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Comparative evaluation of Intraperitoneal instillation of Dexmedetomidine versus Nalbuphine as adjuncts to 0.25% Ropivacaine for post operative analgesia in laparoscopic cholecystectomy

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Abstract
Objective: To evaluate the analgesic efficacy of intraperitoneal dexmedetomidine versus nalbuphine as an adjunct to ropivacaine in laparoscopy cholecystectomy.
Methods: In this randomised double-blinded study, 60 American Society of Anesthesiologists physical status I-II, 20-55 years, scheduled for laparoscopic cholecystectomy under general anaesthesia and were randomly allocated into three groups according to intraperitoneal instillation of study drugs through trocars. Group A: given 50 ml solution of 0.25% ropivacaine with dexmedetomidine 1mcg/kg, Group B: given 50 ml solution of 0.25% ropivacaine with 5 mg nalbuphine and Group C: given 50 ml solution of 0.25% ropivacaine with 10 mg nalbuphine. The primary outcome was duration of analgesia. Secondary outcomes consisted of total cumulative postoperative tramadol consumption, pain rating, haemodynamic variables and adverse effects.
Results: The duration of postoperative analgesia for group A was significantly longer than for group B and group C (7.36±1.69 vs 4.11±0.832 vs 4.53±0.834 h; P=0.000). Group A also required less total tramadol consumption (650 vs 1250 vs 950 mg; P=0.025), less total number of rescue analgesia (13 vs 25 vs 19; P=0.025), less total number of patients required rescue analgesia (55 vs 90 vs 75%; P= 0.043), less pain scores and higher mean sedation score (P<0.05).
Conclusion: Greater postoperative analgesia and analgesic sparing effects were observed in patients receiving intraperitoneal instillation of 1mcg/kg, dexmedetomidine as adjunct to ropivacaine following laparoscopy cholecystectomy.

Keywords: Intraperitoneal instillation, Postoperative pain, Analgesic, Adjunct, Dexmedetomidine, Nalbuphine, Ropivacaine

Introduction

Laparoscopy surgeries are associated with more of visceral pain in contrast to parietal pain experienced in laparotomy.[1] Also, the incidence of postoperative shoulder pain due to diaphragmatic irritation by residual carbon-dioxide following laparoscopic surgery may reach up to 80% [2, 3].

Various multimodal approaches have been tried to ameliorate postoperative pain, such as parenteral analgesics, local infiltration with local anaesthetics, epidural and intrathecal opioids or local anaesthetics, interpleural and intercostals nerve blocks as well as intraperitoneal routes [4]. Intraperitoneal instillation of local anaesthetic agents alone or with various adjuvants have been found to reduce post-operative pain following laparoscopic cholecystectomy [5]. The proposed rationale for the mechanism of intraperitoneal analgesia is conduction block of visceral nociceptive stimuli which irritate the peritoneum, as well as absorption of drug from the large peritoneal surface.

Dexmedetomidine and nalbuphine have been shown to prolong the duration of analgesia when added with ropivacaine intraperitoneally following laparoscopic cholecystectomy [6, 7]. In view of very few studies with inconsistent findings, the present study was designed with the aim to evaluate the efficacy of intraperitoneal dexmedetomidine versus intraperitoneal nalbuphine as an adjunct to ropivacaine in prolonging the postoperative analgesia, evaluate the total analgesic consumption in 24 hours, difference in pain scores and adverse effects.

Methods

It is prospective, double blind, randomized comparative study which was conducted amongst 60 patients belonging to American Society of Anesthesiologists grade 1 or 2, aged group 20-55 years, body mass index 18-30 kg/m^2, admitted in hospital for elective laparoscopic cholecystectomy surgery under general anaesthesia. Ethical approval was obtained from institutional ethical committee (PHMA/GSMCH-16/IEC/96-OT-dated-28.11.2016) and written consent was obtained from all the patients after explaining in detail the entire research protocol.

Patients refusing to give informed consent, with history of severe cardiac, cerebrovascular, respiratory, hepatic or renal disease, known hypersenstivity to ropivacaine, dexmedetomidine and nalbuphine were excluded from the study. Using computer generated random number table, the patients were randomly allocated to one of the following groups using 60 coded opaque sealed envelopes:

1. Group A: patients were given 50 ml solution having 49 ml of 0.25% ropivacaine with dexmedetomidine 1mcg/kg in 1ml.
2. Group B: patients were given 50 ml solution having 49 ml of 0.25% ropivacaine with 5 mg nalbuphine in 1ml.
3. Group C**:** patients were given 50 ml solution having 49 ml of 0.25% ropivacaine with 10 mg nalbuphine in 1ml.

The study drugs were prepared in similar looking 50 ml syringes by one anesthetist and administrated by another anaesthetist who was unaware of the nature of drug solution. All the observations were done by the anesthetist who was not involved in the study.

Preoperatively, preanesthetic evaluation and investigation were performed. The concept of a visual analog scale (VAS), [8] was introduced to the patient at preanesthetic clinic.

On the day of surgery, fasting status and written informed consent were confirmed on arrival at operation theatre complex. Patients were connected to a multipara monitor and baseline heart rate (HR), non-invasive systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP), oxygen saturation of blood (SpO_2), respiratory rate (RR) were recorded.

Injection glycopyrrolate 0.2 mg, injection midazolam 1 mg, injection ondansetron 4 mg, injection fentanyl 2 mcg/kg was given intravenously (IV), 10 min before surgery. After preoxygenating the patient with 100% oxygen for 3 min, induction was carried out with injection thiopentone sodium 3–5 mg/kg IV. Intubation with oral cuffed endotracheal tube was done after giving injection succinylcholine 1.5 mg/kg and intermittent positive pressure ventilation with oxygen (O2), nitrous oxide (N2O) and isoflurane. After induction of anaesthesia, end-tidal carbon dioxide (EtCO2) was also monitored along with above parameters. Intra-operative muscle relaxation was achieved by injection vecuronium 0.08 mg/kg IV. A nasogastric tube was introduced, and the laparoscopic procedure was carried out in a standard fashion. Intra-abdominal pressure was maintained between 10-12 mmHg. After the removal of gall bladder, intraperitoneal instillation of the total volume of 50 ml of the prepared solution in the above-mentioned doses was carried out under both the copulae of diaphragm guided by the camera and the patients were kept in trendelenburg position until the end of the procedure (10-15 min). After skin closure local infiltration of each port site with 3-5 ml of 0.25% ropivacaine was done. Reversal of residual neuromuscular blockade was achieved with injection neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg IV. The patient's trachea was extubated and the patients were shifted to post anaesthesia care unit.

Postoperative pain was assessed using visual analog scale (VAS) score. Mark 0 corresponds to 'no pain' and mark 10 corresponds to the 'worst imaginable pain'. VAS > 3 was managed with injection tramadol 50 mg IV. The following parameters were evaluated in all groups.

• Primary outcome

Duration of analgesia (defined as the time that elapsed between extubation and first request of analgesic medication).

• Secondary outcomes

Assessment of pulse rate, non-invasive blood pressure, oxygen saturation, respiratory rate and VAS score was done every hourly for first 8 hours and then 4 hourly for next 16 hours. The total analgesic consumption of IV tramadol - 50 mg in 24 hours following extubation. Nausea, vomiting, bradycardia (decrease in HR > 20% from baseline), hypotension (decrease in BP > 20% from baseline), shivering, sedation, allergic reactions and any other complications and side-effects were looked. The degree of sedation was graded as per filos:

Grade 1- Awake and alert.
Grade 2- Drowsy, responsive to verbal stimuli.
Grade 3- Drowsy, arousable to physical stimuli.
Grade 4- Unarousable.

Statistical analysis

All the results were analysed by SPSS software version 17.0. The data were described in terms of range; mean±standard deviation (SD), frequencies (number of cases), and relative frequencies (percentage). Chi- square, Kruskal Wallis, Friedman test and Fisher exact tests were used for assessment of level of significance. P- value of less than 0.05 was considered as statistically significant.

Results

There was no statistically significant difference in the three groups with respect to age, gender, BMI and ASA status and duration of surgery.

Differences in preoperative as well as intraoperative mean heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), respiratory rate (RR), ETCO2 between the groups were not statistically significant. Also, Differences in postoperative HR, SBP, DBP, MAP, RR, SpO_2 were not significant.

In regard to the duration of analgesia, for group A, it was 7.36±1.69 h, for group B, it was 4.11±0.832 h and for group C, it was 4.53±0.834 h. The difference was statistically

significant in group A (P=0.000) in comparison to group B and group C. However, there was no significant difference in duration of analgesia between group B and group C (P=0.878). [Table 1]

Total analgesic consumption over 24 hours were significantly higher in group B among all the three groups (P=0.025). Also, the total analgesic consumption over 24 hours in group B were higher as compared to group A (P=0.019). But when the total analgesic consumption over 24 hours was compared between group A and group C (P=0.513), and between group B and group C (P=0.527), it was not statistically significant. [Table 1]

In group A, 55% patients required rescue analgesia whereas in group B 90% and in group C 75% patients required rescue analgesia. This difference was statistically significant with P< 0.05. The patients requiring rescue analgesia were significantly higher in group B as compared to group A (P=0.015). However, there were no significant differences in patients who required rescue analgesia when group A was compared to group C (P=0.204) and when group B was compared to group C (P=0.160). [Table 1]

Total number of doses of rescue analgesia given over 24 hours were significantly higher in group B among all the three groups (P=0.025). Also, the total number of doses over 24 hours in group B were higher as compared to group A (P<0.05). But when the number of doses over 24 hours was compared between group A and group C (P>0.05), and between group B and group C (P>0.05), it was not statistically significant. [Table 1]

Mean VAS scores were lower in group A as compared to group B and group C and we found significantly lower values of mean VAS scores in group A at 3rd and 4th postoperative hour (p value< 0.05). Thereafter, no significant difference was seen in VAS scores among all the three groups (p value> 0.05). Also, VAS scores correlated well with the heart rates. Higher VAS scores were observed at 7th postoperative hour in group A and at 4th hour in group B and C. [Table 2] [Figure 1]

Group A has higher sedation scores as compared to group B and group C and significantly high at 2nd and 3rd postoperative hours (p value< 0.05). Thereafter, no significant difference was seen with regard to sedation score among all three groups (p value> 0.05). [Figure 2]

In group A incidence of nausea and vomiting was seen in one patient (5%) each, in group B it was seen in eight patients (40%) each and in group C it was seen in nine patients (45%) for nausea and in eight patients (40%) for vomiting. No episodes of hypotension, bradycardia, allergic reaction, decreased respiratory rate and hypoxia or any other side effects.

Table 1: Comparison of duration of analgesia, total analgesic required, total number of patients and doses of rescue analgesics

Analgesic profile	Group A (Dexmedetomidine) (n=20)	Group B (Nalbuphine 5) (n=20)	Group C (Nalbuphine 10) (n=20)	P value
Duration of analgesia (hours)	7.36±1.69	4.11±0.832	4.53±0.834	0.000
Total analgesic consumption over 24 hours(mg)	650	1250	950	0.025
Number of patients given rescue analgesia	11 (55%)	18 (90%)	15 (75%)	0.043
Total number of doses of rescue analgesia over 24 hours	13	25	19	0.025

The data are presented as mean ± standard deviation or number (%). n=number of patients

Table 2: Comparison of postoperative VAS score (mean±SD) in studied groups

Time (hours)	Group A (Dexmedetomidine) (n=20)		Group B (Nalbuphine 5) (n=20)		Group C (Nalbuphine 10) (n=20)		p value
0	1.05	1.05	1.10	0.71	1.2	0.95	0.843
1	1.05	0.82	1.25	0.85	1.4	0.94	0.474
2	1.2	0.89	1.35	0.33	1.3	0.66	0.786
3	1.25	0.78	2.25	1.33	1.8	0.89	0.026
4	1.35	0.67	3.2	1.79	2.65	1.49	0.001
5	1.60	0.75	1.95	1.53	2	1.62	0.966
6	1.55	1.15	1.25	1.16	1.35	1.09	0.14
7	2.3	1.59	1.5	0.51	1.5	0.51	0.306
8	1.6	1.31	1.65	0.67	1.55	0.51	0.832
12	1.8	1.10	1.85	0.81	2.1	1.07	0.327
16	1.75	0.85	2.25	1.58	1.9	1.07	0.740
20	1.75	0.63	2.2	0.89	2	0.91	0.217
24	1.75	0.55	1.90	0.912	2.2	0.76	0.164

The data are presented as mean ± standard deviation, n=number of patients
VAS: visual analogue scale

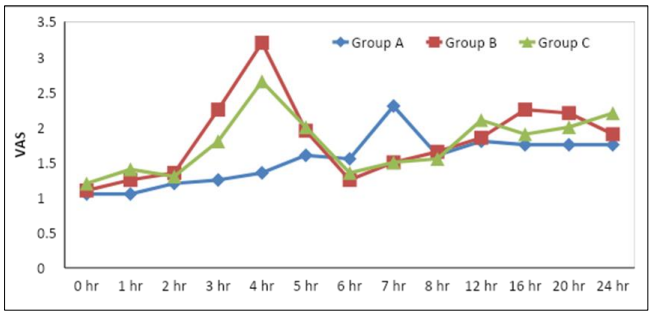

Fig 1: Visual Analog Scale at different time intervals

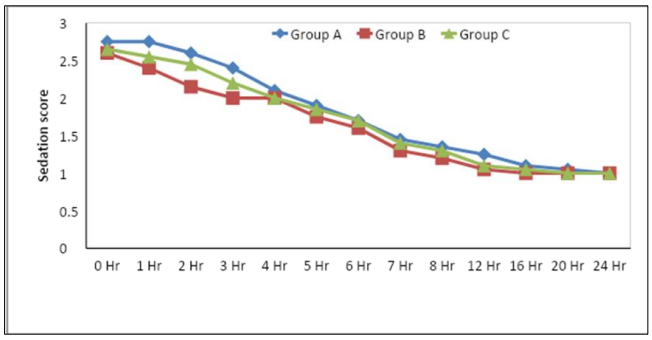

Fig 2: Sedation score at different time intervals

Discussion

Two main findings emerged from the present study, comparing intraperitoneal dexmedetomidine with intraperitoneal nalbuphine as an adjunct to ropivacaine for laparoscopic cholecystectomy. First, dexmedetomidine as an adjunct resulted in longer duration of analgesia compared to adjunct nalbuphine. The second important finding is that tramadol consumption was significantly less in dexmedetomidine group. This difference is not only statistically significant (P=0.025), but is clinically meaningful. Our results correlated with that of Rapolu S et al., they observed that mean time to first dose of rescue analgesia was 7.61±0.56 hours when 1 mcg/kg of dexmedetomidine was given in combination with 0.25% bupivacaine in laparoscopic cholecystectomy [9].

The next important finding was that the adverse effects were quite low and not serious in all the three study groups. Dexmedetomidine was more sedating than nalbuphine, but no one in either group was grossly sedated. Our results were supported by study conducted by Patel HS et al. who concluded that addition of dexmedetomidine in dose of 1 mcg/kg to bupivacaine lead to higher sedation scores [10]. high mean sedation scores were noted at 2nd and 3rd postoperative hours (p value< 0.05).

Other adverse effects such as nausea and vomiting (PONV) were greater in patients who were given intraperitoneal nalbuphine after laparoscopic cholecystectomy. These figures were supported by study of Singh S et al. [11]

Laparoscopic cholecystectomy has improved surgical outcome in terms of reduced pain, compared to open cholecystectomy, but it is not a pain-free procedure. Pain is responsible for overnight stay on the day of surgery in 26%-41% of patients. In this modern era of surgery, intraperitoneal instillation of local anaesthetic agents (IPLA) has become an important method to control postoperative pain. Intraperitoneal local anaesthetic is likely to produce analgesia by blocking the free afferent nerve endings in peritoneum and also, by systemic absorption of local anaesthetic from the peritoneal cavity [12].

The antinociceptive effect of dexmedetomidine is seen at dorsal root neuron level, where it blocks the release of substance P in the nociceptive pathway, through action on inhibitory G protein, which increases the conductance through potassium channels [13]. The rationale of preferring ropivacaine in our study is that it is a long-acting agent, which has less cardiotoxicity than bupivacaine and large volume can be given safely [14]. This drug possesses antiinflammatory activity that may further reduce pain when administered locally [15].

Chiruvella et al. also demonstrated that intraperitoneal adminis tration of 1 mcg/kg dexmedetomidine in combination with 0.2% ropivacaine in laparoscopic cholecystectomy was associated with increased time to first request for analgesia. However, in their study, they used 30 ml of 0.2% ropivacaine and found that time to first request of analgesia was 126±24 minutes.[14] This may be due to lesser volume of ropivacaine used in their study as compared to our study which was 50 ml.

Also, a study done by Singh S et al. concluded that patients who were given 2 mg nalbuphine intraperitoneally along with 20 ml of 0.2% ropivacaine demanded the first dose of rescue analgesic in the 4th postoperative hours.[11] Other studies also showed that intraperitoneal instillation of alpha-2 agonists and opioids in addition to bupivacaine provided better pain relief than bupivacaine alone. [12, 16]

Total number of doses of rescue analgesia and total analgesic consumption over 24 hours were significantly lower in dexmedetomidine group as compared to both nalbuphine group. (p value< 0.05). Our results were similar to Chiruvella et al. who stated that intraperitoneal administration of 1 mcg/kg dexmedetomidine in combination with 0.2% ropivacaine in laparoscopic cholecystectomy was associated with a reduction in postoperative analgesic requirements.[14]

Our results were also supported by Fares KM et al. who found that total analgesic requirement over 24 hours was significantly decreased in patients in whom dexmedetomidine was given intraperitoneally in addition to 0.25% bupivacaine.[17] Ahmed et al. also observed that intraperitoneal instillation of meperidine or dexmedetomidine in combination with bupivacaine significantly decreased total rescue analgesia requirement in postoperative period.[12]

This study had a few limitations, first, present study had small sample size. Further studies with a larger sample size comparing this approach of analgesia are required. Second, we did not measure the plasma levels of ropivacaine, dexmedetomidine and nalbuphine administration. However, we did not exceed the maximum dose allowed and no cases of toxicity were reported in the study. Third limitation is the post-operative pain, which is a subjective experience and can be difficult to quantify (objectively) and compare when comparing various treatment options. Fourth, only ASA physical status 1 and 2 patients were included in the study so the results of the present study should not be generalised to higher grades of ASA physical status. We believe that none of these limitations can be invalidate the findings of the study.

As there are very few studies on addition of dexmedetomidine and nalbuphine as an adjuvant to intraperitoneal ropivacaine, further studies are needed to provide maximal benefit in terms of postoperative pain relief with minimal adverse effects after laparoscopic surgeries.

In conclusion, this study shows that greater postoperative

analgesia was observed in patients receiving intraperitoneal 1mcg/kg, dexmedetomidine with 50ml ropivacaine as compared to 5mg or 10 mg, of nalbuphine with 50ml ropivacaine. Intraperitoneal dexmedetomidine when used as an adjunct had more analgesic sparing effects as compared to intraperitoneal nalbuphine when used in conjunction with 0.025% ropivacaine in patients following laparoscopic cholecystectomy.

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