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ANALGESIC EFFECT OF INTRAVENOUS VERSUS INTRAPERITONEAL DEXMEDETOMIDINE AS AN ADJUVANT TO INTRAPERITONEAL BUPIVACAINE (0.125%) IN LAPAROSCOPIC CHOLECYSTECTOMY: A RANDOMIZED, DOUBLE BLIND, INTERVENTIONAL STUDY

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ABSTRACT

Background and Aims: Laparoscopic cholecystectomy has emerged as a gold standard technique for gall bladder stones. The aim of the present study was to compare the analgesic effect of intravenous (IV) vs intraperitoneal (IP) dexmedetomidine as an adjuvant to intraperitoneal (IP) bupivacaine in laparoscopy. **Methods:** A prospective, randomized, double blind, interventional study was conducted on 100 patients undergoing laparoscopic cholecystectomy where they were divided into following 2 groups: Group A: Patients received IV 1µg/kg dexmedetomidine diluted to 30 ml with normal saline over 10 min and 40 ml of 0.125% bupivacaine IP after removal of gall bladder. Group B: Patients received IV 30 ml of normal saline and 1µg/kg IP dexmedetomidine in 40 ml of 0.125% IP bupivacaine after removal of gall bladder. The primacy outcome was noted as a difference in mean duration for need of first rescue analgesia. The total consumption of analgesic in first 24hours was recorded and compared between the two groups. **Results:** Both the groups were comparable in terms of demographic profile and intraoperative hemodynamic parameters with no statistical difference. Comparison of time to first analgesic requirement between the two groups showed statistically significant results with unpaired t test. The time of first rescue analgesia in Group A was 151.80 min ± 76.624. and in Group B was 94.80min ± 21.499. The total analgesic requirement in 24 hours in Group A was 136.64 ± 31.251 and in Group B was 144.12 ± 21.49. **Conclusion:** In our study we concluded that intravenous dexmedetomidine provided superior analgesia as compared to intraperitoneal dexmedetomidine when used as an adjuvant with Bupivacaine intraperitoneally.

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INTRODUCTION

Laparoscopic cholecystectomy, although a minimal invasive surgery leads to remarkable pain due to various reasons such as diaphragmatic irritation, peritoneal inflammation and stretching of abdominal cavity. Parietal, visceral and referred shoulder pain are the three main components of pain in this surgery. Various drugs in different composition and routes have been described in literature to alleviate pain [1–3]. Use of local anesthetics for post-operative pain relief is a growing practice for laparoscopic surgeries. Pain due to laparoscopic surgeries is because of, stretching and peritoneal inflammation. Shoulder pain is due to irritation of phrenic nerve. Parietal pain is due to incision. Peritoneal origin of pain suggests that analgesia delivered locally to the peritoneal cavity may be of benefit post operatively.

Dexmedetomidine, a novel highly selective $\alpha_2:\alpha_1$ adrenoreceptor agonist, produces dose dependent sedation, anxiolysis and analgesia without respiratory depression [4]. The intraperitoneal instillation of local anaesthetics have been found to be a simple, safe and effective analgesic in postoperative period following laparoscopic surgeries. Various adjuvants are added to intraperitoneal local anesthetics for improving the duration and efficacy of analgesia. Intraperitoneal instillation of dexmedetomidine in combination with local anesthetics for postoperative analgesia have been evaluated for various laparoscopic surgeries in previous studies [5-8]. However, there is insufficient literature comparing IV dexmedetomidine vs IP dexmedetomidine in laparoscopic surgery. The aim of our prospective study was to compare postoperative analgesic efficacy of intravenous versus intraperitoneal dexmedetomidine as an adjuvant to intraperitoneal bupivacaine in patients planned for laparoscopic cholecystectomy. The primary objective was to determine the difference in mean time duration for need of first rescue analgesia in both groups and to determine total consumption of analgesic in first 24 hour postoperatively. The secondary objective was to determine difference in mean VAS score at 30 min, 1, 2, 4, 6, 12, 24 hour post-operative period in both groups and to determine difference in proportion of cases who develop side effects in first 24 hours in both groups.

MATERIAL & METHODS

After gaining approval from Institute ethics committee the present randomized double blinded interventional study was performed with due registration in CTRI (ctri/2022/02/040024)

whereby 100 patients of ASAPS 1& II in the age range of 18-55 years were included in our study.

Patients with BMI >30kg/m², allergic to studied drugs, refusal to participate in study, renal/ hepatic/ neurologic or psychiatric disease, on antihypertensive drugs, Heart Rate \leq 45 beats/min were excluded from the study.

The sample size was calculated and 46 cases were found to be adequate for each of the 2 groups at 95% confidence and 80% power to verify the expected difference of 31.12 (\pm 71.05) minutes in mean time duration taken for need of first rescue analgesia in both groups as per previous study [9]. The randomization was done in ratio of 1:1 allocation by opaque sealed envelopes into two different groups. The anaesthesiologist who gave the drugs was different from the one who recorded the study variables.

Patients in Group A received 1 μ g/kg IV dexmedetomidine diluted in 30ml of 0.9% normal saline over 10min and 40ml of 0.125% bupivacaine intraperitoneally after removal of gall bladder. Patients in Group B received IV 30ml of 0.9% normal saline and 1 μ g/kg dexmedetomidine in 40ml of 0.125% bupivacaine intraperitoneally after removal of gallbladder.

The patients were instructed the use of VAS on a 10cm scale ranging from 0 (no pain) to 10 (worst imaginable pain). In the OR standard monitoring (HR, NIBP, ECG, SPO₂, EtCO₂) was instituted and baseline parameters were recorded in both the groups. A balanced anesthesia with endotracheal intubation and standard doses of routine anesthetic drugs as per institute protocol was given to both the groups. The minute ventilation was adjusted to maintain normocapnia and pneumoperitoneum was created by insufflation of CO₂ limiting the intrabdominal pressure to 13mmHg with recording of intraoperative vitals at every 5min interval. A 15-20° of reverse Trendelenburg position was given for surgery.

During surgery immediately after removal of gall bladder the allocated drugs were administered as per the study protocol. The intraperitoneal instillation of the drugs was done by the surgeon via trochar in Trendelenburg position instilling 20ml at gallbladder bed and 20 ml around the hepatoduodenal ligament. After extubating all the patients were kept in recovery room for 4 hours and were then shifted to ward.

In the recovery room and ward pain was recorded with VAS Score at 30min, 1, 2, 4, 6, 12 and 24 hour after surgery. Sedation was also recorded at 30 min, 1, 2, 4, 6,12 and 24 hour in both the groups by Ramsay sedation scale (1) anxious or agitated (2) cooperative, oriented, tranquil (3) responds to commands only (4) brisk response to glabellar tap (5) sluggish response to high glabellar/verbal stimuli (6) no response. In postoperative period PR, SBP, DBP were recorded after shifting to postoperative area at interval of 15 minute till end of first hour and half hourly till end of 4 hour.

The `time to first request of analgesia`: Time taken from intravenous or intraperitoneal drug administration to first demand of rescue analgesia by the patient (VAS \geq 4). Postoperative pain outcome was assessed using VAS pain score (between 0 to 10) which was recorded initially at 30 min and then at 1, 2, 4, 6, 12, 24 hr postoperatively. Patient was allowed to receive rescue analgesic on VAS score 4 or $>$ 4. injection tramadol 1 mg/kg IV was given. Incidence of adverse effects like nausea, vomiting, sedation, hypotension, bradycardia, local anaesthetic toxicity and any other side effect were recorded.

Hypotension defined as fall of \geq 20% of baseline systolic blood pressure and was treated with bolus of Lactated Ringer's solution or mephentermine 3–6 mg bolus IV, if required.

Bradycardia defined as HR \leq 45 bpm and was treated with atropine 0.6 mg IV.

Statistical Analysis

The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Descriptive statistics included computation of percentages, means and standard deviations. The quantitative data was compared using unpaired t test. Chi-square test was used for comparison of qualitative data.

RESULTS

Table 1 shows that the mean VAS score was significantly less in Group A than Group B at 30 minutes, 1 to 4 hours and the difference became statistically non-significant after 4 hrs in postoperative period. Mean time to first analgesic requirement was 151.8 min in Group A and 94.8 min in Group B (Table2). The time required to rescue analgesic was longer in Group A than Group B which means Group A has longer duration of pain

relief. Comparison of time to first analgesic requirement among groups showed statistically significant results with unpaired t test.

Mean Total analgesic consumption (figure 2) was 136.64 in group A and 144.12 in group B. The total analgesic dose consumption the higher in Group B than Group A although statistically not significant (p value 0.21). The vital parameters and the sedation score were comparable between the two groups (figure3).

Table 1: Comparison of VAS score (Mean \pm SD)

TIME	Group A		Group B		p-value
	Mean	S.D.*	Mean	S.D.	
0	.00	.000	.00	.000	---
30 min	1.03	1.150	1.68	.868	0.003 (s)
1 hrs	2.16	1.530	3.04	.832	0.001 (s)
2 hrs	1.96	1.456	2.62	1.627	0.003 (s)
4 hrs	2.48	1.474	1.46	1.249	0.001 (s)
6 hrs	2.56	1.343	2.80	.833	0.28 (ns)
12 hrs	3.32	.957	3.54	.788	0.21 (ns)
24 hrs	3.12	1.100	2.98	1.134	0.53 (ns)

*SD: Standard Deviation, s: significant, ns: non-significant

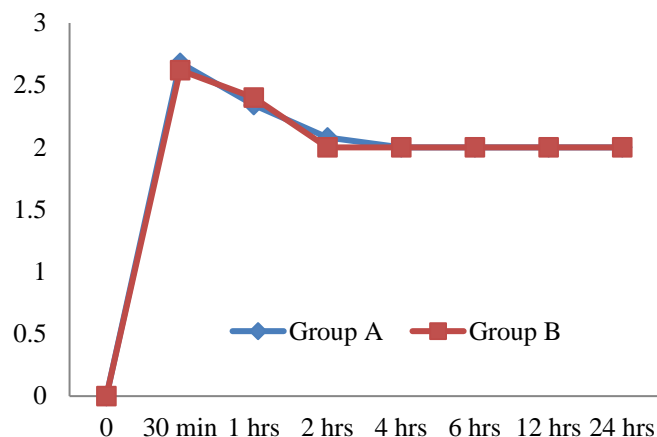


Figure 1: Comparison of Mean Sedation score

Table 2: Mean Time to First Rescue Analgesic Requirement

	Group A		Group B		p-value
	Mean	S.D.	Mean	S.D.	
Time to first Rescue Analgesic Requirement (minutes)	151.80	76.624	94.80	21.499	0.001(s)

SD: Standard deviation, P value $<$ 0.05 Significant, s: Significant

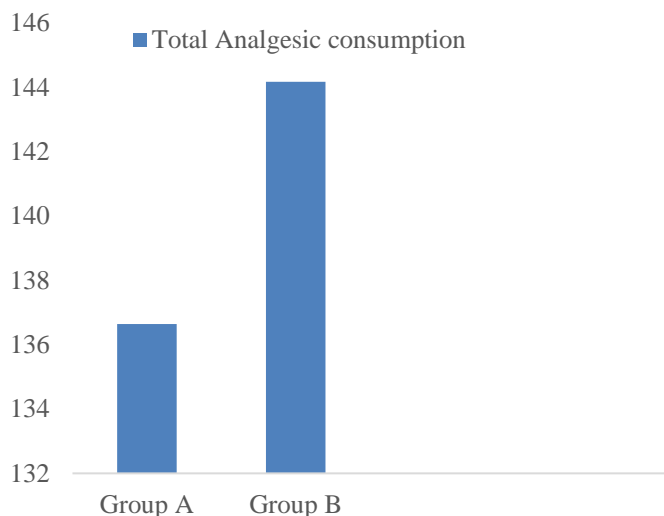


Figure 2: Mean total analgesic consumption (in milligram)

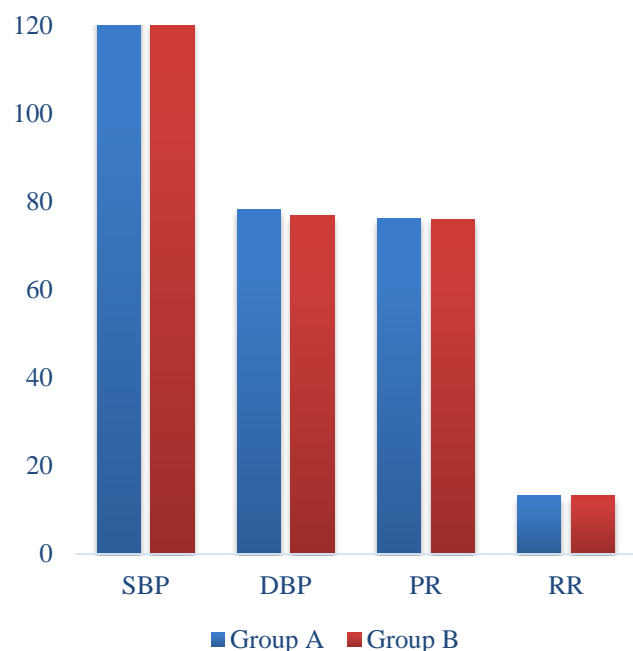


Figure 3: Comparison of mean of vital parameters between the two groups

SBP: Systolic blood pressure (mmHg), DBP: Diastolic blood pressure (mmHg), PR: pulse rate (per minute), RR: Respiratory rate (per minute)

DISCUSSION

Multimodal analgesia for perioperative pain relief is a common practice in the anesthetic management of laparoscopic cholecystectomy. The pharmacokinetic profile of dexmedetomidine, a highly selective alpha 2 agonist with sedative, analgesic and opioid sparing activity has shown promising results as an excellent analgesic in relief of

somatovisceral pain [10, 11]. In our present study we compared two different routes of administration of dexmedetomidine (IP vs IV) 1 microgram/kg added as an adjuvant to 0.125% intraperitoneal bupivacaine in laparoscopic cholecystectomy. IP administration of dexmedetomidine causes analgesia by inhibiting the release of substance P at spinal level and by enhanced conductance of potassium channel via inhibitory G protein thereby causing hyperpolarization.

Our study showed that IV dexmedetomidine group had longer pain relief as compare to IP dexmedetomidine group. Most of the previous studies showed that the intraperitoneal dexmedetomidine as an adjuvant to intraperitoneal bupivacaine improved the duration of postoperative analgesia and prolonged time to first rescue analgesia as compared to intraperitoneal bupivacaine alone in surgical patients [12–14]. However, Chilkoti *et. al* in their study concluded that low dose of bolus intraperitoneal dexmedetomidine was found to be as efficacious as intravenous dexmedetomidine along with intraperitoneal bupivacaine in laparoscopic cholecystectomy [9]. The dose of dexmedetomidine used in our study was higher than that by Chilkoti *et. al*. Shukla *et. al* in their study have reported superior analgesic efficacy of intraperitoneal dexmedetomidine in a dose of 1 µg/kg as an adjuvant to bupivacaine as compared to bupivacaine alone however we compared the analgesic effect of IV vs IP has been done in our study.

In our study, we used VAS pain score at various time intervals, i.e., 30 min, 1, 2, 4, 6, 12, 24 h postoperatively to assess the intensity of pain. We observed that mean VAS score was significantly less in IV dexmedetomidine group than intraperitoneal Dexmedetomidine Group B at 30 minutes, 1 to 4 hours and the difference became statistically non-significant after 4 hrs in postoperative period.

This was probably subjected to the peak pharmacokinetic effect of intravenous dexmedetomidine whereas in group B intraperitoneal spread of drug took time. Previous authors have reported significantly less VAS scores with intraperitoneal dexmedetomidine than IP localanesthetic alone. However, Chilkoti *et. al* found that mean VAS pain scores in IV dexmedetomidine group and IP dexmedetomidine group were comparable at various time points except at the end of first hour. The difference from our study could be attributed to higher dose of dexmedetomidine in our study.

Thakur *et. al* in their study found that low bolus dose of IV dexmedetomidine is more efficacious as compared to IP dexmedetomidine (0.5 µg/kg) along with IP bupivacaine in laparoscopic cholecystectomy [16]. However they used lesser dose of Dexmedetomidine than in our study and we used 0.125% bupivacaine in place of 0.25% levobupivacaine used in their study but in both the studies intravenous dexmedetomidine was found to be more efficacious as compared to IP dexmedetomidine along with IP local anesthetic in laparoscopic cholecystectomy. Hence the overall outcome of our study is that IV dexmedetomidine provided more effective analgesic than IP dexmedetomidine at a dose of 1 microgram / kg when used with IP bupivacaine without any significant increase in sedation and sideeffects. Hence intravenous dexmedetomidine is a good alternativa as a part of multimodal analgesia in laparoscopic surgery.

Limitation

Limitation of this study was that the postoperative pain is a subjective experience and we used VAS scale for pain assessment which is a subjective scale hence objective verification was not done.

CONCLUSION

In our study we concluded that intravenous dexmedetomidine along with intraperitoneal bupivacaine provided better postoperative analgesia than intraperitoneal dexmedetomidine with bupivacaine in terms of better pain scores, increased duration of pain relief and lesser demand of rescue analgesic.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

AUTHOR CONTRIBUTION

Dr Chitra Singh and Dr Priyanka Jain planned the study, did literature survey and designed the manuscript. Dr, Shailja and Dr Pratibha collected the data and did statistical analysis. All the authors helped in proofreading and reviewing the final manuscript

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