power 90%, a sample of 16 patients with 8 in each group was required. However, due to the availability of time and resources, we considered a sample size of 30 with 15 in each group.

Statistical analysis was performed using SPSS version 21.0. Continuous variables were expressed in means and standard deviation, whereas categorical data were expressed in percentages. Statistical significance for continuous variables was assessed by unpaired t-test, whereas for categorical variable, Chi-square test was used. A P value less than 0.05 was considered statistically significant.

Results

A total of 35 patients were assessed for eligibility, and five were excluded. Out of five patients who were excluded, two had restricted mouth opening, two were morbidly obese, and one had uncontrolled diabetes. Finally, a total of 30 patients were included in the study [Figure 2]. Both groups were comparable with respect to age, gender, ASA physical status, weight, size of swelling of hernia, and mean duration of surgery [Table 1].

The mean time to first request of analgesia (in hours) was found to be significantly higher in group BC [9.60 (± 5.23) h] when compared to group B [5.33 (± 3.53) h] ($P < 0.05$). [Table 2] The mean rescue tramadol consumption (in mg) in 24 h was found to be significantly higher in group B (88.00 ± 60.97) when compared to group BC (46.00 ± 48.08) highlighting the increased demand for postoperative rescue analgesia (tramadol) consumption in patients receiving only bupivacaine. [Table 2]

On intergroup analysis, the mean postoperative NRS score in group BC was observed to be lesser than group B at all-time points, but this change was not statistically significant. [Figure 3]

The RSB was administered after induction of GA; therefore, we assessed the intraoperative opioid consumption to evaluate and compare the efficacy of RSB with and without adjuvant.

Table 1: Patients' characteristics

Parameters	Group B (*n*=15)	Group BC (*n*=15)	Significance
Age (in years) (Mean±SD)	42.53 (±10.54)	42.93 (±7.31)	0.905
Gender (M: F)	6:9	7:8	0.713
ASA Grade (I: II)	9:6	8:7	0.713
Weight (kgs)(Mean±SD)	68.20 (±10.69)	63.87 (±7.63)	0.212
Hernia swelling (in length) (cm) (Mean±SD)	5.80 (±4.02)	5.27 (±2.46)	0.665
Hernia swelling (in breadth) (cm) (Mean±SD)	5.47 (±3.38)	4.53 (±2.39)	0.390
Duration of surgery (mi) (Mean±SD)	88.67 (±35.98)	109.33 (±29.39)	0.096

Group-B=Bupivacaine only; Group BC=Bupivacaine with clonidine

Table 2: Time to first request of analgesia (hr) and Postoperative Tramadol consumption (mg) in 24 h

	Group B (*n*=15)	Group BC (*n*=15)	Sig.
Time to first request of analgesia (hours)(Mean±SD)	5.33 (±3.53)	9.60 (±5.23)	0.034*
Post-operative Tramadol consumption (mg) in 24 h (Mean±SD)	88.00 (±60.97)	46.00 (±48.08)	0.045*

**P<0.05: Statistically significant; Group-B=Bupivacaine only; Group BC=Bupivacaine with clonidine*

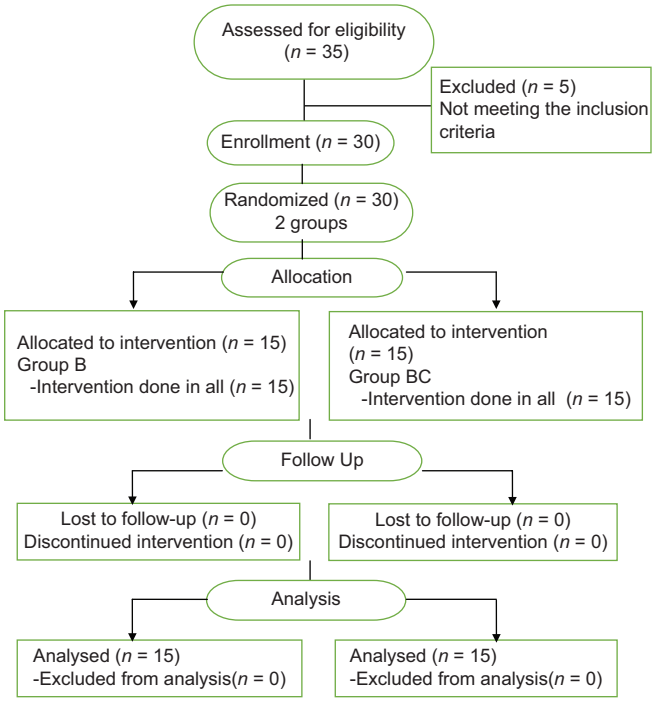

Figure 2: Consort flow diagram

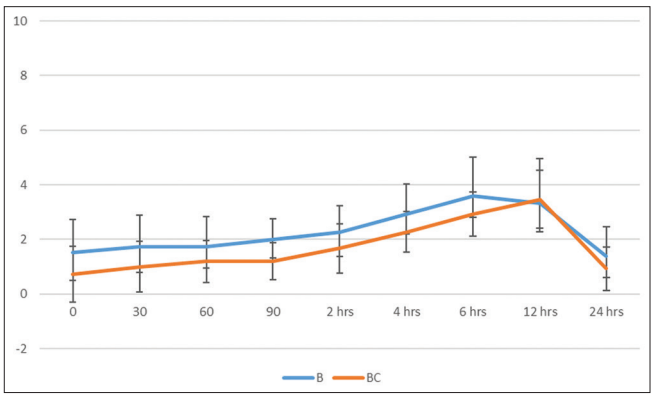

Figure 3: Postoperative Numerical Rating Score (NRS) at various time points. *Group-B = Bupivacaine only; Group BC = Bupivacaine with clonidine*

The intraoperative fentanyl consumption between the two groups was comparable i.e., 87.33 (± 23.74) vs 84.67 (± 14.07) for group B and Group BC, respectively.

Intraoperative mean HR was significantly higher in Group BC for the initial 10 min, thereafter it remained comparable between the two groups [Figure 4] It was observed that MBP was significantly lower ($P < 0.05$) in Group BC only between 35 to 45 min after induction of GA compared to group B. [Figure 5]

In group BC, two patients had hypotension; whereas, in group B only one had hypotension. Except for one patient in group BC, none of the patients required active intervention. In group BC, one of the patients had bradycardia; whereas, none of the patient had bradycardia in group B. None of the patients had dry mouth, sedation, and nausea or vomiting in any of the groups. Only two patients in the control group i.e., group B had technical difficulties in the form of more than two attempts of needle piercing. The difference between Ramsay scoring between the two groups was not found to be significant.

The patients' satisfaction score in Group BC was 1.60 (± 0.74) vs 2.13 (± 0.74) in Group B; however, the difference was not statistically significant ($P = 0.058$).

Discussion

This randomized, double-blind, controlled trial demonstrated that the addition of clonidine to bupivacaine in single-shot RSB for incisional hernia repair following GA significantly prolongs the time to first request of analgesia, reduces postoperative analgesic consumption in 24 h with minimal side effects.

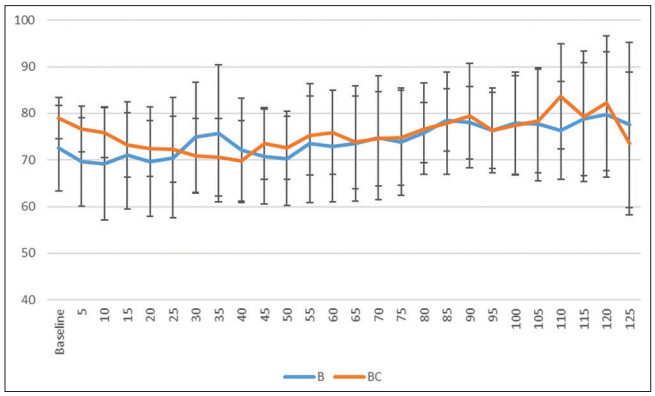

Figure 4: Mean intra-operative Heart rate between the two groups. *Group-B = Bupivacaine only; Group BC = Bupivacaine with clonidine*

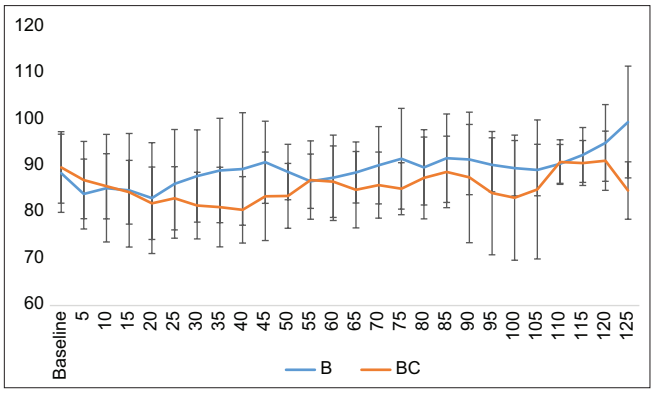

Figure 5: Intra-operative mean blood pressure between both groups. *Group-B = Bupivacaine only; Group BC = Bupivacaine with clonidine*

Clonidine, alpha 2 adrenoreceptor agonist, has been very commonly used as an adjuvant with LA for epidural anesthesia,[8,9] peripheral nerve blocks,[6,10] abdominal plane block,[11,12] and local infiltration.[13] Clonidine acts by binding to presynaptic C fiber and post synaptic dorsal horn neurons and shows analgesics action by depressing the release of c-fibers, transmitter, and hyperpolarizing post synaptic dorsal horn; thus, significantly prolonging the sensory and motor block. Amongst abdominal plane blocks, clonidine as an adjuvant in transversus abdominis plane (TAP) block has been found to have better postoperative analgesia in patients undergoing cesarean delivery.[14] The possible mechanism for extended analgesia with clonidine as an adjuvant in TAP block is systemic absorption.[15]

Most of the research studies utilizing RSB have either compared preoperative and postoperative RSB[16,17] or compared its efficacy along with GA[16,18,19] [or compared RSB with local infiltration.[1,20] However, till now, only a few RCTs have evaluated an adjuvant in RSB.[4,5] Ammar *et al.*[4] compared 50 μg/kg of midazolam and bupivacaine with bupivacaine alone in patients undergoing umbilical hernia repair.[4] They observed significantly lesser morphine consumption in the postoperative 48 ho, lower visual analog scale (VAS) score, and longer duration of analgesia with the addition of midazolam in RSB. In the present study, by utilizing clonidine as an adjuvant, we observed an improved time to first request analgesia when compared to midazolam[4] as an adjuvant in RSB i.e., 9.60 (± 5.23) h vs 7.06 (5.7–7.3) h.

Various studies have demonstrated the safety and efficacy of RSB for postoperative pain management in elective open umbilical hernia repair.[1,4,18,20,21] USG-guided RSB when used along with GA has been found to be more effective in reducing postoperative pain and opioid consumption when compared to GA alone in adult patients undergoing umbilical hernia repair[18] and abdominal cancer surgery.[19] In the present study, we had to use single-dose RSB after induction of GA, the reason being better patient compliance and low cost when compared to the bilateral continuous infusion catheters. Like our study, the majority of studies evaluating the efficacy of RSB for postoperative pain management have used single dose.[1,4,16,18,20-22]

Pre-emptive analgesia is an antinociceptive treatment preventing central sensitization triggered by surgical incisions and intraoperative inflammatory insults. Therefore, the timing of RSB is paramount. By far, a single RCT has compared and evaluated the two timings of RSB i.e., preoperative with postoperative RSB for postoperative pain management after laparoscopic cholecystectomy.[17] In this study, the total rescue analgesic consumption at 24 h postsurgery, NRS score at 1 h, 8 h, and 18 h were significantly lower in the preoperative-RSB group than postoperative-RSB group. They concluded that the preoperative-RSB reduced the analgesic requirements in patients undergoing laparoscopic cholecystectomy; thus, suggesting the pre-emptive effect of RSB. A similar study by Jin *et al.*[23] also observed that preoperative RSB not only preserves the first postoperative sleep by inhibiting the increase in IL-6 but it also does not shorten the analgesic time compared with postoperative RSB in female patients undergoing elective midline incision transabdominal gynecological surgery. Considering the aforementioned evidence, in the present study, we had administered USG-guided RSB following administration of GA and before surgical incision.

The limitation of the study was that the volume of the drug was prefixed; however, it may have been given according to weight and height as the drug volume affects the spread of the drug. However, no evidence could be retrieved in this context.

We conclude that clonidine as an adjuvant with bupivacaine in single-shot USG-guided RSB bilaterally along with GA is efficacious for providing significant improvement in

the postoperative analgesia with minimal side effects when compared to bupivacaine alone in patients undergoing midline incisional hernia repair. Further RCTs with a larger sample size evaluating the optimal dose of clonidine as an adjuvant in RSB for incisional hernia repair are desired.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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