

To Assess the Efficacy and Safety Profile of Pre-emptive Epidural Dexmedetomidine in the Patients Undergoing Upper Abdominal Surgery Under General Anesthesia: A Prospective Randomized Double Blind Study

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Abstract

Introduction: Effective pain control is the mainstay of treatment in patients who have undergone upper abdominal surgeries as pain has many adverse effects on various systems of body. Epidural analgesia provides not only pain relief but also reduces postoperative stress response, pulmonary complications and duration of hospital stay. **Aims and Objectives:** To assess the efficacy of epidural dexmedetomidine as an adjuvant to Ropivacaine on analgesia, perioperative hemodynamics and requirement of anesthetic agents in patients undergoing upper abdominal surgeries under general anesthesia. **Materials and Methods:** 70, ASA Grade I and II patients, 18–60 years of either sex planned for upper abdominal surgery were included and randomly allocated into two Groups: Group RD - Patients received 1 mcg/kg Dexmedetomidine hydrochloride with 0.25% isobaric Ropivacaine hydrochloride (total volume 20 ml). Group R - Patients received 20 ml of 0.25% isobaric Ropivacaine hydrochloride. Prior to induction of anesthesia with injection Midazolam 20 mcg/kg, injection Fentanyl citrate 2 mcg/kg, injection Propofol 2 mg/kg and injection Atracurium 0.5 mg/kg to facilitate endotracheal intubation, epidural catheterization was done. Then, the epidural study medications were injected. Anesthesia was maintained with O₂:N₂O 1:2, Sevoflurane upto 3% and Atracurium as necessary to achieve muscle relaxation. Pain characteristics, sedation level, intraoperative hemodynamics and requirement of sevoflurane were noted. At end of surgery, patients were extubated and shifted to PACU. Categorical (qualitative) data were presented as number (percentage) and compared using Chi-square test. Continuous variables (quantitative) were presented as mean ± SD and compared using *t* - test. *p* value < 0.05 was considered as statistically significant. **Result:** The duration of analgesia was prolonged in the patients who received Dexmedetomidine as an adjuvant with Ropivacaine (472.14 ± 44.90 mins v/s 309.85 ± 35.72, *p* - value - 0.000). Number of rescue analgesia doses needed in Group RD was less than Group R (2.11 ± 0.323 v/s 3.14 ± 0.550, *p* - 0.00). The mean concentration of sevoflurane in Group RD was 2.380 ± 0.22% and in Group R was 2.680 ± 0.278%, and this difference was statistically highly significant (*p* - 0.000). Vitals remained stable in both the Groups. **Conclusion:** Epidural Ropivacaine with dexmedetomidine give better and longer postoperative pain relief in upper abdominal surgeries and also reduce requirement of anesthetic agents intraoperatively.

Keywords: Dexmedetomidine; Ropivacaine; Epidural Anesthesia; General Anesthesia.

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Introduction

Pain is an unpleasant subjective sensation that originates from ongoing and impending tissue damage and can be experienced not expressed.¹ Effective pain control is the mainstay of treatment in patients who have undergone upper abdominal surgeries as pain has many adverse effects on various systems of body.² Research continues concerning different techniques and drugs that could provide better surgical anesthesia and postoperative pain relief. Epidural analgesia provides not only pain relief but also reduces postoperative stress response, pulmonary complications and duration of hospital stay.³

Sedation, stable hemodynamics and an ability to provide smooth and prolong postoperative analgesia are the main qualities of an adjuvant in neuraxial anesthesia.⁴ Alpha-2 adrenergic agonists have both analgesic and sedative properties when used as an adjuvant in regional anesthesia.⁵⁻¹⁰ However, there is limited literature evaluating the effect of epidural Dexmedetomidine (a highly selective alpha-2 agonist) on perioperative hemodynamics, surgical relaxation and requirement of other anesthetic agents along with postoperative follow up in patients undergoing upper abdominal surgery under general anesthesia.¹¹⁻¹³

We undertook a study on epidurally administered dexmedetomidine as an adjuvant to ropivacaine in patients undergoing upper abdominal surgeries under general anesthesia with regard to its effect on perioperative analgesia and hemodynamics, requirement of anesthetic agents intraoperatively as well as rescue analgesic requirement postoperatively.

Materials and Methods

After institutional ethical committee approval, this prospective, randomized, double blinded, comparative case - control clinical study was conducted in the Department of Anesthesiology, MB Government Hospital affiliated to RNT Medical College, Udaipur (Rajasthan).

To ensure double blindness to the study, the study drugs were prepared according to group allocation by an independent anesthesiologist not involved in the study. Data were recorded by another anesthesiologist who was conducting the study himself and was not aware of group allocation. Patient, surgeon and postoperative ward staffs were also not aware of the group allocation.

A prior study conducted by Sarabjit Kaur *et al.* reported that the mean dosages of rescue analgesics required for patients undergoing lower limb orthopedic surgery with epidural Ropivacaine were 2.56 ± 0.675 . We postulated that the addition of dexmedetomidine to epidural Ropivacaine given preoperatively in the patients undergoing upper abdominal surgery will result in a reduction of the number of dosages by at least *0.5/day* for it to be clinically significant.

For the study to have 2 sided confidence interval of 95% and a power of 80%, 29 patients were required in each group. To compensate for possible drop outs, we decided to include 35 patients in each group.

The study group comprised of ASA physical status I and II patients aged 18-60 years of either sex planned for elective upper abdominal surgeries.

Patients with known allergy to the study drug, suspected coagulopathy, and infection at the site of epidural block, cardiac and renal diseases, neurological illness, mental illness and deformity of spinal cord were excluded from the study.

All the patients under study were subjected to detailed preanesthetic evaluation to rule out any anatomical or systemic disorder. Written informed consent was obtained from all patients after explaining about the procedure and benefits of epidural analgesia and details about 10 - point VAS¹⁴ in the preoperative period.

Seventy patients were randomly allocated into two Groups (35 patients in each group) using a sealed envelope technique and computer generated sequence of random numbers.

Group RD: Patients received 1 mcg/kg Dexmedetomidine hydrochloride added to 0.25% isobaric Ropivacaine hydrochloride to make a total volume of 20 ml.

Group R: Patients received 20 ml of 0.25% isobaric Ropivacaine hydrochloride.

Prior to induction of anesthesia under strict aseptic precautions an epidural catheterization was performed in T11-12 space in lateral or sitting position using 8-9 cm long, 18 G Tuohy needle. The catheter was secured 3 to 4 cm into epidural space. The patients were then positioned supine. All epidural study medications were injected after induction of general anesthesia. General anesthesia was induced with injection Propofol 2 mg/kg, injection Midazolam 20 mcg/kg, injection Fentanyl citrate 2 mcg/kg and injection Atracurium 0.5 mg/kg to facilitate endotracheal intubation.

Anesthesia was maintained with O₂:N₂O (1:2), Sevoflurane upto 3% and Atracurium as necessary to achieve muscle relaxation. Vital parameters were monitored continuously and recordings were made after tracheal intubation and epidural anesthesia and then after 15 minutes until the end of surgery.

The inhaled concentration of Sevoflurane was adjusted to achieve hemodynamic changes less than 20% of the baseline value. If the target hemodynamics were not achieved with the maximum Sevoflurane concentration (3%), Injection Fentanyl 1 mcg/kg was administered and repeated as needed. Maintenance concentration of Sevoflurane in volume % and total dose of Fentanyl administered were also recorded.

The occurrence of intraoperative hypotension (defined as Mean arterial blood pressure < 65 mm Hg) was treated with injection Ephedrine 6 mg and bradycardia (Heart rate < 50/min) was treated with 0.3-0.6 mg injection Atropine. The time from epidural block to the end of surgery was noted.

After the end of surgery, patients were reversed with inj Neostigmine (0.05 mg/kg) and inj Glycopyrrolate (0.01 mg/kg). After extubation patients were transferred to Postanesthetic Care Unit (PACU) and were monitored for respiratory rate, SpO₂, heart rate and blood pressure.

The intensity of postoperative pain was measured with Visual Analogue Scale (VAS) (a 10 cm scale, with '0' indicating no pain and 10 indicating worst pain ever) and was assessed at the end of surgery and then every 4 hour for 24 hours postoperatively. Rescue analgesia (inj tramadol 100 mg diluted to 10 ml) via epidural was given on demand when pain scores were 4 or more (VAS ≥ 4).

The duration of analgesia (from the time of epidural injection to the time to first request for analgesia) was noted. Total dose of rescue analgesic consumption was also recorded for 24 hours postoperatively.

The degree of sedation was assessed 30 min and 120 min after admission to recovery room using modified Ramsay scale.

Modified Ramsay Scale²

Awake levels

1. Anxious, agitated or both
2. Cooperative oriented, tranquil
3. Response to commands only

Asleep levels

1. Brisk response to loud auditory stimulus
2. Sluggish response to loud auditory stimulus
3. No response to loud auditory stimulus

Statistical analysis

Data were entered into MS Excel and analysed using Statistical Package for Social Sciences (SPSS) version 16 [International Business Management (IBM), Corporations, New York, USA]. Categorical (qualitative) data were presented as number (percentage) and compared using Chi-square test. Continuous variables (quantitative) were presented as mean ± SD and compared using *t* - test. *p* - value i.e. *p* < 0.05 was considered as statistically significant and *p* < 0.01 was considered as statistically highly significant.

The primary outcome measured was to assess the analgesic efficacy of epidural dexmedetomidine as an adjuvant to ropivacaine in patients undergoing upper abdominal surgeries.

The secondary outcomes measured were evaluation of the effect of dexmedetomidine on perioperative hemodynamics and requirement of anesthetic agents.

Results

The mean age of patients in Group R and RD were 42.71 ± 13.63 and 41.89 ± 11.47 years respectively whereas the mean weight was 55.46 ± 8.59 and 54.71 ± 7.49 kg in Group R and RD respectively. The demographic data was comparable in both the Groups (*p* > 0.05). The duration of surgery in the two Groups was comparable (125.71 ± 16.19 min in Group R vs 127.00 ± 17.95 min in Group RD, *p* = 0.754).

The time to first request for rescue analgesia was significantly higher in group RD as compared to Group R (472.14 ± 44.90 vs 309.85 ± 35.72, *p* = 0.000). The total dose of rescue analgesia consumed in 24 hours was more in Group R (314.29 ± 55 mg) as compared to Group RD (214.29 ± 35.50 mg) and this was statistically significant, *p* = 0.000, (Table 1).

Majority of patients (*n* = 24, 68.6%) in Group R required 3 doses of rescue analgesia in 24 hours where as maximum number of patients (*n* = 31, 88.6%) in Group RD required only 2 doses of rescue analgesia, (Table 2). Moreover, total number of rescue analgesic requirement in Group RD (2.11 ± 0.323) was less than Group R (3.14 ± 0.550) which was statistically significant (*p* = 0.000), (Table 1).

VAS score measured in our study was lower in Group RD as compared to Group R at all time intervals in our study although statistically significance was achieved at time of end of surgery [Group R (2 ± 0.42) *v/s* Group RD (1.63 ± 0.55), p 0.002], at 4th hour [Group R (4.37 ± 0.55) *v/s* Group RD (1.91 ± 0.92), p 0.00], at 12th hour [Group R (3.89 ± 0.47) *v/s* Group RD (3.49 ± 0.89), p 0.021] and at 20th hour [Group R (2.03 ± 0.6) *v/s* Group RD (1.31 ± 0.53), p 0.000]. The mean 24 hour VAS was 3.041 ± 0.468 in Group R and 2.342 ± 0.74 in Group RD and the difference was statistically significant (p 0.009), (Fig. 1).

Thirty-four out of 35 patients in Group RD had Modified Ramsay Sedation Score of 3 (i.e. patients were awake and responding to verbal commands) at 30 min as compared to score of 2 (i.e. patients were awake, cooperative and oriented) in all 35 patients of Group R. This difference was highly significant, ($p = 0.00$), (Fig. 2). All the 35 patients of both the Groups had Modified Ramsay Sedation Score of 2 at 120 mins. Thus all the patients were awake and comfortable.

The heart rate in Group RD was statistically significantly lower than Group R from 15 min of epidural drug administration to 120 minutes of

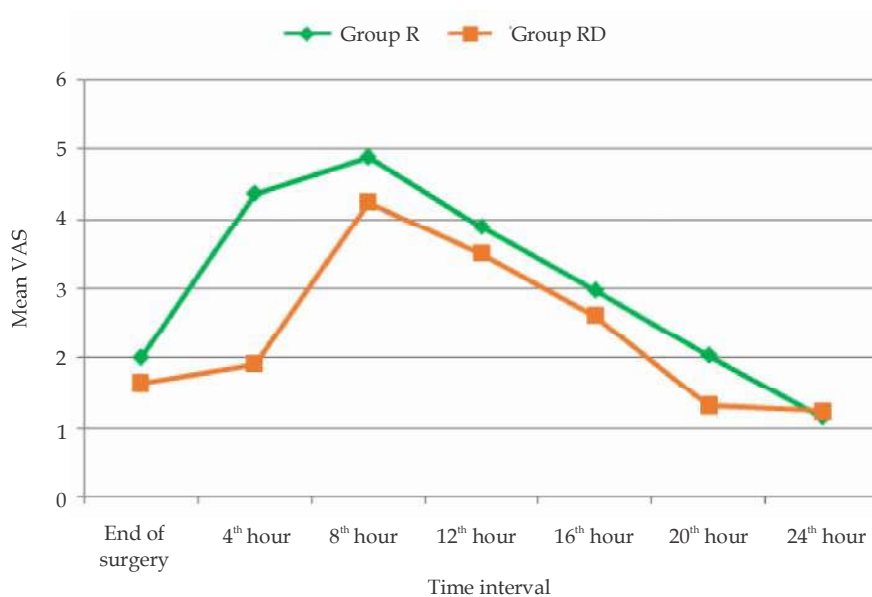


Fig 1: Comparison of VAS in two groups

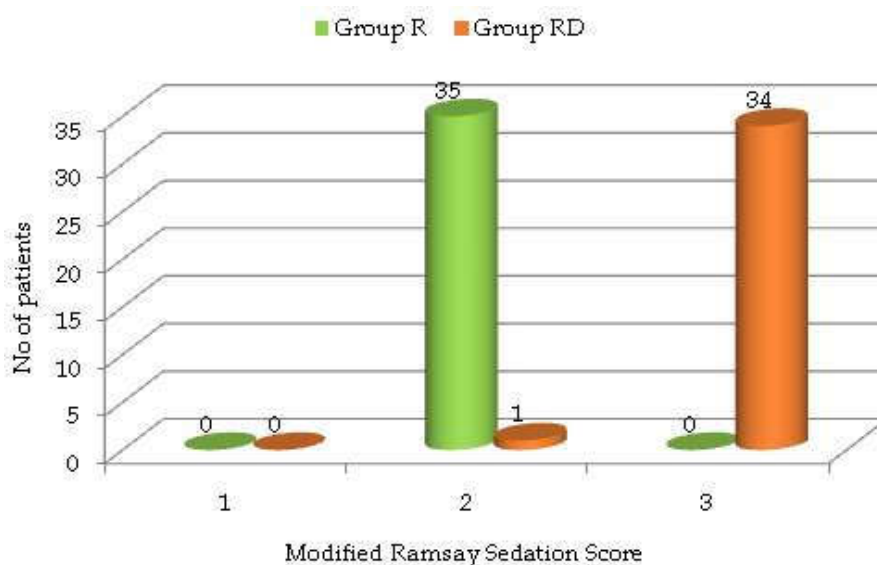


Fig. 2: Modified Ramsay Sedation Score at 30 min

intraoperative period. The heart rate was also lower in Group RD during the remaining intraoperative period although the difference was not statistically significant. 3 patients in Group RD had episode of bradycardia which was managed with intravenous atropine. There were no episodes of bradycardia in Group R, (Fig. 3).

The mean blood pressure in Group RD was statistically significantly lower than Group R from 60 mins of epidural drug administration to 105 minutes of intraoperative period. The MAP was also lower in group RD during the remaining intraoperative period although the difference was not statistically significant, (Fig. 4). There were no episode of hypotension in any of the two Groups.

The concentration of sevoflurane needed was lower in Group RD as compared to Group R throughout the intraoperative period although statistical significance was reached at 30,45,60,75,90,105 and 120 mins only. The mean concentration of sevoflurane in Group RD was $2.380 \pm 0.22\%$ and in Group R was $2.680 \pm 0.278\%$, and this difference was statistically highly significant (p 0.000), (Fig. 5). None of the patients in any of the groups required additional doses of fentanyl. 3 patients in Group R and 6 patients in Group RD had complaints of nausea which was managed with administration of injection ondansetron 4 mg IV.

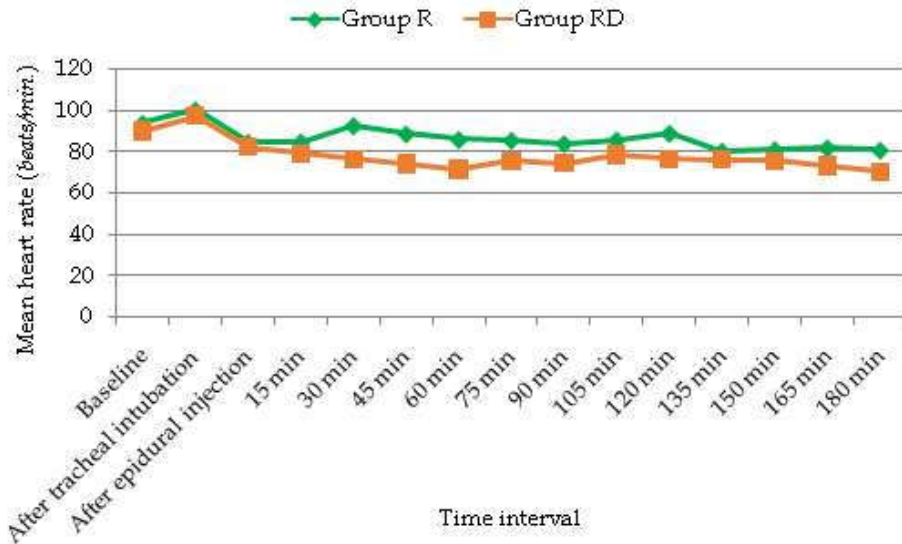


Fig. 3: Comparison of heart rate in two groups

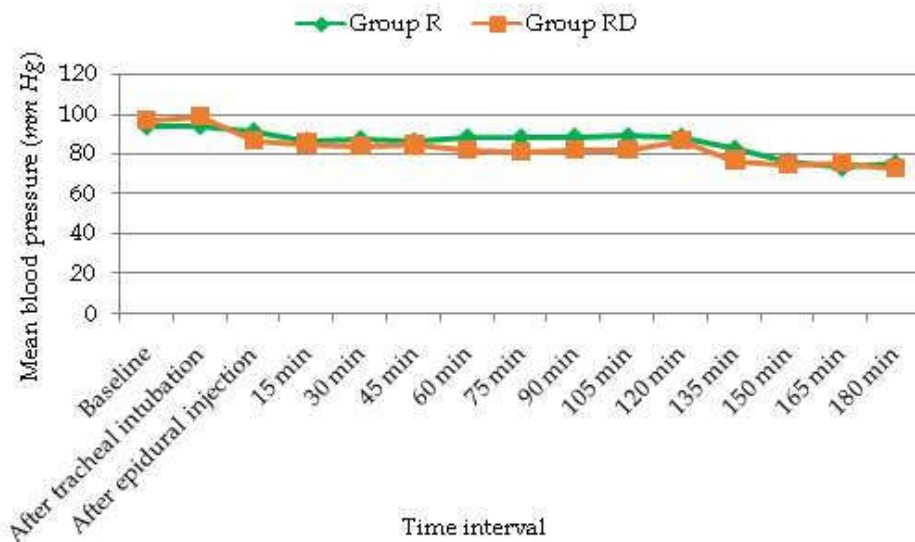


Fig. 4: Comparison of mean blood pressure in two groups

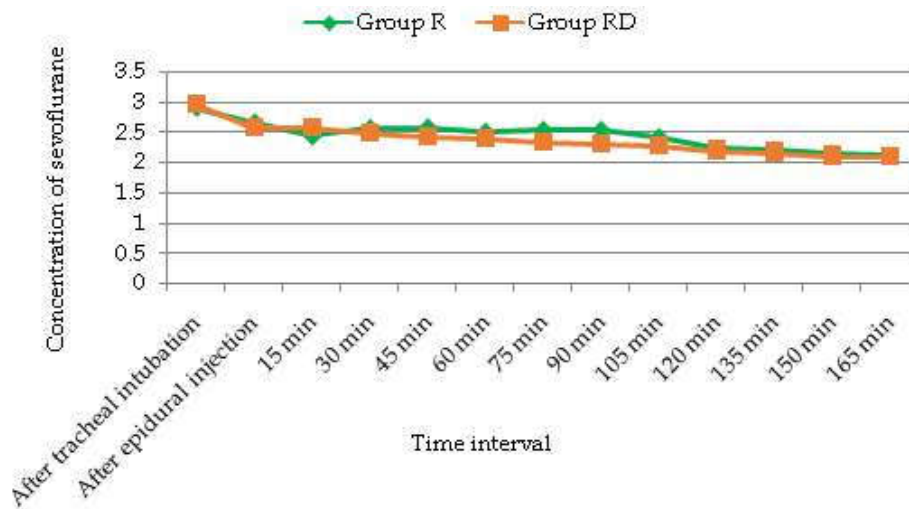


Fig. 5: Comparison of concentration of sevoflurane in two groups

Discussion

Upper abdominal surgeries are associated with significant amount of pain which can cause considerable amount of morbidity in form of pulmonary complications like atelectasis of lower lung fields, postoperative stress and prolonged hospital stay.

Epidural analgesia is a safe and effective means for providing perioperative analgesia. The commonly used local anesthetic drugs for epidural analgesia like Ropivacaine, Bupivacaine and Lignocaine, have shorter duration of action which necessitates frequent dosing. So, there is a need for addition of adjuvants to increase the duration of analgesia as well as quality of analgesia and to minimize the adverse effects of high doses of local anesthetic agent.

Dexmedetomidine is a centrally acting highly selective α -2 adrenergic agonist with α -2: α -1 selectivity ratio of 1620:1 especially for the α -2a subtype, which makes Dexmedetomidine more effective for analgesia and sedation. The mechanism by which α -2 adrenergic agonists prolong the motor and sensory block of local anesthetics may be an additive or synergistic effect secondary to the different mechanisms of action of local anesthetics. Dexmedetomidine acts by binding to the presynaptic C-fibers and postsynaptic dorsal horn neurons. They produce analgesia by depressing the release of C-fiber transmitters and by hyperpolarization of postsynaptic dorsal horn neurons.¹⁵⁻¹⁷ The complimentary action of local anesthetics and α -2 adrenergic agonists accounts for their profound analgesic properties. The use of

Dexmedetomidine has been studied as an epidural adjuvant by various authors who have observed its synergism with local anesthetics without any additional morbidity.^{4,18}

In our study, the demographic parameters like age distribution, gender distribution were similar in two Groups and were comparable. This helped to eliminate the variability due to demographic differences which could lead to error in interpretation of data.

Time duration from time to epidural injection of study drug to first request for rescue analgesia (VAS \geq 4) by the patient was defined as duration of analgesia. The mean duration of analgesia in our study was 309.85 ± 35.72 min in Group R as compare to Group RD in which the mean duration was 472.14 ± 44.90 min and this difference was statistically significant, ($p = 0.000$, shown as (Table 1).

Table 1: Rescue analgesia characteristics

	Group R	Group RD	<i>p</i> - value
Time to first request for rescue analgesia (min)	309.85 ± 35.72	472.14 ± 44.90	0.000
Total dose of rescue analgesia (mg)	314.29 ± 55.00	214.29 ± 35.50	0.000
Total number of rescue analgesia doses in 24 hours	2.11 ± 0.323	3.14 ± 0.550	0.000
Total number of rescue analgesics required	3.14 ± 0.550	2.11 ± 0.323	0.000

Kaur S *et al.*¹⁹ observed in their study that mean time at which patient demanded first dose of rescue analgesia was delayed in Group B (Ropivacaine

+ Dexmedetomidine) (496.56 ± 16.086 min) as compared to Group A (Ropivacaine) (312.64 ± 16.217 min). The first dose of rescue analgesia was demanded between 8th and 9th hour in Group RD and between 4th and 5th hour in Group R. In our study the first dose of rescue analgesia was demanded between 6th and 7th hour in Group RD and between 3rd and 4th hour in Group R. This difference is attributed to the difference in concentration of Ropivacaine administered epidurally. Kaur S *et al.* had used 0.75% 20 ml ropivacaine as compared to 0.25% 20 ml ropivacaine used in our study.

Thangavelu S *et al.*² conducted a comparative study on adding Dexmedetomidine vs Clonidine to epidural 0.125% Bupivacaine for postoperative analgesia in patients undergoing upper abdominal surgeries and found that the mean duration for 1st rescue analgesia (defined as the time at which patient demands some mode of pain relief i.e. when VAS more than 4) was 425.6 ± 64.27 minutes in Group D and 226 ± 24.83 minutes in Group C. Their results are similar to our study, shown as (Table 2).

Table 2: Distribution of patients according to number of doses of rescue analgesia

No of rescue analgesia doses	Group R (n = 35)	Group RD (n = 35)
2	3 (8.6%)	31 (88.6%)
3	24 (68.6%)	4 (11.4%)
4	8 (22.9%)	0 (0%)
Total	35 (100%)	35 (100%)

Anand VG *et al.*²⁰ studied the effect of Dexmedetomidine to caudal Ropivacaine for lower abdominal surgery in pediatric population and found that duration of postoperative analgesia was prolonged in Dexmedetomidine group with a median of 14.5 hours (13.90–15.09) in Group RD compared with 5.5 hours (4.97–6.03) in Group R, with a *p*-value of < 0.001.

Our study showed total number of rescue analgesia doses needed in 24 hours was less in Group RD (2.11 ± 0.323) as compared to Group R (3.14 ± 0.550). In study by Kaur S *et al.*,¹⁹ they observed that patients in Group B (Ropivacaine + Dexmedetomidine) required significantly less number of doses of rescue analgesia as compared to Group A (Ropivacaine) (1.44 ± 0.501 vs 2.56 ± 0.675) in the postoperative period (*p* < 0.001). Their study supports our findings.

In the present study, the VAS score was lower in Group RD as compared to Group R during the 24 hour of postoperative period. At the end of surgery the VAS score was [Group R (2.00 ± 0.42) vs (1.63 ± 0.55) in Group RD, *p* 0.002], at 4th hour [Group R

(437 ± 0.55) vs Group RD (1.91 ± 0.92), *p* 0.00], at 12th hour [Group R (3.89 ± 0.47) vs Group RD (3.49 ± 0.89), *p* 0.021], and at 20th hour [Group R (2.03 ± 0.6) vs Group RD (1.31 ± 0.53), *p* 0.000]. In our study mean VAS score in Group R was 3.041 ± 0.468 and in Group RD was 2.342 ± 0.74 , (*p* 0.009).

In study by Thangavelu S *et al.*,² at 360 minutes, the mean VAS score in Group D was 0.84 ± 0.89 and in Group C was 1.76 ± 0.99 . There was statistical significant difference in both Groups (*p* < 0.05). The mean VAS score in Group D was 2.96 ± 1.01 and in Group C was 2.08 ± 1.07 at 720 minutes which was found to be statistically significant (*p* < 0.05). At 1440 minutes, the mean VAS score in Group D was 3.48 ± 0.82 and in Group C was 3.52 ± 1.04 and was found to be statistically not significant. Their result supported our finding

In study conducted by Kaur S *et al.*,¹⁹ in Group A (0.75% Ropivacaine), VAS score increased more rapidly and patient demanded first dose of rescue analgesia (injection diclofenac sodium 75 mg I/M) between 4th and 5th h (mean VAS was 2.93 ± 1.04 and 3.13 ± 1.00 respectively). At 5th h, mean VAS score in Group A was 3.13 ± 1.00 and in Group B was 0.57 ± 0.62 and the difference between the two Groups was highly significant (*p* = 0.00). In Group B (0.75% Ropivacaine with 1 mcg/kg Dexmedetomidine), VAS started increasing at 4th h (0.10 ± 0.30) and patient demanded first dose of rescue analgesia (injection diclofenac sodium 75 mg I/M) between 8th and 9th h (mean VAS was 3.03 ± 1.21 and 3.27 ± 0.78 respectively). Thus requirement of rescue analgesia was delayed in Group B as compared to Group A. The mean VAS score in Group A (R) was 3.13 ± 1 and in Group B (RD) was 0.57 ± 0.62 and the difference between the two Groups was significant with *p* value of 0.00. Their study results support our findings.

The result of our study clearly indicates that the sedation score at 30 min was higher in Group RD as compared to Group R and this was statistically significant. At 30 min of postoperative period majority of the patients (i.e. 34 out of 35) in Group RD had MRSS 3 as compared to score of 2 in all the patients in Group R. We observed that none of the patients in our study had respiratory depression or any fall in saturation. Patients of Group RD had arousable sedation, awaken by gentle tactile stimulation. We further noted that all the patients of both the Groups had MRSS 2 at 120 min of postoperative period.

Bajwa Set al.⁴ showed epidural dexmedetomidine produced more sedation as compared to epidural clonidine. 36% of patients in dexmedetomidine Group (MRSS 2) and were arousable by gentle

tactile stimulation compared to achievement of similar sedation level in 16% patients in clonidine Group. Their results were similar to our study.

Kaur S *et al.*¹⁹ showed that after 30 min, patients were more sedated in Dexmedetomidine Group as compared to plain Ropivacaine Group and the difference in sedation score was statistically highly significant. This was in accordance with our study which showed significant sedation produced by addition of dexmedetomidine to ropivacaine.

The hypnotic effect of Dexmedetomidine is mediated by hyper-polarization of noradrenergic neurons in the locus ceruleus of the brain stem (a small bilateral nucleus that contains many adrenergic receptors), which is the primary site in modulating wakefulness.⁶

In our study, heart rate was less in Group RD as compared to Group R. The fall in heart rate is due to postsynaptic activation of α -2 adreno receptors in CNS resulting in decreased sympathetic activity both centrally and peripherally. 3 patients in Group RD had bradycardia whereas none of the patients had bradycardia in Group R.

In study by Kaur S *et al.*,¹⁹ heart rate remained stable in both the Groups at all time interval and was comparable. Although 2 patients in Group A (Ropivacaine) and 5 patients in Group B (Ropivacaine-Dexmedetomidine) had bradycardia intraoperatively which was managed with inj atropine. This difference can be explained due to difference in concentration of ropivacaine which was 0.75% (20 ml) in Kaur S *et al.* as compared to 0.25% (20 ml) in our study.

In study by Jain *et al.*,²¹ they noticed a significant fall in pulse rate 5 to 10 minutes following administration of epidural dexmedetomidine as compared epidural saline at all time intervals. Their finding supports our results.

In our study the mean blood pressure remained stable in both the Groups. Although the MBP was lower in Group RD as compared to Group R, none of the patients had hypotensive episode requiring inj Ephedrine. The difference in MBP was statistically significant from 60 mins to 105 mins of observation period but that was clinically of no significance.

In the study by Shahi V *et al.*,²² there was no statistically significant difference between the Groups ($p > 0.05$) in MBP. This difference can be attributed to the difference in the dose of inj Dexmedetomidine which was 1 mcg/kg in our study as compared to 0.5 mcg/kg in Shahi V *et al.*

In our study, lower concentration of sevoflurane was needed in Group RD as compared to Group R.

The mean concentration of Sevoflurane in Group RD was 2.380 ± 0.22 and in Group R was 2.680 ± 0.278 , and this difference was statistically highly significant, $p < 0.000$.

In study by Schnaider TB *et al.*,²³ control group patient who received 0.75% (20 ml) ropivacaine the concentration of inspired isoflurane was higher [$> 1, < 3$] as compared to the inspired isoflurane concentration in dexmedetomidine Group [0.84 + 0.12%]. These results supports our finding.

Limitations

The patients with comorbidities were excluded, so, the results of this study should not be generalized to other patients with severe underlying disease. Further studies should consider this limitation.

Conclusion

We conclude that the addition of dexmedetomidine to epidural ropivacaine not only reduces the requirement of anesthetic agents intraoperatively but also gives better and longer postoperative pain relief in patients undergoing upper abdominal surgeries.

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Conflict of interest: None.

Ethical approval: Institute Ethics Committee.

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