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A randomised, prospective, double blind study of intraperitoneal instillation of 0.25% bupivacaine with clonidine versus 0.25% bupivacaine with dexmedetomidine for post-operative analgesia in patients undergoing laparoscopic cholecystectomy

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ABSTRACT

Background: Laparoscopic cholecystectomy is the standard and most accepted technique for Cholecystectomies due to lesser postop pain and short recovery time. The origin of abdominal and shoulder pain after laparoscopic procedures has led to the use of intra peritoneal instillation of local anaesthetic agent to reduce postoperative pain.
Objectives: To assess the efficacy and quality of postoperative analgesia between the study groups using Visual Analogue Scale (VAS) score at various time intervals along with side effects if any.
Materials and Methods: 60 patients belonging to ASA 1 and 11 categories posted for Laparoscopic Cholecystectomy were given General Anaesthesia. After completion of surgery, before removing the trocar, anaesthetic study solution was sprayed on the surface of liver, gall bladder bed, right sub-diaphragmatic space, and port sites in Trendelenburg position. Volume and dilution of two drugs were same in both groups. Bupivacaine (0.25%) 50 mL; Dexmedetomidine (1 μg/kg) (BD) or Clonidine (1 μg/kg) (BC) was used. VAS score, Heart rate and BP measured at various time intervals and the time of first rescue analgesia noted.
Result: VAS of BD group was 5.27 ± 0.64 to 3.70 ± 0.837 from 1^{st} hour to 6^{th} hour post extubation, when compared to BC group of 6.03 ± 0.669 in 1^{st} hour reduced to 4.17 ± 0.699 at 6^{th} hour post extubation.
Conclusion: Dexmedetomidine combination significantly reduced the total dose of rescue analgesic required in 24 hours as compared to Clonidine combination.

1. Introduction

Laparoscopy is a credible alternative to open surgery for a range of procedures in various surgical specialities. Laparoscopic cholecystectomy has become the standard and the most accepted technique for gall bladder surgeries,[1] as they have lesser postoperative pain, shorter recovery time, lower morbidity and mortality.[2] Laparotomy results mainly in parietal pain, whereas patients complain of visceral pain after operative laparoscopy.[2,3] Shoulder pain secondary to diaphragmatic irritation caused by pneumoperitoneum is a frequent observation after laparoscopy.[4]

Abdominal pain following laparoscopy can occur due to stretching of parietal peritoneum, release of inflammatory mediators of pain, visceral pain from the operation itself and the irritation produced by blood.[5]

Previous studies have agreed that postoperative pain from Laparoscopic Cholecystectomy consists of visceral, parietal and referred shoulder pain distinguishing from each other in the intensity, latency and duration.[6] Several studies

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suggested that parietal pain is the predominant cause of pain in laparoscopic surgeries.[7,8]

Various methods are tried for postoperative analgesia in laparoscopic cholecystectomy including epidural analgesia, instillation of local anaesthetics intraperitoneally by various authors with varying results.[9–15]

Bupivacaine is one such local anaesthetic agent with limited side effects unlike gastritis caused by NSAIDs or nausea and vomiting and fear of drug dependence as in opioids.[10] α2-Adrenergic agonists like Clonidine[16] and Dexmedetomidine[17] have been introduced to clinical anaesthesia for their sympatholytic, sedative, anaesthetic sparing and haemodynamic stability.

There are various research showing the efficacy intraperitoneal instillation of Bupivacaine with adjuvants like opioids which has relatively a shorter duration of analgesia. Hence, this research was done intending to provide longer duration of post-operative analgesia using α2-Adrenergic agonists as adjuvants.

The objective of the study was to assess the efficacy and quality of postoperative analgesia between the study groups using Visual Analogue Scale (VAS) score at various time intervals and to observe side effects like nausea, vomiting and shoulder tip pain if any between the study groups.

2. Materials and Methods

This study was a Prospective, Randomized, Double blind clinical study conducted between March 2022 and October 2022. An approval by the Institutional Ethical Committee (AIMS/IEC/3197/2022-23) was obtained. Following the approval 60 patients were randomly allocated for the study group. After obtaining informed written consent, patients were randomly allocated by a computer-generated table of random numbers by a person blinded to the procedure to avoid selection bias into two groups of 30 each as group BC (n=30) and group BD (n=30). All ASA1 and 2 patients aged between 25-45 were included. ASA 3 and 4 patients with ischemic heart disease (last attack >6 months back), comorbid illnesses like uncontrolled diabetes, hypertension, unpleasant anaesthesia experiences in the past, allergies to the study drugs were excluded.

During general examination, patient's general condition assessed, weight, pulse and BP measured. Laboratory data including ECG, Chest X-ray and Echocardiography was reviewed. Coronary vasodilators/betablockers/ antihypertensive medications which patient might have been receiving were continued perioperatively. All patients were introduced to VAS scale on the day before the surgery. All the surgeries were carried out under General anaesthesia with intubation, muscle relaxants and controlled ventilation. During laparoscopy, intra-abdominal pressure was maintained between 12 and 14 mmHg. The CO_2 was removed by manual compression of the abdomen at the end of the procedure with an open trocar.

After completion of surgery, before removing the trocar, anaesthetic study solution was sprayed on the upper surface of liver, gall bladder bed, under surface of diaphragm, in the right sub-diaphragmatic space, operation site and at the port sites in the Trendelenburg's position at 20-degree inclination. Volume and dilution of the two drugs were same in both groups. Bupivacaine (0.25%) 50 mL; Dexmedetomidine (1 μg/kg, diluted in 5 mL NS) or Clonidine (1 μg/kg in 5 mL NS) was used.

Patients were reversed from Neuro-muscular blockade adequately using Neostigmine (0.05 mg/kg) and Glycopyrrolate (0.02 mg/kg) and were extubated.

In post-operative room pain was assessed beginning from the first hour of surgery every hourly till four hours post-operative and thereafter at 6^{th}, 8^{th}, 12^{th} and 24^{th} hour after the surgery. Mean of VAS at different times was calculated and noted. A thorough assessment of post-operative problems like location of pain, shoulder tip pain if any, nausea and vomiting, pain on deep inspiration and during cough were made. The Heart rate, SpO_2, Blood pressure and Respiratory rate was assessed at the above times. Rescue medication of 75 mg Diclofenac was given on VAS≥3. Time to the rescue analgesia, total dose of analgesia and adverse or side effects over 24 hours post-operatively was noted.

Inj. Ondansetron 4 mg was given intra-venously for nausea or vomiting.

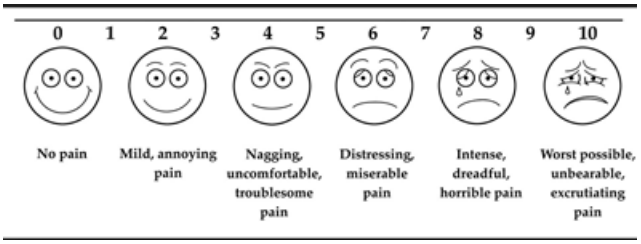

Fig. 1: Visual analogue scale

Based on the above scale, if the score is ≥ 3, we took it as an end point and need for rescue analgesia in the postoperative period.

2.1. Statistical methods

The collected data underwent thorough analysis using appropriate statistical tests. Demographic data were presented using the mean and standard deviation (SD). Mean scores and SD for the Visual Analog Scale (VAS) were calculated. To assess the significance of differences between quantitative variables, the student's t-test was employed, while the Chi-square test was utilized for qualitative variables.

Haemodynamic variables were represented as mean ± SD. A 'p' value less than 0.05 indicated a significant relationship, whereas a 'p' value less than 0.001 was

considered highly significant.

3. Results

The demographic data showing age, weight, ASA grading was comparable between the study groups and was not statistically significant. Also, the mean duration of surgery and duration of anaesthesia was not statistically significant.

VAS score was most significantly reduced in Group BD i.e, from 5.27 ± 0.64 to 3.70 ± 0.837 from 1^{st} hour to 6^{th} hour post extubation, when compared to Group BC where VAS score 6.03 ± 0.669 in 1^{st} hour reduced to 4.17 ± 0.699 at 6^{th} hour post extubation as shown in Table 1.

Mean VAS score reduction in 24 hours was 5.20 ± 0.925 in Group BD when compared to Group BC which was 4.40 ± 0.932 which is also most significant as shown in Table 2.

Mean time interval to receive 1^{st} rescue analgesic in 24 hours in Group BD was prolonged i.e., 6.98 ± 2.107 hours when compared to Group BC i.e., 5.70 ± 2.196 hours, was also significant as shown in Table 3.

Mean total dose of analgesic (diclofenac in mg) administered to patients in 24 hours in Group BD was 62.50 ± 36.05 mg only when compared to Group BC i.e., 82 ± 33.73 mg, which was significant. Side effects like PONV was more in Group BC patients than in Group BD similarly to shoulder tip pain.

4. Discussion

In this study we compared the postoperative pain relief in laparoscopic cholecystectomy cases using intraperitoneal instillation of Bupivacaine 0.25% 50mL with Clonidine 1μg/kg body weight and Bupivacaine 0.25% 50mL with Dexmedetomidine 1μg/kg body weight.

In our present study of the two groups, we observed in the postoperative period the VAS, the vital parameters like Heart Rate, SBP, DBP and for adverse effects like nausea, vomiting and shoulder tip pain. Time for first rescue analgesia and total dose of analgesics administered were noted.

The Laparoscopic procedure was completed successfully in all the cases without any intraoperative complications or in need of conversion to an open procedure. No statistically significant differences were noted in the vital parameters like post operative Heart rate, Respiratory rate, SpO_2 or in the blood pressure between the two study groups.

The mean VAS in our study for the Bupivacaine and Clonidine group was 4.66 ± 0.76 when compared to Bupivacaine and Dexmedetomidine group 4.11 ± 0.53 over a period of 24 hours. However, it was statistically significant for the first 6 hrs postoperatively. The volume of drug we used (50 ml) was with reference to the previous studies conducted by Usha Shukla et al.[18] and Ahmed et al.[18]

In our study we found out that the difference in the VAS scores of the two groups at the three time points at 8^{th} hour, 12^{th} hour and 24^{th} hour post-operatively across 24-hour time period and is not clinically significant. The present study showed that 0.25% Bupivacaine of 50mL volume with Clonidine 1μg/kg body weight (Group BC) and 0.25% Bupivacaine 50mL volume with Dexmedetomidine 1μg/kg body weight (Group BD) were effective in decreasing the VAS scores up to 24-hour post op. There was a significant reduction in VAS over the first 6-hour period in Group BD with P value of < 0.001.

α-2A adrenoceptor act by activation of presynaptic receptors in the locus ceruleus by inhibiting the release of nor-epinephrine and results in the sedative and hypnotic effects. Stimulation of alpha-2 adrenoceptors in this area terminates the propagation of pain signals leading to analgesia. Postsynaptic activation of alpha-2 receptors in the CNS results in decrease in sympathetic activity leading to hypotension and bradycardia.[19] At the spinal cord, stimulation of alpha-2 receptors at the substantia gelatinosa of the dorsal horn leads to inhibition of the firing of nociceptive neurons and inhibition of release of substance P which all contributes to analgesic and anti-nociceptive property of Dexmedetomidine and Clonidine.

Usha Shukla et al,[20] compared the effect of intraperitoneal 0.25% Bupivacaine of 50mL volume with Dexmedetomidine 1μg/kg body weight and 0.25% Bupivacaine of 50mL volume with Tramadol 1mg/kg body weight in laparoscopic cholecystectomy. They found that intraperitoneal instillation of Dexmedetomidine 1μg/kg in combination with Bupivacaine 0.25% had significantly reduced the post-operative pain which correlates with our results.

Using 20 ml of 0.5% Bupivacaine, Pasqulucci et al[12] noted a decrease in pain and consumption of analgesics in the post operative period noticed probably due to a complete block of afferents with higher concentrations than volumes itself as used by other authors. They found beneficial pain relief up to 24 hours postoperative, which concurs with our study.

Rademaker et al[21] failed to demonstrate any reduction in postoperative pain by utilizing a volume 20 mL of either 0.25% Bupivacaine or 0.5% lignocaine. A possible explanation of the failed effect given by them was due to the small amount of local anaesthetics used, as compared to Narchi et al.[19]

Chundrigar et al[22] noted pain relief for up to 2 hours post op with the intraperitoneal administration of 0.25% Bupivacaine 20 mL, although in the present study we could note pain relief up to 24 hours post op which could be attributed to higher volume. The other reason could be attributed to the fact that the local anaesthetic was instilled in the Trendelenburg position which could have resulted in better seepage and dispersion of the drug at the subhepatic region and hence the beneficial effect for up to 24-hour post op as instillation in the supine position prevents the flow of

Table 1: Mean VAS at various time interval (in hours after extubation) between groups

VAS (in hours after extubation)	Group	Mean	Standard deviation	P value
VAS0	BC	6.90	.759	<0.001
	BD	7.23	.728	
VAS1	BC	6.03	.669	<0.001
	BD	5.27	.640	
VAS2	BC	5.40	.621	<0.001
	BD	4.43	.504	
VAS3	BC	4.93	.583	<0.001
	BD	4.10	.548	
VAS4	BC	4.80	.610	.023
	BD	3.93	.640	
VAS6	BC	4.17	.699	.001
	BD	3.70	.837	
VAS8	BC	3.93	.640	.123
	BD	3.30	.750	
VAS12	BC	3.33	.547	.2
	BD	3.10	.607	
VAS24	BC	2.50	.572	.102
	BD	2.03	.556	

Table 2: Mean VAS reduction in 24 hr between groups

Group	Mean	Standard deviation	P value
BC	4.40	0.932	<0.001
BD	5.20	0.925	

Table 3: Mean time interval in hours at which 1^{st} rescue analgesics were administered between groups in 24 hrs post-operatively

Group	Mean(Time in hours)	Standard deviation	P value
BC	5.70	2.196	0.024
BD	6.98	2.107	

local anaesthetic over the coeliac plexus and phrenic nerve endings which can be an important pathway for post op pain relief.

There are very few studies in the literature that compares the analgesic effects of a-2 agonists intraperitoneally. Our results are in correlation with study done by Ahmed et al,[18] which has compared the intraperitoneal instillation of Meperidine vs Dexmedetomidine in combination with bupivacaine 0.25%. Their results have decreased the post-operative analgesic requirements and incidence of shoulder pain in patients undergoing laparoscopic gynaecological surgeries.

Time to first request of analgesia in post operative period was significantly delayed in Group BD as compared to Group BC. Memis et al[23] found no difference between tramadol or clonidine groups and in present study, the time was significantly shorter in Clonidine group than Dexmedetomidine group. Dose of requirement of Diclofenac in postoperative period were found statistically higher in Group BC as compared to Group BD, which is in agreement with Ahmed et al.[18]

In our study, only 3 (10%) patients in Group BD suffered from shoulder tip pain as compared to 8 (26.6%) patients in Group BC. Incidence of shoulder tip pain was also lower in dexmedetomidine group in study done by Ahmed et al.[18] The adverse effects noted like nausea and vomiting were in only about 3.33% of patient in Group BD as compared to 20% patients in Group BC. This difference was statistically significant.

Limitation of the present study is the postoperative pain, which is a subjective experience and can be difficult to quantify objectively while comparing with various treatment options.

5. Conclusion

Based on our study's findings and results, it is evident that the combination of Dexmedetomidine with Bupivacaine surpasses the efficacy of Clonidine with Bupivacaine when used for Intraperitoneal instillation in Laparoscopic Cholecystectomies to achieve superior postoperative analgesia. Notably, both groups exhibited no statistically significant differences in hemodynamic parameters, and no significant adverse effects were observed throughout

the study. Moving forward, there is substantial potential for further investigation in terms of optimizing the concentration and volume of the Local anaesthetic agent to enhance the overall outcomes of this approach.

6. Source of Funding

None.

7. Conflict of Interest

None.

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