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Research Article

Evaluation of the Efficacy of Intraperitoneal Instillation of Ropivacaine with Dexmedetomidine Versus Ropivacaine with Ketamine for Post Operative Pain Relief Following Laparoscopic Cholecystectomy: A Randomized Controlled Study

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ABSTRACT

Background: Adjuvants are added to intraperitoneal local anesthetics to prolong analgesia however no study compares Dexmedetomiditine with Ketamine as adjuvant to Ropivacaine for laparoscopic cholecystectomy.
To compare efficacy of intraperitoneal instillation of Ropivacine with Dexmedetomidine versus Ropivacaine with Ketamine for postoperative pain relief following laparoscopic cholecystectomy.
Methods: Sixty patients ASA I and ASA II undergoing laparoscopic cholecystectomy were randomly allocated in three groups and received Ropivacaine 0.2 % (group R), Ropivacaine 0.2 % alongwith Dexmedetomidine 0.7 micogrms/ kg (group RD) and Ropivacaine with Ketamine 0.5 mg/kg (group RK) to a total volume of 40ml.The primary outcome measured was time to request of rescue analgesia while secondary outcomes were post op numeric rating scale, total dose of rescue analgesia required in 24 hours and haemodynamic parameters in postoperative period.
Results: The median time to request of rescue analgesia was shortest in R group 55 [42.5-70] minutes followed by RK group 60 [50.50-72.50] and maximum in the group RD the time being 900 [86.25 -1440] minutes while haemodynamics remained stable in all the groups. Similar findings were seen for total demand of analgesia in 24 hours as well as NRS scale both static and dynamic which was measured periodically in the first 24 hours.
Conclusion: Dexmedetomiditine 0.7 micrograms per kg when used as adjuvant with Ropivacine is effective combination that prolongs duration than Ropivacaine alone or when used with Ketamine 0.5 mg per kg body weight however total dose of rescue analgesia was significantly less in Ketamine group compared to Ropivacine alone and least when Dexmedetomiditine is used as adjuvant.

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Introduction

Amongst a wide array of surgical procedures laparoscopic cholecystectomy still is one of the most commonly performed surgeries as it has almost replaced the erstwhile common surgery that is open cholecystectomy. Even though the postoperative pain associated with the laparoscopic procedure is significantly less than open cholecystectomy, the patients may still suffer from pain during movement, respiration, coughing or mobilization during the first few postoperative hours [1].

Pain after laparoscopic cholecystectomy is not attributed to a single factor rather a multitude of factors contribute to postoperative pain [2]. Patients usually experience pain in the abdomen in the initial hours followed by shoulder and back region over the next few hours in the first 24 hours in the postoperative period. The pain sensation in shoulder is mainly attributed to irritation of the phrenic nerve caused by residual carbon dioxide in the peritoneal cavity, while the visceral pain due to stretching of the abdominal cavity; and minimal component of somatic pain is attributed to due to the small surgical incisions.

Significant visceral pain occurs after laparoscopic cholecystectomy due to the presence of silent nociceptors present via signalling through the enteric nervous system which relays sensations from the gall bladder and the peritoneum covering it [3]. These receptors are activated by both painful and non-painful stimuli arising from peritoneal inflammation and injury.

Intraperitoneal instillation of local anaesthetics is a well-established technique for postoperative pain relief whilst avoiding the side effects such as sedation, nausea, vomiting, and respiratory depression which are often associated with the intravenous administration of opioids [4]. They also promote early ambulation and Enhanced Recovery After Surgery [5]. The use of these adjuncts also reduces the requirement for opioids in the postoperative period thus promoting early ambulation and discharge [4,6]. Intraperitoneal local anaesthetics inhibit visceral nociception by inhibiting the release of prostaglandins which cause inflammation. When local anaesthetics are used intraperitoneally the serum levels are known to escalate possibly because the absorption through this route into systemic circulation is similar to epidural administration or for peripheral nerve blockade.

Amongst the various local anaesthetics available, intraperitoneal Ropivacaine has emerged as a safe and better alternative to the more commonly used Bupivacaine as it is less cardiotoxic and can be used in large doses [5]. The use of adjuncts such as Dexmedetomidine prolongs the duration of analgesia however it may be associated with side effects such as bradycardia. Ketamine alone or in combination with bupivacaine has been shown to provide pain relief and has anti-inflammatory properties as well. However, on an extensive search of the literature, no study was found comparing these two adjuncts along with Ropivacaine for postoperative pain relief.

With this background, the present randomized controlled study was designed to compare the efficacy of intraperitoneal instillation of Ropivacaine with Dexmedetomidine versus Ropivacaine with Ketamine for postoperative pain relief following laparoscopic cholecystectomy.

Methods

This randomized controlled double-blinded trial was conducted in a tertiary care hospital after approval from the ethics committee. Sixty ASA grade I and II patients, belonging to either gender, aged 20 to 55 years undergoing laparoscopic cholecystectomy were enrolled for this study between November 2019 and October 2021.

Exclusion criteria were patients with known cardiovascular, pulmonary, psychological or neurological diseases, known epileptic, patients with history or symptoms of raised intracranial tension, with known allergies to the study drugs, with cardiovascular abnormalities like heart block, left bundle branch block. Obese patients (BMI $\geq$ 30) were excluded from the study also patients in whom the procedure was converted to open cholecystectomy or those in whom subhepatic drain was inserted after the removal of gall bladder were excluded from the study.

Procedure: Randomization Sixty patients fulfilling the above-mentioned selection criteria were selected and randomly allocated into one of the following three groups on the day of surgery by a computer generated random number chart.

Group R (n=20): [control group]: Each patient received 0.2% plain Ropivacaine in a total volume of 40 ml of instilled solution.

Group RD (n=20): Each patient received 0.7µg/kg Dexmedetomidine mixed with 0.2% Ropivacaine in a total volume of 40 ml of instilled solution.

Group RK (n=20): Each patient received 0.5 mg/kg of Ketamine mixed with 0.2% Ropivacaine in a total volume of 40 ml of instilled solution.

The preparation of the study drugs solution was done by an anaesthesiologist who was not involved in the study. Similarly, the anaesthesiologist who observed the patient and the surgeon involved were oblivious of the study group until the end of the study.

A thorough pre-anaesthetic evaluation and necessary investigations of all the patients enrolled in the study were done. All the patients were explained the detailed procedure, one day before surgery and only those patients willing to be enrolled were included in the study. The patients were explained about the Numeric Rating Scale (NRS) which is a 10-point scale (score of 0 is no pain, 1-

3 mild pain, 4-6 moderate pain, and 7-10 severe pain) during the preoperative visit. A written and informed consent for anaesthesia was taken from the patients. The patients were kept nil per orally for at least 6 hours before surgery and received Alprazolam tablet (0.25 mg) orally on the night before the surgery. Upon arrival into the operating room, pre-induction monitors such as electrocardiography for heart rate (HR), non-invasive blood pressure (NIBP), and oxygen saturation (SpO2), were attached and baseline parameters were noted. An 18G intravenous (IV) catheter was inserted on the dorsum of the hand and 6 mL/kg/h crystalloid was infused through the same. Standard general anaesthesia was administered induction with Propofol, Fentanyl and neuromuscular blockade with Vecuronium, endotracheal intubation maintenance of anaesthesia with nitrous oxide and oxygen along with Sevoflurane. Minute ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide [EtCO2] between 34 and 38 mm Hg). Patients were placed in 15–20º Reverse Trendelenburg's position with the left side tilt position. During laparoscopy, the intra-abdominal pressure was maintained between 12–14 mmHg. Intraoperative vital parameters like HR, NIBP, SpO2 and EtCO2 were monitored throughout the surgery. The preparation of study drugs was done by the anesthesiologists not involved in the study.

After the removal of the gall bladder, a total of 40 ml of study drug solution was instilled through the trocar of which 10 ml was given on either side into the subdiaphragmatic space in a fan shaped manner by the surgeon who was blinded to the identity of drugs and the remaining solution was instilled in the gall bladder bed, near and above the hepatoduodenal ligament and in the hepatodiaphragmatic space. After the instillation of the study drug, the patient was kept in the Trendelenburg position for 2 minutes. Injection Paracetamol 20 mg/kg body weight was given IV 30 minutes before extubation.

Intravenous Ondansetron 0.1mg/kg was given in both groups. At the end of the surgery, the residual neuromuscular blockade was reversed with Neostigmine 0.05 mg/kg and Glycopyrrolate 0.01 mg/kg and the trachea was extubated. The time to extubation and hemodynamic parameters was noted. Subsequently, the patient was shifted to the postanaesthetic care unit.

The intensity of postoperative pain was assessed using the NRS both at rest (static) in the supine position and at the right lateral position while encouraging the patient to cough (dynamic) immediate postoperatively and then at 30 min, 1 h, 2h, 3h, 4 h, 6h, 8 h, 12 h, 18 h and 24 h postoperatively. In patients with either NRS ≥ 4, a bolus dose of Tramadol 50 mg intravenous along with Ondansetron 0.1 mg/kg intravenous was administered as rescue analgesia (not repeated before 8 hours). Time to demand of first rescue analgesic and its total consumption in 24 hours was noted

To maintain adequate analgesia, after 8 hours postoperative all patients received IV 20 mg/kg body weight Paracetamol 6 hourly and Diclofenac Sodium 1 mg/kg IV 12 hourly for the subsequent 24 hours. During this period surgical team was instructed not to give any other analgesics

Hemodynamic parameters were measured every 5 minutes for the first 15 minutes postoperatively and then every 30 minutes up to 2 hours. Thereafter, hemodynamic monitoring was done hourly till 8 hours postoperative. Bradycardia was defined as heart rate ≤ 50 beats/minute, managed with IV Atropine and hypotension which was defined as a fall of 20% from baseline SBP or an absolute value of ≤ 80 mmHg SBP was managed with IV fluids and vasopressors.

Statistical analysis

All the three groups were compared by one way ANOVA followed by Tukey's test. Since we found that many variables in our data were skewed distributed and followed Non Gaussian distribution, therefore for these parameters we have applied non parametric tests i.e. Kruskal Wallis Test followed by Mann Whitney U test. The whole analysis was carried out in SPSS 20.0 and p values <0.05 were taken as significant.

Results

As depicted in the CONSORT diagram (Figure 1) (Out of the 70 patients who were assessed for inclusion, 63 patients were enrolled and 7 were excluded from the study. Amongst 63 participants, one from Group R and one from Group RD were excluded because of the surgery being converted from laparoscopic to open cholecystectomy. One from Group RK had to be excluded because of subhepatic drain insertion. Finally, 60 patients were included in the study with 20 patients in each group. The demographic parameters, including age weight and gender distribution, were comparable in the three groups.

The baseline and intraoperative haemodynamic parameters were also comparable in the three groups. As depicted in (Figure 2 and Table 1) the median time to request the first dose of rescue analgesia was lowest in Group R being 55.00 [42.75- 70.00] minutes followed by Group RK where the median time to request of the first dose of rescue analgesia was 60.00 [50.50-72.50] minutes. It was found to be maximum in Group RD, the median time being 900.00 [86.25-1440.00] minutes. The difference in time to request the first dose of rescue analgesia was found to be statistically significant in the three groups with p-value being < 0.05.

There was also a statistically significant difference between Group R and RD as well as Group RD and RK, however, no statistical significance was observed between Group R and RK.

The intensity of postoperative pain was assessed using the NRS at rest (static) in a supine position at various time intervals: immediate postoperatively (0 minutes) and then at 30 min, 1 h, 2h, 3h, 4 h, 6h, 8 h, 12 h, 18 h and 24 h postoperatively.

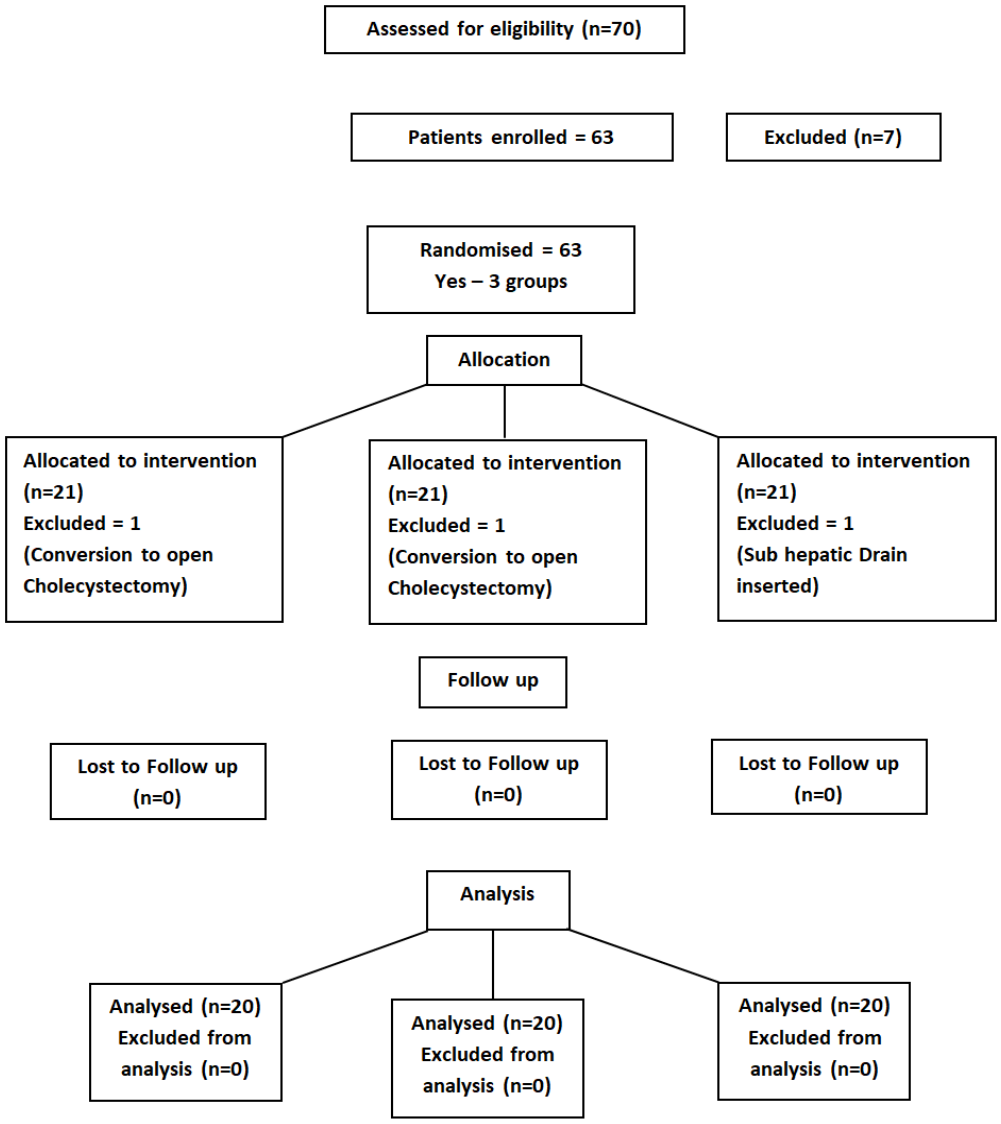

Figure 1- Consort Diagram

Table 1- Showing administration of Rescue analgesia (Injection Tramadol 50 mg IV) given at various time intervals during the first 24 h post operative period

Parameters	Group R (n=20) (Mean±SD)	Group RD (n=20)(Mean±SD)	Group RK (n=20)(Mean±SD)	Significance (KW Test)	P value (Mann Whitney U Test)
Rescue Analgesia 0 mins (mg)	0.00±0.000	0.00±.000	0.00±0.000	1.000	1.000* 1.000# 1.000^
Rescue Analgesia 30 mins (mg)	20.00±25.131	0.00±0.000	17.50±24.468	0.007	0.002* 0.004# 0.747^
Rescue Analgesia 1hr (mg)	20.00±25.131	12.50±22.213	22.50±25.521	0.400	0.317* 0.190#

Rescue Analgesia 2hr (mg)	5.00±15.390	2.50±11.180	7.50±18.317	0.579	0.752^ 0.553* 0.298#
Rescue Analgesia 3hr (mg)	0.00±0.000	0.00±0.000	2.50±11.180	0.368	0.637^ 1.000* 0.317#
Rescue Analgesia 4hr (mg)	0.00±0.000	2.50±11.180	0.00±0.000	0.368	0.637^ 0.317* 0.317#
Rescue Analgesia 6hr (mg)	0.00±0.000	7.50±18.317	5.00±15.390	0.223	1.000^ 0.075* 0.637#
Rescue Analgesia 8hr (mg)	22.50±25.521	0.00±0.000	5.00±15.390	0.001	0.152^ 0.001* 0.152#
Rescue Analgesia 12hr (mg)	12.50±22.213	0.00±0.000	7.50±18.317	0.068	0.014^ 0.018* 0.075#
Rescue Analgesia 18hr (mg)	15.00±23.508	0.00±0.000	0.00±0.000	0.001	0.435^ 0.009* 1.000#
Rescue Analgesia 24hr(mg)	17.50±24.468	0.00±0.000	0.00±0.000	0.000	0.009^ 0.004* 1.000#

0.004^

*Between R and RD, #Between RD and RK, ^Between R and RK (p-value < 0.05 is significant)

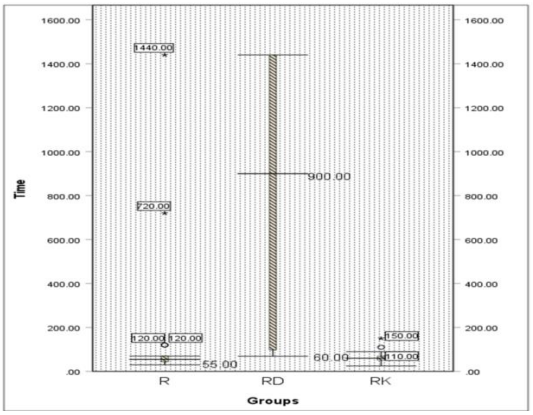

Figure 2- Median time (mins) to first request of analgesia in the three groups; Group RD: 900, Group RK: 60, Group R: 55

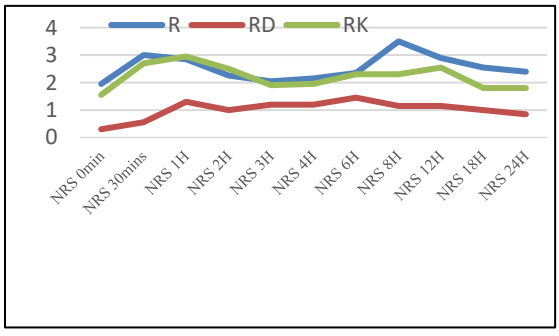

Figure 3- Comparison of static NRS score between the three groups.

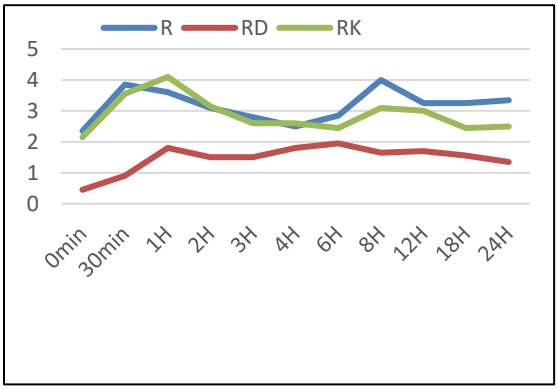

Figure 4- Comparison of dynamic NRS score between the three groups

Patients were asked to indicate the severity of pain as follows: a score of 0 is no pain, 1-3 mild pain, 4-6 moderate pain, and 7-10 severe pain. A comparison of the three groups was done using the Kruskal Wallis test followed by the Mann Whitney U test. As depicted by (Figure 3). The mean NRS at rest (static) in the entire postoperative period ranged from 1.95±1.731 to 3.00±2.052 in Group R, followed by 1.55±0.999 to 2.95±0.999 in Group RK and least in Group RD, values being 0.30±0.657 to 1.45±1.395. Further, there was a statistically significant difference in mean NRS scores amongst the three groups at all time intervals (0 minutes, 30 minutes, 1 h, 2h, 3h, 4 h, 6h, 8 h, 12 h, 18 h and 24 h). It was observed that there was a statistically significant reduction in NRS scores in Group RD compared to Group

R as well as Group RD compared to Group RK at all time intervals; however, differences in NRS scores were not found to be statistically significant between Groups R and RK. However, an exception was noted at the 8th postoperative hour where the difference in NRS was statistically significant between Group R and RK, being lower in RK. NRS dynamic also showed a similar pattern depicted in (Figure 4).

Discussion

Intraperitoneal local anaesthetic instillation alone fails to address parietal pain and does not improve pain while coughing, therefore it is recommended that adjuvants be used along with local anaesthetics [7].

In the present study, we have added adjuncts like Dexmedetomidine and Ketamine along with Ropivacaine to prolong the analgesic effect and to reduce the time to request the first dose of rescue analgesia as the parietal pain is not significantly managed by intraperitoneal local anaesthetics alone.

Bisgaard et al, [8] have described three components of pain after laparoscopic cholecystectomy: incisional pain due to small port incisions (parietal component), deep intraabdominal pain (visceral pain due to stretching of the abdominal cavity) and shoulder tip pain (resulting from the irritation of the phrenic nerve caused by residual carbon dioxide in the peritoneal cavity [9]. In a study conducted by Joris et al,3 visceral pain was found to be predominant during the first 24 hours which significantly worsened on coughing. Therefore, NRS was assessed at rest and on coughing static and dynamic at periodic intervals.

Time to request the first dose of analgesia: The primary outcome measure in the present study was time to request the first dose of rescue analgesia.

The median time to request the first dose of rescue analgesia was found to be 900.00 [86.25-1440.00] minutes which was considerably higher than the Ropivacaine alone as well as when Ropivacaine was combined with Ketamine. Dexmedetomidine is shown to prolong the duration of analgesia than Ropivacaine alone. Praveena et al12 made similar observations where they found Dexmedetomidine to be superior to fentanyl when used in combination with Ropivacaine.

On an extensive search of the literature, we did not find any study where Ropivacaine was used along with Ketamine for intraperitoneal instillation. However, in a study conducted by Moharari et al [10] comparing the analgesic efficacy of intraperitoneal instillation of 0.25% Bupivacaine vs 0.5 mg/kg Ketamine alone it was observed that the time to demand of the first dose of rescue analgesia was 21.43±0.50 minutes in Ketamine group compared to Bupivacaine where it was 6.32±0.64 minutes. In the present study, the median time to request the first dose was comparatively higher (60.00 [50.50-72.50] minutes) in the Ketamine with Ropivacaine group and the longer time to request can be explained by the fact that we used Ropivacaine and Ketamine combination [11].

Postoperative NRS scores: In the present study, we have assessed postoperative pain at various time intervals using the NRS scale: 0 min, 30 minutes, 1 h, 2 h, 3 h, k4 h, 6 h, 8 h, 12 h,18 h and 24 h.

In the present study mean NRS scores were also lower in the RD group both at rest as well as upon movement while coughing in the right lateral position, the mean values ranging from 0.30±0.657 to 1.45±1.395 (static NRS) and 0.45±0.999 to 1.95±1.538(dynamic NRS) throughout the postoperative observation period up to 24 hours.

These findings correlate with those of Praveena et al. [12] wherein the overall VAS in 24h was found to be significantly lower in Ropivacaine with Dexmedetomidine group (1.68± 0.46) compared to Ropivacaine with Fentanyl group (4.47 ±0.94).

In a study conducted by Fares et al4 it was found that Dexmedetomidine (1 µg/kg) when instilled intraperitoneally along with Bupivacaine significantly reduced VAS scores in patients undergoing laparoscopic colorectal surgeries ($p< 0.05$). There was also a reported incidence of one patient having bradycardia (HR reaching 47/min) and two patients having hypotension (blood pressure up to 80/50) postoperatively however, no patient in the present study had these side effects. This might be attributed to the use of a comparatively higher dosage of Dexmedetomidine (1µg/kg). However, in the present study, we have found that 0.7µg/kg provides adequate postoperative analgesia without serious side effects.

Total demand for rescue analgesia: In the present study, the median value for total consumption of rescue analgesia consumed was observed to be highest in Group R 125 [100-150] mg followed by 50 [0.00-50.00 mg in Group RK and it was found to be the least in Group RD being 25.00±25.649 mg. The difference in mean rescue analgesic consumption was found to be statistically significant in all groups while comparing Group RD with Group R, Group RD with Group RK as well as Group R and RK.

This observation correlated with the study conducted by Praveena et al, [12] where it was found that the total consumption in intraperitoneal Ropivacaine with Dexmedetomidine group was found to be lower (95.3 ± 15.6 mg) than the Ropivacaine with Fentanyl group (135.7 ± 75.1 mg). In the present study, it was found to be even lesser, the median value being 25.00±25.649 mg in the RD group.

Moharari et al [10] found that intraperitoneal Ketamine with Normal saline reduced the total consumption of rescue analgesia when compared to Bupivacaine alone when given intraperitoneally. The total consumption of

rescue analgesia in the RK group was found to be even lesser in the present study (50 [0.00-50.00 mg]) which might be because Ropivacaine was used in combination with Ketamine.

Thus, in the present study, it is observed that both the adjuvants i.e. Ketamine and Dexmedetomidine reduce the total consumption of rescue analgesia however the total consumption is significantly less in Dexmedetomidine when compared to Ketamine.

Postoperative Hemodynamic parameters: Mean values of post-operative heart rate, systolic blood pressure and diastolic blood pressure were found to be comparable among R and RK groups however there was a statistically significant reduction in the postoperative hemodynamic parameters in group RD at multiple time intervals. The hemodynamic parameters in the postoperative period remained within the normal physiological limits, and there was no incidence of hypotension or bradycardia.

Limitations

The limitations of the present study include that pain is a subjective experience and it is not quantifiable by any objective assessment. Pain thresholds of different individuals are different, thus there is interindividual variability in demand for analgesia for the same surgical procedure. Therefore, assessment and management of postoperative pain continue to be a challenge despite using multimodal analgesia. The exact dosage, mechanism, duration of action and amount of systemic absorption of the intraperitoneal Ropivacaine alone and when used with Dexmedetomidine and Ketamine is still being studied.

Conclusion

Intraperitoneal Ropivacaine with Dexmedetomidine is superior to Ropivacaine with Ketamine or Ropivacaine when used alone when we compare the time to demand of rescue analgesia. The total demand of rescue analgesia and NRS too was found better for Dexmedetomidine when used in combination with Ropivacaine than Ropivacaine alone or with ketamine (however the difference between Ketamine and Ropivacaine alone too was statistically significant), thus Dexmedetomidine 0.7µg/kg as an adjunct to Ropivacaine is safe and effective for postoperative pain relief in laparoscopic cholecystectomy. Ketamine, when used as an adjunct to Ropivacaine, reduces the total consumption of rescue analgesia however statistically the time to demand of rescue analgesia is comparable to plain Ropivacaine.

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