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A STUDY OF COMPARISON OF ANTINOCICEPTIVE EFFECT OF INTRAPERITONEAL INSTILLATION OF BUPIVACAINE WITH CLONIDINE TO BUPIVACAINE WITH DEXMEDETOMIDINE IN LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT

Nowadays laparoscopic cholecystectomy is the method of choice over open cholecystectomy. But it frequently results in significant immediate postoperative pain. **Aims**: The primary aim of this study was to compare the analgesic effects of intraperitoneal bupivacaine with dexmedetomidine and clonidine in patients undergoing laparoscopic cholecystectomy. **Material and Methods:** A total of 80 patients were included in this prospective, randomized study divided into two equal sized (*n* = 40) study groups . Patients of Group BC who received intraperitoneal lnj. Bupivacaine 30 ml 0.25% + Clonidine 1 ug/kg and Group BD who received lnj. Bupivacaine 30 ml 0.25% + Dexmedetomidine 1ug/ kg. The analgesia was assessed by visual analogue scale score (VAS). Time to the first request of analgesia, the total doses of analgesic in the first 24 hrs and adverse effects were noted. **Results:** In this study, bupivacaine in combination with dexmedetomidine has significantly lower VAS scores at all the points of time and overall VAS score than group BC. The mean number of doses of rescue analgesia required more in group BC was 3.38±0.63 then Group BD was 2.25 ± 0.78 in 24 hours postoperatively. The mean time for first request of rescue analgesia was less 115.50±109.87min in group BC than mean time in group BD 227.75±158.33 min. **Conclusions: T**his study concluded that intraperitoneal instillation of dexmedetomidine in combination with bupivacaine in elective laparoscopic cholecystectomy significantly reduces the postoperative pain, the analgesic requirement in postoperative period as compared to bupivacaine with clonidine.

KEYWORDS: Bupivacaine Hydrochloride, Intraperitoneal, Laparoscopic, Dexmedetomidine Hydrochloride, Clonidine.

INTRODUCTION

Cholecystectomy is one of the most frequently performed operation. Laparoscopic cholecystectomy has better quality-of-life, shorter hospital stay and a quicker convalescence than open surgery.[1,2] The pain in the conventional cholecystectomy is a parietal pain. In laparoscopic cholecystectomy, pain is derived from multiple sites, Incisional pain (somatic), Deep intra-abdominal pain (visceral), and Shoulder pain (visceral pain due to phrenic nerve irritation).[3] Many methods have been proposed to relieve the post-operative pain following laparoscopic cholecystectomy. Early pain after cholecystectomy is reduced by minimizing residual pneumoperitoneum and by giving incisional local anaesthetics, epidural analgesia, and non-steroidal anti-inflammatory drugs.[4] Intraperitoneal instillation of local anaesthetic agents alone or in combination with opioids, ∝-2 agonists such as clonidine and dexmedetomidine have been found to reduce post-operative pain following laparoscopic cholecystectomy.[5] The primary aim of this study was to compare the antinociceptive effects of intraperitoneal dexmedetomidine combined with bupivacaine to intraperitoneal bupivacaine with clonidine in patients undergoing laparoscopic cholecystectomy. The Secondary aim of this study was to compare the time of first request of analgesia in the post-operative period, the total number of doses of analgesic used in 24 hours period post-operatively and any adverse effects.

MATERIAL AND METHOD

This study was a prospective randomized, conducted on 80 patients. After Institutional Ethics Committee approval, the study was conducted in a tertiary care level institute. The patients were selected from 18 to 60 years of age with an ASA (American Society of Anaesthesiologists) I or II status posted for elective laparoscopic cholecystectomy. The Patients allergic to study drugs, acute cholecystitis, severe cardiac, pulmonary, and neurological diseases, history of drug or alcohol abuse, history of chronic pain or daily intake of analgesics, patient who are not able to appreciate the VAS score, uncontrolled medical disease (diabetes

mellitus and hypertension), and history of intake of non-steroidal anti-inflammatory drugs or steroids within 24 h before surgery and in whom procedure had to be converted to open cholecystectomy were excluded from this study.

By computerized randomization, patients were divided into 2 groups of 40 each.
Group BC (n=40) who received lnj. Bupivacaine 30 ml 0.25% + Clonidine 1 ug/kg
Group BD (n=40) who received lnj. Bupivacaine 30 ml 0.25% +Dexmedetomidine 1ug/ kg.

After confirming NBM status and written, informed consent of the patient, an intravenous cannula of 18G size was secured and Ringer Lactate solution was started. The pulse oximeter, NIBP (noninvasive blood pressure), ECG(Electrocardiogram) were attached. Thirty minutes before, premedication was given with lnj. Glycopyrrolate 0.2ug/kg intramuscularly. Intravenous premedication given with lnj. Ondansetron 0.08mg/kg, inj. Midazolam 0.02mg /kg, lnj.Fentanyl 2 ug /kg. Preoxygenation done with 100% O_2 for 3 min and Patients was induced with Inj.Propofol 2 mg/kg, lnj. Succinylcholine 2mg/kg given Intravenously. Under direct laryngoscopic vision, patients were intubated with portex cuffed endotracheal tube of appropriate size. Then tube was connected to close circuit, $EtCO_2$ and air entry confirmed. The patients were maintained on O_2:N_2O (50%-50%), Isoflurane as inhalational agent and lnj. Vecuronium as a skeletal muscle relaxant. Intraoperatively pulse rate, blood pressure, Oxygen saturation and $EtCO_2$, intraabdominal pressure were monitored every 15 min. At the end of the surgery, the prepared solution was given intraperitoneally before removal of trocar in Trendelenburg's position, into the hepato-diaphragmatic space, on gall bladder bed and near and above hepato-duodenal ligament. Infiltration of incision sites with additional lnj Bupivacaine 0.25% 5 ml was done in both the groups. The neuromuscular blockade were antagonized with inj. neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg and patients were extubated uneventfully. The patients were shifted to post-anaesthesia care unit (PACU) and observed for 4 h after the surgery. Post-operatively Pulse rate, Blood pressure, Respiratory rate and VAS score at 0, 30 min, 1h, 2h, 4h, 6h, 12h and 24 h were recorded. All the study patients were instructed about the use of the VAS score before induction of anaesthesia (VAS score **:** No pain (0), Mild pain (1-2), Moderate pain (3-7), Severe pain (8-9), Worst pain imaginable (10)). Patients who reported VAS 3 or >3 was given inj. diclofenac 1.5 mg/kg intramuscularly as rescue analgesia. The patients also observed for postoperative nausea and vomiting. Patients who suffered from nausea or vomiting were given inj. ondansetron 0.08 mg/kg IV. Time to the first request of analgesia (considering the extubation time as 0), the total number of doses of analgesia and adverse or side effects over 24 h postoperatively were noted.

Power analysis: The study was conducted between October 2016 and October 2017. The population of surgery over this period was 150 patients. The sample size of the patients was calculated using population based formula. By exclusion and inclusion criteria and loss to follow-up, we divided 80 the patients using simple computerized randomization in two independent groups.

Statistical Analysis: The data was managed in Microsoft excel spreadsheet. It was expressed as mean ± SD. Two independent sample t-test, Chi square test and Fisher's exact test used to investigate and model impact of various parameters like gender distribution, age, weight, haemodynamic, duration of surgery, duration of recovery and side effects. Demographics and General information like count, average and percentage for various parameters with all permutations and combinations were calculated in Microsoft excel. A *P* value <0.05 was considered statistically significant**.** All graphs were drawn and all statistical analysis was done using Statistical Package for Social Sciences (SPSS) software version 20:0.

RESULTS

There were no significant difference between mean age, sex, ASA grading, weight (kg) and were comparable in both the Group BC and Group BD. (*P* value > 0.05).

There was statistically significant difference between mean heart rate, systolic blood pressure and respiratory rate in Group BC and Group BD at immediate postoperatively 0 min, 30 min, 1h, 2h, 4h, 6h, 12h, 24h but clinically it was insignificant. (*P* value <0.05).

There was statistically significant difference between VAS score in Group BC and Group BD at immediate postoperative period at 0 min, 30min, 1h, 2h, 4h, 6h, 12h, 24h. [Fig. 1]. Mean VAS score was significantly lower in Group BD as compared to Group BC.(*P* value < 0.05)

Fig. 1: Comparison of VAS.

There was statistically significant difference between mean time to requirement of rescue analgesia in Group BC (115.50±109.87min) and Group BD (227.75±158.33 min). [Fig.2]. Patients in group BC required rescue analgesia at earlier time than patients in Group BD. (*P* value < 0.05)

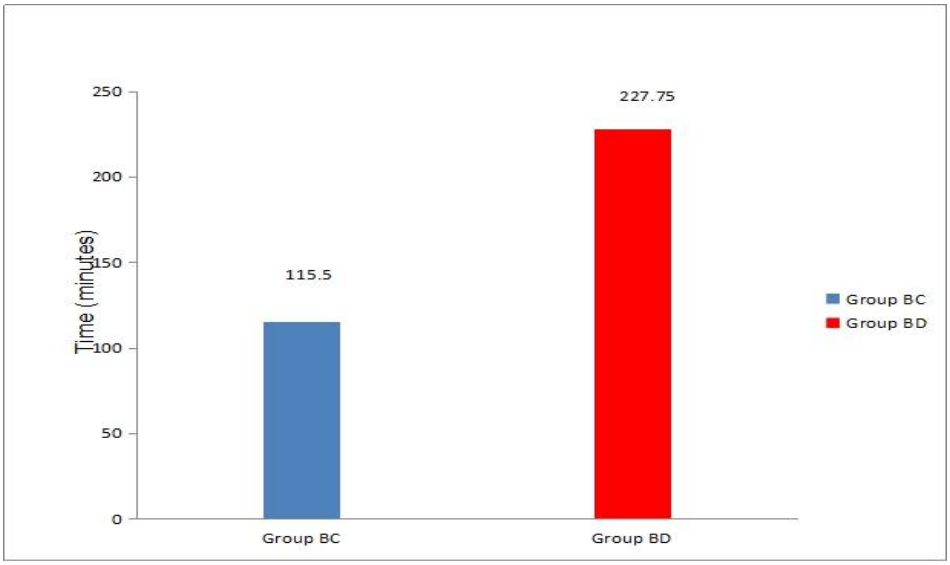

Fig. 2: Comparison of time to rescue analgesia.

There was significant difference between mean number of doses of rescue analgesia required in 24 hours in Group BC (3.38±0.63) and Group BD(2.25 ± 0.78). [Fig. 3]. Patients in group BC required rescue analgesia more frequently than patients in Group BD (*P* value < 0.001)

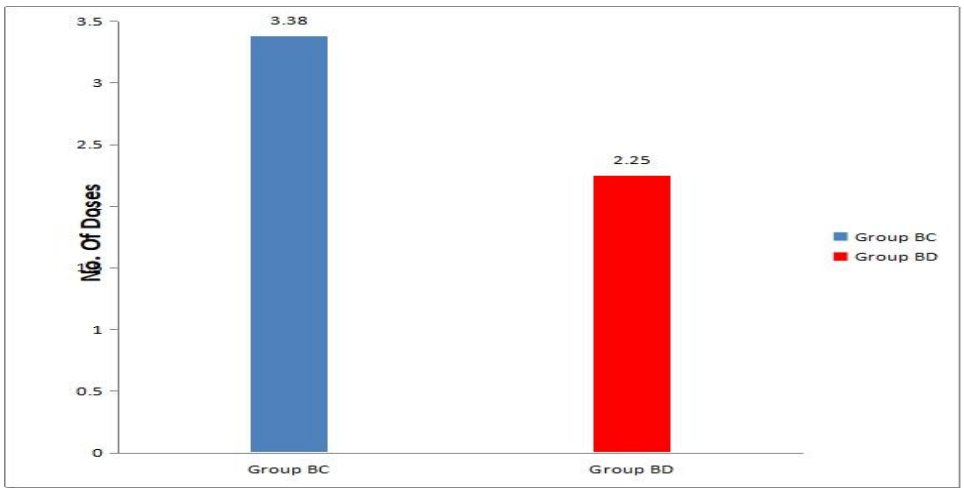

Fig. 3: Comparison of number of rescue analgesic dosages.

There was no significant difference in Group BC and Group BD with respect to occurrence of postoperative nausea and vomiting. (*P* value>0.05)[Fig. 4].

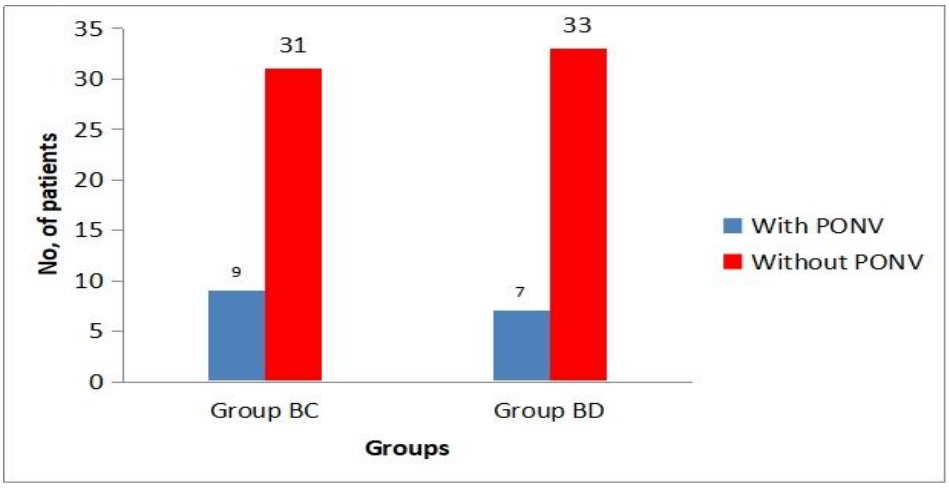

Fig. 4: Patients with postoperative nausea and vomiting (PONV).

No statistically significant difference was found about the adverse effects among the two study groups. Only 5 (12.5%) patients in Group BD suffered from shoulder pain as compared to 16 (40%) in Group BC. Incidence of post-operative adverse effect was also lower in dexmedetomidine group than in clonidine group.

DISCUSSION

In Laparoscopic cholecystectomy pain mainly consist of three component, visceral pain, parietal pain and shoulder pain due to residual gases which is used to create pneumoperitoneum. Various studies shows that pain in laparoscopic cholecystectomy is mostly visceral as small incision and limited trauma occur to abdominal wall. Multimodal efforts like parenteral opioids, non-steroidal anti-inflammatory drugs or local wound infiltration have been done to reduce overall pain of patients undergoing laparoscopic surgeries.[5,6,7,8] There are very few studies in the literature which examined the analgesic effects of ά-2 agonists intraperitoneally. In this study, intraperitoneal route was selected to block the visceral afferent signals and modifies visceral nociception. The local anaesthetic agents provide antinociception by affecting nerve membrane associated proteins and by inhibiting the release and action of prostaglandins, which stimulates the nociceptors, and cause inflammation.[9] Various studies shows intraperitoneal instillation of 0.25% bupivacaine provide effective analgesia, in addition, in this study, either dexmedetomidine or clonidine was used to compare the antinociceptive efficacy between these two alpha agonist.

This is prospective randomized study which was conducted on 80 patients. The study was conducted in a tertiary care level institute. The patients from 18 to 60 years of age with an ASA (American Society of Anaesthesiologists) I or II status posted for elective laparoscopic cholecystectomy were included in this study after ethics Committee approval. In this study patients were divided into 2 groups of 40 each by computer-generated randomization.

Group BD - patients were given intraperitoneal 30 ml inj bupivacaine 0.25% with dexmedetomidine 1 µgm/kg, and Group BC - patients were given intraperitoneal 30ml inj bupivacaine 0.25% with clonidine 1 µgm/kg.

Hernandez-Palazon J, et.al[3] in 2003 studied intraperitoneal application of bupivacaine 0.25% plus morphine for pain relief after laparoscopic cholecystectomy. They concluded that the intraperitoneal administration of these drugs reduced the analgesic requirements during the first 6 postoperative hours compared with the control group. In this study, comparison was done between the antinociceptive efficacy of 0.25% bupivacaine with clonidine or dexmedetomidine. Group BD required less post-operative analgesic doses as compared to group BC.

Govil N, Kumar P [11] in 2017 studied intraperitoneal levobupivacaine with or without clonidine for pain relief after laparoscopic cholecystectomy. They concluded that intraperitoneal instillation of levobupivacaine along with clonidine in a dose of 1ug/kg is superior to levobupivacaine alone without having any significant adverse effects. In this study, bupivacaine in combination with dexmedetomidine (group BD) has significantly lower VAS scores at all points of time ($P < 0.05$) and overall VAS score and postoperative analgesia was statistically lower in group BD than group BC. The prominent effect of dexmedetomidine may be due to its higher efficacy in this study and higher efficacy of clonidine in the study by Govil et al.[11]

Memis D, et.al[12] in 2005 studied the efficacy of

intraperitoneal bupivacaine with clonidine or tramadol on postoperative analgesia in patients undergoing laparoscopic hysterectomy. They found that combination of tramadol or clonidine with intraperitoneal bupivacaine to be more effective than bupivacaine alone. They found no significant difference between tramadol and clonidine groups in terms of efficacy. This study showed, dexmedetomidine to have better efficacy than clonidine in combination with bupivacaine.

Fares KM et al[13] in 2015 studied efficacy and safety of intraperitoneal dexmedetomidine with bupivacaine in laparoscopic colorectal cancer surgery. The study concluded that intraperitoneal administration of Dexmedetomidine combined with bupivacaine improves the quality and the duration of postoperative analgesia and provides an analgesic sparing effect compared to bupivacaine alone without significant adverse effects. Results of this study correlate with study done by Fares KM et al which has shown that dexmedetomidine in combination with bupivacaine decreases the post-operative analgesic requirements compared to clonidine with bupivacaine.

In this study, time to first request of analgesia in post-operative period was significantly delayed in group BD as compared to group BC. This results correlate with study done by Srinivas Rapolu et al[14] which has shown that intraperitoneal instillation of dexmedetomidine with bupivacaine prolongs the duration of postoperative analgesia as compared to that with bupivacaine alone.

In this study, total number of analgesic required in postoperative period in 24 h was statistically higher in group BC than group BD. The mean number of doses of rescue analgesia required in 24 hours in Group BC is 3.38±0.63 and Group BD is 2.25 ± 0.78 which was in agreement with Shukla et al[15] which shows total diclofenac consumption was lowest in Group BD (45 ± 15 mg) than Group BT (85 ± 35) and Group B (175 ± 75). Memis et al[12] found the mean dosage of meperidine used as rescue analgesia was 76.7+/-10.5 mg in Group 1, 63.9+/-8.4 mg in Group 2, and 70 +/-5.2 mg in Group 3. When Group 1 was compared to Group 2, there were significant differences found ($P < 0.05$). The prominent effect of dexmedetomidine may be due to its higher efficacy in our study and higher efficacy of clonidine in the study by Memis *et al*.[12]

In this study, no statistically significant difference was found about the adverse effects among the two study groups. Only 5 (12.5%) patients in Group BD suffered from shoulder pain as compared to 16 (40%) in Group BC. Incidence of shoulder pain was also lower in dexmedetomidine group in study done by Ahmed *et al*.[6] Incidence of post-operative adverse effect was also lower in dexmedetomidine group than in clonidine group.

Limitation of this study is Further studies needed to evaluate optimal the doses of ά-2 agonists like dexmedetomidine and clonidine for intraperitoneal instillation.

CONCLUSION

Bupivacaine with dexmedetomidine was superior when compared to bupivacaine with clonidine as an antinociceptive agent in patients undergoing laparoscopic cholecystectomy because of better haemodynamic stability, more effective antinociceptive effect, increased duration of analgesia, decreased dosage of rescue analgesic required and less adverse effect. Thus we concluded that intraperitoneal instillation of dexmedetomidine 1 µg/kg in combination with bupivacaine 0.25% in elective laparoscopic cholecystectomy significantly reduces the postoperative pain and significantly reduces the analgesic requirement in postoperative period as compared to bupivacaine 0.25% with clonidine 1 µg/kg .

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