E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.48047/ijprt/16.01.14

Research Article

Triple-Arm Randomized Trial of Intraperitoneal Levobupivacaine, Dexmedetomidine, and Placebo for Analgesia After Laparoscopic Cholecystectomy

Dr. Kumaragurubaran T. R.[1], Dr. Rakesh Nongthombam[2], Dr. Ramkumar I.[1]

[1] Department of anaesthesiology, Assistant Professor, Mahatma Gandhi Medical College and Research Institute (MGMCRI), Puducherry, India
[2] Department of anaesthesiology , Associate Professor, Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Imphal, Manipur, India
Correspondence to: Kumaragurubaran T. R
Mail ID: **rkb.sasi@gmail.com**

Abstract:

Background: Pain after laparoscopic cholecystectomy is still a major clinical issue. The use of analgesic agents through intraperitoneal instillation may lead to better multimodal analgesia. The current research was aimed at comparing the analgesic effects of levobupivacaine and dexmedetomidine against placebo. Methods: In this trial, patients were enrolled in a 99-patient (ASA I–II; 18–65 years) elective laparoscopic cholecystectomy double-blind, controlled study that was both randomized and prospective. They were divided into three groups (n=33 each): Group L (levobupivacaine 0.2%), Group D (dexmedetomidine 1 μg/kg), and Group NS (normal saline). The pain level was measured using the Numerical Rating Scale (NRS) at specific intervals for 24 hours. Among the secondary outcomes were the time until the first rescue analgesia, total analgesic consumption, side effects, and patient satisfaction. Between-group comparisons were made by using ANOVA and Chi-square tests. Effect estimates were reported along with 95% confidence intervals (CI).Results: Group L showed significantly lower mean NRS scores at all postoperative time points compared to Group D and NS ($p<0.001$), with differences in means favoring levobupivacaine and 95% CIs not including zero. Time until first rescue analgesia was significantly extended in Group L compared to Group D and NS ($p<0.001$; 95% CI suggesting a clinically relevant delay). Total 24-hour rescue analgesic consumption was significantly lower in Group L compared to placebo ($p<0.001$; 95% CI confirming consistent reduction). Dexmedetomidine also provided significantly better analgesia than placebo ($p<0.01$; 95% CI ruling out null effect). The occurrence of side effects was similar among the groups ($p=0.509$; 95% CI including one). Patient satisfaction was

significantly greater in Group L (p=0.014; 95% CI favoring levobupivacaine). Conclusion: Intraperitoneal levobupivacaine offers statistically and clinically superior postoperative analgesia to dexmedetomidine and placebo with longer analgesic duration, lower rescue analgesic requirement, and higher patient satisfaction. Confidence interval analysis substantiates the strength and accuracy of these findings, recommending their use in multimodal analgesic protocols.

Keywords: pain, Laparoscopic cholecystectomy, intraperitoneal analgesia, levobupivacaine, dexmedetomidine

INTRODUCTION

Laparoscopic cholecystectomy is considered as the treatment of choice for symptomatic cholelithiasis and second most common operative procedure performed today.[1] Laparoscopic cholecystectomy further offers the long term benefit of negligible incidence of wound infection, incisional hernia, nerve entrapment and post operative adhesions. In the laparoscopic technique, cholecystectomy has been the first major surgery performed and has paved the path for laparoscopic intervention for other intra abdominal pathologies. Advantages over open procedures are less bleeding, better cosmetic, less postoperative pain, and shorter postoperative stay in hospital.[2]

Pain is a protective mechanism that occurs when tissues are being damaged. Surgery produces tissue injury with consequent release of inflammatory mediators that activates peripheral nociceptors, which initiate nociceptive information to the central nervous system to produce pain. The etiology of pain after laparoscopic cholecystectomy is multifactorial such as intra-abdominal cavity stretch, inflammation of the peritoneum, and irritation of diaphragm by carbon-dioxide residue in the abdominal cavity. Post-operative pain is the major problem in laparoscopic surgeries, wherein lack of control on it has many side-effects such as tachycardia, hypertension, hypotension, myocardial ischemia, decreased alveolar ventilation and prolonged hospital stay. Pain causes reflex withdrawal reaction, anxiety, depression, anger and skeletal muscle excitability.[3,4]

Acute pain after laparoscopic cholecystectomy is complex in nature and the pain pattern does not resemble pain associated with other laparoscopic procedures, suggesting that analgesic treatment might be procedure specific and multimodal. Intensity of pain is more severe, immediately after surgery and less after twenty four hours. Methods used for postoperative pain relief after laparoscopic surgery include non-steroidal anti-inflammatory drugs, parenteral

opiods, intraperitoneal instillation of local anaesthetics, alone or in combination with opioids, alpha-2 agonist dexmedetomidine etc.[5,6,7]

Systemic absorption of local anaesthetic from the peritoneal cavity may also play a part in reducing pain although this would expect to occur after any local anaesthetic technique. Normally, overall pain after laparoscopic cholecystectomy carries a high interindividual variability in intensity and duration and is largely unpredictable. Pain is most intense on the day of surgery and on the following day and subsequently declines within 3–4 days. However, pain may remain severe in approximately 13% of patients throughout the first week after laparoscopic cholecystectomy. There are several arguments for a procedure-specific assessment of the evidence of analgesic treatment after laparoscopic cholecystectomy and in this modern era of surgery, intraperitoneal instillation of local anaesthetic agents have become a method to control postoperative pain, nausea, vomiting and reduced hospital stay.[8,9]

Pain following laparoscopic cholecystectomy is the most common complaint especially in the abdomen, back, and shoulder region. Nevertheless minimal postoperative pain is one of the biggest advantages of laparoscopy compared with open surgery. However, postoperative pain is not completely solved and is still a matter of concern.[10] Uncontrolled Pain can increase the morbidity rate and is the primary reason for prolonged hospitalization after laparoscopic cholecystectomy.[2,11]

Evidence shows that administration of non-steroidal anti-inflammatory drugs (NSAIDs) and narcotics, complete gas drainage, intraperitoneal saline and intraperitoneal local anaesthetics instillation and opioids were carried out to reduce pain after a laparoscopic cholecystectomy. While, use of these methods for pain relief after laparoscopic cholecystectomy had side effects or was not associated with consistent result.[12-14] Therefore, the clinical significance of pain control after laparoscopic surgery remains controversial.

Many analgesic interventions were done with varying targets and mechanisms have been investigated for their influence on early pain after laparoscopic cholecystectomy. In our study, we have compared the post-operative analgesic effect of intraperitoneal instillation of levobupivacaine, dexmedetomidine and normal saline in patients undergoing laparoscopic cholecystectomy under general anaesthesia.

MATERIALS AND METHODS

This study was designed as a prospective, double-blind, randomized controlled trial and was conducted in the Department of Anaesthesiology at Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Imphal, Manipur. The study population included patients aged 18–65 years of either gender, classified as American Society of Anaesthesiologists (ASA) physical status I or II, who were scheduled for elective laparoscopic cholecystectomy under general anaesthesia and who provided valid informed consent. Patients were excluded if they refused participation, belonged to ASA grade III or IV, were physically dependent on narcotics, had a history of drug allergies or head injury, or had cardiac, pulmonary, hepatic, renal disorders, or peripheral neuropathy. The sample size was calculated based on a previous study assessing 24-hour analgesic effect using the visual analogue scale (VAS), with a mean score of 6.25 ± 0.63 and a treatment effect of 0.7; with an alpha level of 0.05 and a power of 80% (two-sided), 33 patients were required in each group. Consecutive sampling was used, and all eligible patients posted for laparoscopic cholecystectomy during the study period were recruited after applying the inclusion and exclusion criteria.

Randomization, Procedures, and Data Collection

Randomization was performed using restricted block randomization with a block size of three, labeled A, B, and C. Patients were allocated to different study groups based on numbers generated from these blocks. After obtaining approval from the Institutional Ethics Committee, JNIMS, Imphal, and written informed consent, this prospective, randomized, double-blind study was conducted in ASA physical status I and II patients aged 18–65 years undergoing elective laparoscopic cholecystectomy under general anaesthesia. A thorough pre-anaesthetic evaluation, including history, physical and systemic examination, and airway assessment, was carried out. Patients were kept nil per oral and premedicated with oral alprazolam 0.5 mg and ranitidine 300 mg the night before surgery. In the operating room, standard monitoring (ECG, non-invasive blood pressure, and SpO_2) was instituted, baseline values were recorded, and general anaesthesia was induced with intravenous fentanyl, propofol, and vecuronium to facilitate tracheal intubation. Anaesthesia was maintained with nitrous oxide, oxygen, and sevoflurane, with ventilation adjusted to maintain normocapnia. Hemodynamic variations were managed appropriately. Laparoscopic surgery was performed with standard positioning and intra-abdominal pressure maintained at 12–14 mm Hg. Study drugs were prepared and administered intraperitoneally by an anaesthesiologist not involved in patient assessment, ensuring double blinding. At the end of surgery, neuromuscular blockade was reversed, the

trachea was extubated, and patients were observed in the post-anaesthesia care unit. Postoperative data, including pain scores using the Numerical Rating Scale (NRS), hemodynamic parameters, time to first rescue analgesia, total analgesic consumption, and adverse effects, were recorded for 24 hours at predefined intervals. Rescue analgesia was administered when NRS exceeded four or on patient request.

The primary outcome was postoperative pain assessed using the NRS, while secondary outcomes included time to first rescue analgesia, total analgesic requirement within 24 hours, postoperative hemodynamics, and complications. Data were analyzed using SPSS version 22 with appropriate descriptive and inferential statistical tests, considering a p value <0.05 as statistically significant. Ethical approval and informed consent were obtained prior to study initiation.

Results

A total of ninety nine patients were enrolled for this study. ASA classification I & II were taken up for the study.

Table-1: ASA Classification at different age groups

Groups		ASA Classification		p-value
		I	II	
	L (n=33)	25	8	0.530
	D (n=33)	21	12	
	NS(n=33)	24	9	
Total (n=99)		70	29	

They were allocated randomly in a double - blind trial into three equal number of 33 each. L received levobupivacaine, D received dexmedetomidine and NS (placebo) received Normal

Saline. A standard anaesthetic technique was followed in all patients. The patients were assessed by an observer in the postoperative period who was blinded for the group (Table 1). Among the total population enrolled in this study, majority of them are female in all the three groups (Table 2). Mean age of the patient in group-L, group-D and group-NS are 34.76 ±10.860, 40.39 ± 8.437, and 37.97 ± 10.036 respectively. There was no significant difference observed between the groups (p-value=0.699) (Table 3). The above table shows physical parameters between the groups. Respiratory rate shows almost similar in all the three groups. Duration of surgery was significantly different while compared in all the three groups (Table 4). Mean time for group-L was high compared other two groups. But while three groups are compared, there is no significant difference observed.(p-value=0.608) (Table 5).

Table:2 Gender Distribution

	Gender		
Group	**Female(%)**	**Male(%)**	**p-value**
L (n=33)	23(70)	10(30)	**0.831**
D (n=33)	21(64)	12(36)	
NS(n=33)	23(70)	10(30)	

Note: p-value <0.05 considered as significant: L - levobupivacaine, D– dexmedetomidine, NS- (placebo) Normal Saline.

Table-3: Age Distribution

Groups	Age In years (Mean)	SD	p-value
Group-L (n=33)	34.76	±10.860	**0.699**
Group-D (n=33)	40.39	±8.437	
Group-NS (n=33)	37.97	±10.036	

Note: p-value <0.05 considered as significant.

Table:4 Mean Age, Weight, Temperature, Respirartory Rate of Participants

Group		AGE (Mean in Yrs)	Wt (kg)	TEMP (cl°)	RR	Duration of Surgery in minutes
Group-L	Mean	34.76	59.88	37.8636	14.06	51.27
	SD	10.860	6.594	.87136	1.247	11.998
Group-D	Mean	40.39	61.45	38.4182	14.12	60.61
	SD	8.437	7.803	.98058	2.219	8.276
Group-NS	Mean	37.97	60.36	37.7848	15.35	54.09

	SD	10.036	8.678	1.40715	3.810	8.413
p-value		0.699	0.877	0.485	0.070	**0.021**

Note: p-value <0.05 considered as significant

Table:5 Duration of surgery between groups

	Group	Mean time	Std. Deviation	Std. Error Mean	p-value
Duration of surgery in minutes	Group-L (n=33)	59.03	±6.998	1.218	**0.608**
	GroupD (n=33)	58.18	±6.361	1.107	
	GroupNS (n=33)	54.09	±8.413	1.464	

Table:6 Comparison of pain score (NRS) at different time interval

Pain score		0hr	30th mint	1hr	2hrs	3hrs	4hrs	5hrs	6hrs	8hrs	12hrs	18hrs	24hrs
Group-L	Mean	1.76	6.15	4.96	3.70	3.39	3.42	2.67	2.12	2.88	2.70	1.88	.88
	SD(±)	.902	1.253	2.663	.918	.609	.614	.595	.415	.696	.984	1.023	.781
Group-D	Mean	3.88	6.73	6.09	5.88	5.88	5.88	5.88	5.15	5.88	5.88	3.55	1.70
	SD(±)	1.576	1.376	.843	.857	.857	.857	.857	1.121	.857	.857	1.301	1.591
Group-NS	Mean	8.12	7.91	5.67	5.03	5.03	5.03	5.03	4.30	4.27	4.36	3.61	2.30
	SD(±)	.992	.879	1.164	1.334	1.334	1.334	1.334	1.185	.876	.859	.609	1.015
	p-value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000

Note: p-value <0.05 considered as significant

From the above table we observe that, while comparing the pain score at different time interval there is statistically significant difference observed (p-valve 0.000). In the Group-L the pain score was mild compared to other two groups and also in placebo the pain score was severe initially and then gradually the pain was reduced (Table 6) (Figure 1).

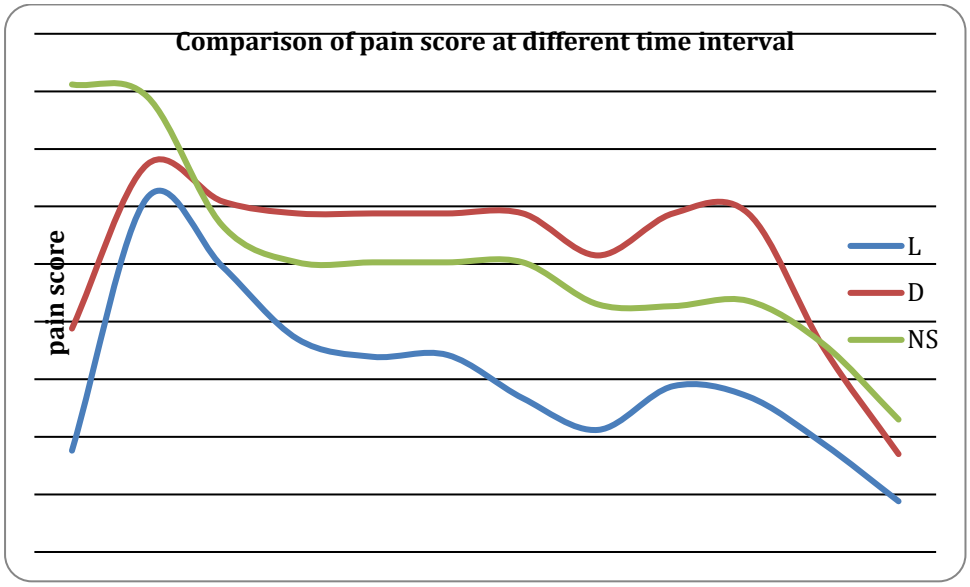

Figure 1 Comparison of Pain score At Different Time Interval

Pain score is minimum in group-L than group-D and group-NS (Figure 1)

Table:7 Time for first dose of rescue analgesia in hours

		0hr	1hr	2hr	4hr	5hr	6hr	p-value
	Group-L	19	0	0	8	0	0	**0.000**
	Group-D	18	1	4	3	1	6	
	Group-NS	25	9	5	0	0	0	
Total		62	10	9	11	1	6	

Note: p-value=0.000 is statistically significant in all three groups.

First rescue analgesic received was statistically significant between Group-L, Group-D, and Group-NS (Table 7). There was no significant difference observed in side effects (p-value=0.509). Vomiting was high in D compared to Group-L (Table 8). Post operative 1st rescue analgesics received was high in placebo when compared with the other groups.In

addition post operative analgesics were more in group D than group L There was a statistically significant difference in dose among the groups (Table 10). Post operative 2nd rescue analgesics received was high in placebo when compared with the other groups. There was statistically significant differences among three groups (Table 11). Patient satisfaction rate was high in those received levobupivacaine followed by dexmedetomidine. While comparing the three groups there was a statistically significant difference (Table 12). There was significant difference observed in post operative pain between three groups (Table 13).

While comparing the SPO2, there is a statistically significant difference observed between three groups (p-value=0.003) (Figure 2)

Table:8 Side Effect

Side Effeccts	**Group**			**Total**	**Chi-square value**
	L	**D**	**NS**		
No side effect	13	7	13	33	**0.509**
Nausea	6	12	13	31	
Vomiting	5	7	4	16	
Pruritis	1	1	0	2	
Bradycardia	4	3	2	9	
Hypotension	4	3	1	8	
Total	33	33	33	99	

Table:9 1st Rescue Analgesia Received

Post operative total Rescue analgesic of Diclofenac Dose given (1.5mg/kg)I.V		Group			Total	
		L	D	NS		
	Yes	19	23	25	51	**0.05**
	No	14	10	8	47	
Total		33	33	33	99	

Note: p-value 0.05 is statistically significant

Table:10 2nd Rescue Analgesia Received

2nd rescue analgesic Fentanyl Received (1.5µg/kg)		Group			Total	
		L	D	NS		
	Yes	18	10	23	51	**0.013**
	No	14	23	10	47	
Total		33	33	33	99	

Note: p-value 0.013 is statistically significant

Table-11 Comparison of Pain Score

Pain		(frequency)			Total	p-value
		Group-L	Group-D	Group-NS		
	Mild	4	0	0	4	**0.012**
	Moderate	6	6	1	13	
	Severe	23	27	32	82	
Total		33	33	33	99	

Note:p-value=0.012 is statistically significant

Table-12 Patient Satisfaction Among Three Groups

PATIENT SATISFACTION					Total	p-value
		Group -L	Group-D	Group-NS		
	Yes	23	21	12	56	**0.014**
	No	10	12	21	43	
Total		33	33	33	99	

Note: p-value=0.014 is statistically significant

Table:13 Descriptive Data And Report On Analgesic

Descriptive Statistics						
		N	Minimum	Maximum	Mean	Std. Deviation
Group-L	ASA	33	1	2	1.24	.435
	Age	33	19	56	34.76	10.860
	Weight	33	49	72	59.88	6.594
	Temp	33	35.50	39.50	37.8636	.87136
	HR	33	75	84	80.30	2.008

	DBP	33	72	82	75.45	2.251
	SBP	33	15	167	125.21	21.450
	RR	33	12	16	14.06	1.247
	Duration of surgery	33	7	80	51.27	11.998
Group-D	ASA	33	1	2	1.36	.489
	Age	33	25	56	40.39	8.437
	Weight	33	52	80	61.45	7.803
	Temp	33	37.00	41.00	38.4182	.98058
	HR	33	75	85	80.97	1.944
	DBP	33	72	82	77.03	2.298
	SBP	33	117	132	124.97	3.423
	RR	33	5	18	14.12	2.219
	Duration of Surgery	33	45	80	60.61	8.276
Group-NS	ASA	33	1	2	1.27	.452
	Age	33	19	54	37.97	10.036
	Weight	33	37	80	60.36	8.678
	Temp	33	31.20	40.30	37.7848	1.40715
	HR	33	78	86	81.76	2.151
	DBP	33	74	90	79.03	3.540
	SBP	33	123	136	129.55	3.615
	RR	33	1	19	15.35	3.810
	Duration of surgery	33	45	80	54.09	8.413

Table-14 Comparison of SPO_2 among Three Groups

SPO2		Group			Total	Chi-square value
		L (Frequency)	D(Frequency)	NS(Frequency)		
	65-70	1	3	0	4	**0.003**
	71-75	4	5	0	9	
	76-80	13	11	3	27	
	81-85	9	11	20	40	
	86-90	6	3	10	19	
Total		33	33	33	99	

Note: p-valve=0.003 is statistically significant

Figure 2 Comparison of Spo2 among three groups

Discussion

We assessed the analgesic effects of local anaesthetics in patients undergoing minimally invasive surgery of laparoscopic cholecystectomy. Most surgical procedures are connected with tissue damage and the majority of operated patients will experience some degree of postoperative pain. After major surgery, pain at rest is usually moderate during the initial two to three post-operative days and, in general, gets relieved within one week after the surgical

procedure. In contrast to this, pain during activity (e.g., walking or coughing) is severe in many patients during the first 72 hours after surgery and pain intensity during activity will often remain moderate to severe for days and even longer.

Laparoscopic surgery, which is considered as a minimally invasive surgery and a modern surgical technique is used for various surgeries. There are numerous arguments for a procedure-specific assessment of the evidence of analgesic treatment after laparoscopic surgery. Postoperative pain in laparoscopic surgery is reduced more quickly compared with open traditional surgeries, but effective analgesic treatment after laparoscopic surgeries have remained a clinical challenge. The patients undergoing laparoscopic surgery tend to expect a painless postoperative period because pain is the main reason for staying overnight in the hospital on the day of surgery being the dominant complaint and the primary reason for prolonged convalescence after laparoscopic surgery. In laparoscopy, due to CO2 gas and high intra-abdominal pressure, peritoneal inflammation and nerve injury occur. Pain has a highly variable personal experience, a subjective sensation or emotion and it may be estimated by NRS score. The justification for intraperitoneal administration of drugs for the treatment of the pain that follows laparoscopic surgery is that the small incisions at the abdominal wall cause visceral component of the pain and shoulder pain only. The efficacy of local anaesthetic instillation in pain control has been demonstrated in numerous other studies in laparoscopic cholecystectomy.

Dexmedetomidine is a potent and more selective alpha-2 agonist and reduces pain score after laparoscopic cholecystectomy with multimodal analgesia. In our study, postoperative NRS score was observed up to 24hrs. There was statistically significant difference in pain score between three groups after 12hrs that was lower in levobupivacaine group when compared to dexmedetomidine group but the score was severe in placebo group. Some authors suggest that intraperitoneal instillation of drugs for pain relief is effective if used before creation of pneumoperitoneum,[15] while others conclude that intraperitoneal drug administration is effective at the end of the surgery applied through a trocar.[16] Postoperative pain after laparoscopic cholecystectomy consists of three components, visceral, parietal and referred shoulder pain distinguishable from each other in intensity, latency and duration.

A patient's gender is a strong and significant predictor for substantial differences in clinical outcomes such as postoperative pain, analgesic use, and surgical complications following laparoscopic cholecystectomy. In our study population, women are more affected than the men, it shows that cholecystectomy was more common in female. A patient's gender is a strong and

significant predictor for substantial differences in clinical outcomes such as postoperative pain, analgesic use, and surgical complications (gangrenous gallbladder, empyema of the gallbladder, gallbladder perforation, and conversion to open surgery) following laparoscopic cholecystectomy. Similarly study done by Bingener et al also said that females present for laparoscopic cholecystectomy more frequently (76% of the cases); the prevalence of surgical complications during cholecystectomy is higher in men, most frequently because of inflammation or deterioration of the gallbladder.[17]

Laparoscopic cholecystectomy results in less postoperative pain as compared with open cholecystectomy and pain may be mild or moderate or even severe for some patients. After laparoscopic cholecystectomy patients complain more of visceral pain as a result of stretching of the intra-abdominal cavity, peritoneal inflammation and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity, whereas after open cholecystectomy the type of pain results mostly in parietal pain. Postoperative abdominal pain usually occurs during the first 24 hours, while shoulder pain most commonly appears on the second day after laparoscopic cholecystectomy. Results from reports of intraperitoneal local anaesthetic after laparoscopic surgery revealed weak evidence for an effect on postoperative pain. Especially after laparoscopic cholecystectomy, the evidence was not compelling, and the clinical significance, at least regarding pain scores, was questionable. The differences between results in the various RCTs are difficult to explain. Local anaesthetics are associated with toxicity which is dose related. Thus, the amount of local anaesthetics used may be of importance. In our study, we noted that intraperitoneal administration of levobupivacaine and dexmedetomidine was associated with reduced postoperative pain and increased time to first rescue analgesia. Side effect was less in levobupivacaine group and with dexmedetomidine group, statistically also there was no significancy compared to Group with normal saline. Patient's satisfaction level was also high in group with levobupivacaine and dexmedetomidine compare to placebo group (NS) Similarly, levobupivacaine injection in subdiaphragmatic area may block diaphragmatic peritoneal stimulation. In the another studies, intraperitoneal local anesthetics application reduced shoulder pain. Gharaibeh and Al-Jaberi[18] used intraperitoneal 0.25% bupivacaine in laparoscopic cholecystectomy and found reduction in frequency of shoulder pain. Furthermore, Louizos *et al.*[19] found that intraperitoneal levobupivacaine application decreased right shoulder pain after laparoscopic cholecystectomy. Similarly, right shoulder pain was less in levobupivacaine group compared to the control group. In contrast, Bakhamees et al.[20] evaluated the patients who received dexmedetomidine and found that they

had less VAS score as compared to placebo in the postoperative period and profound postoperative analgesia. In our study, results shows that the duration of analgesia was higher and had less need of rescue analgesia in levobupivacaine and dexmedetomidine group as compared to placebo group which were statistically significant and increases the duration of analgesia without having any significant adverse events. The study done by Ahmed *et al*.[21] observed that intraperitoneal instillation of dexmedetomidine in combination with bupivacaine significantly decreases total rescue analgesia requirement in postoperative period

In our study, those who received levobupivacaine, had less symptoms of nausea/vomiting compared to other two groups which is comparable to a study done by Bhakhamees *et al study.[22]* In our study, heart rate is normal in groups L and D due to the effect of dexmedetomidine on heart; this findings were comparable with the study done by Bhattacharjee *et al*.[23] who compared the effects of dexmedetomidine on haemodynamics in patients undergoing laparoscopic cholecystectomy. They found that postoperatively significant decrease in heart rate in dexmedetomidine group than saline group. Similar findings were observed in study done by Arain *et al*.[24] who studied the efficacy of dexmedetomidine and morphine for postoperative analgesia after a major surgery, not with levobupivacaine. They showed that there is significant decrease in heart rate in the postanesthesia care unit in dexmedetomidine group than morphine group. Also, our study findings showed that there was no significant difference found regarding vital parameters (heart rate, blood pressure, respiratory rate, oxygen saturation) and adverse during the postoperative period up to 24 hours. There was a significant difference regarding time to rescue analgesia and the total dose of rescue analgesics required during the postoperative 24 hours in Group L (levobupivacaine) as compared to other study groups. Patients who reported NRS moderate pain were given diclofenac 75 mg intramuscularly as rescue analgesia. Dose of diclofenac required in postoperative period- we found statistically higher doses are required in Group NS as compared to Group L or Group D, (P= 0.00, 0.000 respectively) . In our study, no statistically significant difference was found in regard to the adverse effects among the three study groups (P=0.509), but vomiting was high in Dexmedetomidine group compared to levobupivacaine group.

Another study suggest that the predominant cause of pain is parietal, but in contrast, many other studies emphasized that major portion is occupied by visceral pain in early convalescent period. It is because the surgical manipulation and tissue destruction in visceral organs are much more as compared to small incisions and limited trauma to the abdominal wall. Similarly, Todorov G et al,[25] compared the effect of intraperitoneal Levobupivacaine to relieve the pain after

laparoscopic cholecystectomy. There were two groups studied of which one received inj. Levobupivacaine, another group received saline injection intraperitoneally after the dissection. Visual analogue scale and total need of analgesics was compared post operatively.

Study conducted a trial in patients about the repeated instillation of local anaesthetics (Levobupivacaine) intraperitoneally to relieve the pain after surgery. Altogether out of two groups, one group received 0.5% Bupivacaine intraperitoneally after the dissection and eight hours after surgery. Control group received saline in the same period. They compared the VAS score, opioid requirement in two groups. levobupivacaine group showed less visual analogue scale when compared with saline group. Total Fentanyl requirement was significantly less in the study group when compared with the saline group. There was a significant reduction in abdominal pain in levobupivacaine when compared with the saline group at second hour ($p=0.038$), sixth hour after surgery ($p=0.028$) and levobupivacaine group consumed less analgesics. Thus in comparison to other investigators, our findings are of high importance because we have managed to show that a NSAID is useful not only for analgesia but also for minimising sedation and nausea in the postoperative period. Improvements of the latter are critical if patients are to recover and rehabilitate quickly after surgery.

Conclusion

Hence, we conclude that intraperitoneal instillation of local anaesthetic is an easy, cheap, and less noninvasive method which provides good analgesia in the immediate postoperative period after laparoscopic surgery. Intraperitoneal instillation produces better postoperative analgesia with levobupivacaine than what was obtained with dexmedetomidine and intraperitoneal placebo.

REFERENCES

1. Kim TH, Kang HK, Park JS, Chang IT, Park SG. Intraperitoneal ropivacaine instillation for postoperative pain relief after laparoscopic cholecystectomy. J Korean Surg Soc 2010;79:130–6.
2. Bisgaard T, Kehlet H, Rosenberg J. Pain and convalescence after laparoscopic cholecystectomy. Eur J Surg 2001;167:84–96.
3. Hernández-Palazón J, Tortosa JA, Nuño de la Rosa V, Giménez-Viudes J, Ramírez G, Robles R, et al. Intraperitoneal application of bupivacaine plus morphine for pain relief after laparoscopic cholecystectomy. Eur J Anaesthesiol 2003;20:891–6.

4. Esmat ME, Elsebae MM, Nasr MM, Elsebaie SB. Combined low pressure pneumoperitoneum and intraperitoneal infusion of normal saline for reducing shoulder tip pain following laparoscopic cholecystectomy. World J Surg 2006;30:1969–73.
5. Maharjan SK, Shrestha S. Intraperitoneal magnesium sulphate plus bupivacaine for pain relief after laparoscopic cholecystectomy. Journ of Kathmandu Med Coll 2012;1:21-30.
6. Park JK, Cheong SH, Lee1 KM, Lim SH, Lee JH, Cho K et al. Does dexmedetomedine reduce postoperative pain after laparoscopic cholecystectomy with multimodal analgesia? Korean J Anesthesiol 2012;63:436-40.
7. Narchi P, Benhamou D, Fernandez H. Intraperitoneal local anaesthetic for shoulder pain after day case laparoscopy. Lancet 1991;338:1569-70.
8. Salihoglu Z, Yildirim M, Demiroluk S. Evaluation of intravenous paracetamol administration on postoperative pain and recovery characteristics in patients undergoing laparoscopic cholecystectomy. Surg Laparosc Endosc Percutan Tech 2009;19(4):321-23.
9. Kahokehr A, Sammour T, Soop M. Intraperitoneal local anaesthetic in abdominal surgery - a systemic review. ANZ J Surg 2011;81(4):237-45.
10. Boddy AP, Mehta S, Rhodes M. The effect of intraperitoneal local anesthesia in laparoscopic cholecystectomy: a systematic review and meta-analysis. Anesth Analg 2006;103:682–88.
11. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Factors determining convalescence after uncomplicated laparoscopic cholecystectomy. Arch Surg 2001;136:917–21.
12. Erdogan M, Erdogan A, Erbil N, Karakaya HK, Demircan A. Prospective, randomized, placebo- controlled study of the effect of TENS on post-thoracotomy pain and pulmonary function. World J Surg 2005;29:1563–70.
13. Kucuk C, Kadiogullari N, Canoler O, Savlı S. A placebo-controlled comparison of bupivacaine and ropivacaine instillation for preventing postoperative pain after laparoscopic cholecystectomy. Surg Today 2007;37:396–400.
14. Agarwal A, Gautam S, Gupta D, Agarwal S, Singh P, Singh U. Evaluation of a single preoperative dose of pregabalin for attenuation of postoperative pain after laparoscopic cholecystectomy. Br J Anaest 2008;101:700–4.
15. Barczynski M, Konturek A, Herman RM. Superiority of preemptive analgesia with intraperitoneal instillation of bupivacaine before rather than after the creation of pneumoperitoneum for laparoscopic cholecystectomy: a randomized, double-blind, placebo-controlled study. Surg Endosc 2006;20(7):1088-93.

16. Coughlin SM, Karanicolas PJ, Emmerton-Coughlin HM, et al. Better late than never? Impact of local analgesia timing on postoperative pain in laparoscopic surgery: a systematic review and metat analysis. Surg Endosc 2010;24(12):3167-76.
17. Juliana BC, Hargreaves KM. Study of Pain Perception Between Males and Females Following Laparoscopic Cholecystectomy. University of texas health science centre, sanantonia. March 8, 2012.
18. Gharaibeh, K. I. A, Al-jaberi T. M. Bupivacaine Instillation into Gallbladder Bed after Laparoscopic Cholecystectomy: Does It Decrease Shoulder Pain? Journal of Laparoendoscopic & Advanced Surgical Techniques 2000;10(3):137–41.
19. Louizos AA, Hadzilia SJ, Leandros E, Kouroukli IK, Georgiou LG, Bramis JP. Postoperative pain relief after laparoscopic cholecystectomy: a placebo-controlled double-blind randomized trial of preincisional infiltration and intraperitoneal instillation of levobupivacaine 0.25%. Surg Endosc 2005 Nov;19(11):1503-6.
20. Bakhamees HS, El-Halafawy YM, ElKerdawy HM, Gouda NM, Altemyatt S. Effect of dexmedetomidine in morbidly obese patients undergoing laparoscopic gastric bypass. Middle East J Anaesthesiol 2007;19: 537–51.
21. Ahmed B, Elmawgoud AA, Dosa R. Antinociceptive effect of ($\dot{\alpha}_2$ adrenoceptor agonist) dexmedetomidine versus meperidine, topically, after laproscopic gynecologic surgery. J Med Sci 2008;8:400-4.
22. Bhattacharjee DP, Nayek SK, Dawn S, Bandopadhyay G, Gupta K. Effects of dexmedetomidine on haemodynamics in patients undergoing laparoscopic cholecystectomy-A comparative study. J Anaesth Clin Pharmacol 2010; 26:45–8.
23. Todorov G, Tzaneva P, Lukanova T, Velev G, Kojtchev A. The effect of intraperitoneal levobupivacain (Chirocaine) application on postoperative pain in laparoscopic cholecystectomy - a prospective study. Khirurgiia (Sofiia) 2009;4(5):32-5.
24. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery**.** Anesth Analg 2004;98(1):153-8
25. Papadima A, Emmanuel E. Lagoudianakis, Antonakis P, Filis K, Makri I, Arkogiannakis H, et al. Repeated intraperitoneal instillation of levobupivacaine for the management of pain after laparoscopic cholecystectomy. Surgery 2009;146(3):475–82.