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Original Article

Double-blind Randomized Control Study to Compare the Efficacy of Incisional 0.25% Bupivacaine versus both Intraperitoneal and Incisional 0.25% Bupivacaine for Post-operative Pain Relief and Effect on Recovery after Laparoscopic Cholecystectomy

R Zadkar Sanjeevani[1], N Shah Prerana[2], D Patel Rajendra[3], M Nirav Kotak[1], Walzade Atul[4]

[1]Associate Professor, Department of Anesthesia, King Edward Memorial Hospital and Seth Gordhandas Sunderdas Medical College, Parel, Mumbai, Maharashtra, India, [2]Additional Professor, Department of Anesthesia, King Edward Memorial Hospital and Seth Gordhandas Sunderdas Medical College, Parel, Mumbai, Maharashtra, India, [3]Professor, Department of Anesthesia, King Edward Memorial Hospital and Seth Gordhandas Sunderdas Medical College, Parel, Mumbai, Maharashtra, India, [4]Assistant Professor, Department of Anesthesia, King Edward Memorial Hospital and Seth Gordhandas Sunderdas Medical College, Parel, Mumbai, Maharashtra, India

ABSTRACT

Objective: The objective of the study was to (1) compare the efficacy of incisional 0.25% bupivacaine versus both intraperitoneal and incisional 0.25% bupivacaine for post-operative pain relief after laparoscopic cholecystectomy and (2) compare the effect on recovery to normal activity and feeling of well-being.

Materials and Methods: This is a prospective, double-blind, randomized control study of 60 cases. Sixty patients were divided into group intraincisional (IC) 4–5 ml of 0.25% bupivacaine was infiltrated at each trocar insertion site and group (ICP) patients received intraperitoneal instillation of 20 ml of 0.25% bupivacaine along with 4–5 ml of 0.25% bupivacaine at each trocar insertion site. Patients were evaluated for visual analog score (VAS), immediately after extubation and at 1, 2, 4, 6, 12, 24, and 48 h postoperatively. Feeling of well-being (FOB) was assessed using an ordinal one-5 scale for 5 days postoperatively. All statistical analyses were performed using SPSS version 21 for Windows® 10.0. The Chi-square ($\chi 2$) test and Student's *t* test were used.

Results: VAS scores are significantly less at one (4.13 vs. 1.43), 2 (3.23 vs. 2.47), and 4 (3.33 vs. 2.80) h in group ICP as compared with group IC. Recovery room stay in ICP is significantly less, that is, 21.3 min vs. 29.9 min. Post-operative day one in group ICP FOB is significantly better (1.87 ± 0.881 vs. 2.6 ± 0.621, $P < 0.001$).

Conclusion: A combination of intraperitoneal and incisional bupivacaine at the end of the LC results in better pain relief, shorter stay in the recovery room, decreased cumulative analgesic consumption, and decreased incidence of PONV. This also fastens recovery and improves patient's sense of well-being.

Key words: Bupivacaine, Intraperitoneal instillation, Laparoscopic cholecystectomy, Post-operative pain, Recovery

INTRODUCTION

Post-operative pain is still the most important independent factor affecting patient's recovery after laparoscopic cholecystectomy.[1] It is one of the most common reasons for re-admission after daycare laparoscopic cholecystectomy.

Local anesthetic infiltration and intraperitoneal instillation are commonly used techniques of pain relief. Their effectiveness in reducing post-operative pain is well established, but their effect on recovery after surgery is not fully evaluated.[2,3] This study compares the efficacy of a combination of intraperitoneal and incisional 0.25% bupivacaine versus incisional 0.25% bupivacaine in reducing post-operative pain, improving sense of well-being, and fastening recovery.

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Corresponding Author: Dr. R. Zadkar Sanjeevani, Flat no. 3, C.O. Quarter's no 2, KEM Hospital Campus, Parel, Mumbai, India.

MATERIALS AND METHODS

This is a prospective randomized study of sixty cases conducted from August 2016 to July 2017. Institutional Ethics approval was taken. Informed consent was secured from patients who fulfilled the inclusion criteria. The inclusion criteria were age between 18 and 65 years, ASA I-II patients and patients in which laparoscopic cholecystectomy was done using three-four ports. Patients were recruited from the general surgery and surgical gastroenterology department. We excluded patients with a history of allergic reactions to local anesthetic drugs, pregnant and lactating mothers, acute pancreatitis or cholecystitis (<6 weeks), any past or present history of chronic pain treatment, history of alcohol addiction or drug addiction, extreme overweight (BMI > 35), cognitive impairment or communication problems, and patient with h/o psychiatric illness.

Sample size calculation was done on the basis of VAS scores of 4, 8, 12, and 24 h postoperatively, we calculated that minimum 23 patients are needed in each group to obtain 5% type one error and an 80% power. The sample size for VAS scores (1) 4, 8, 12, and 24 h calculated separately highest was 23. It was calculated with the help of OpenEpi, Version three. Considering dropout rate of 15% sample size taken as 30.

Patients were divided randomly into two groups using computer generated random number table. Group (IC) patients received post-procedure 4–5 ml of 0.25% bupivacaine at each site of trocar insertion with a 23G needle and intraperitoneal instillation of 20 ml of 0.9% normal saline. Group (ICP) patients received both intraperitoneal instillation of 20 ml of 0.25% bupivacaine and 4–5 ml of 0.25% bupivacaine at each site of trocar insertion with a 23G needle.

Preoperatively, these participants were given an explanation of the visual analog scale (VAS) and ordinal scale of feeling of well-being which was used postoperatively.

The operating room (OR) nurse staff not involved in the study opened the sealed opaque envelope and followed instructions for the solution preparation. Intravenous access was taken after applying non-invasive monitoring using a continuous electrocardiogram (ECG), pulse-oximetry (SpO_2), end-tidal CO_2, and non-invasive systolic and diastolic blood pressure monitoring (NIBP) including mean arterial pressure (MAP). All parameters were monitored at five minutes interval. General anesthesia was given by standard technique using intravenous (IV) fentanyl 2 $\mu g\ kg^{-1}$ as analgesic, midazolam 0.03 mg kg^{-1} as sedative, induction agent propofol 2 mg kg^{-1}, and muscle relaxant vecuronium 0.1 mg kg^{-1}. Anesthesia was maintained with MAC one sevoflurane in oxygen:nitrous oxide mixture (50:50) and intermittent vecuronium boluses.

Maximum allowable dose of bupivacaine was a maximum dose of 2 mg kg^{-1} in all groups. All patients received IV paracetamol 15 mg kg^{-1} intraoperatively. This study was double-blind as a patient were not aware of group and one research staff (accessor) blinded to the details of the study was scheduled to collect the post-operative data. Patients were evaluated using VAS, immediately after extubation and at 1, 2, 4, 6, 12, 24, and 48 h postoperatively. Incidence of nausea, vomiting in 24 h post-operative period was noted. Feeling of well-being (FOB) was assessed using an ordinal one-5 scale (one-feeling sick, two-not so good, three-Okay, four-fine but not normal, and five-feeling normal) from day one till 5 days postoperatively. The number of patients requiring post-operative analgesia was noted. Rescue analgesic used was IV diclofenac 75 mg for patients demanding post-operative analgesia if VAS was more than four. Not more than three doses of IV diclofenac were given in 24 h and it was not repeated for 6 h. If laparoscopic cholecystectomy gets converted to open cholecystectomy by surgeon or surgical complications like major bleeding or rupture of gall bladder intraoperatively, the patient will be withdrawn from the study.

If there was no relief after IV diclofenac 75 mg, then opioids were given for pain relief and patients have been excluded from study statistics.

Following parameters such as time of discharge (days), duration of surgery – (in minutes), duration stay in recovery room – (in minutes), time to resume walking around without support after surgery (hours), and doing daily routine activities without help (like going to toilet, dressing up in days) were also noted during the study.

Statistical Analysis

All statistical analyses were performed using SPSS version 21 for Windows® 10.0. The Chi-square (χ^2) test was used to compare proportions (No. of patients requiring post-operative analgesic drug). Student's *t* test was used to compare the mean VAS score and FOB score. Results were given as percentages or mean ± SD where appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

All 60 patients successfully completed the study. The mean age of patients in IC was 40.5 ± 13.505 and ICP was 43.6 ± 11.566 in both the groups, there is female predominance (M:F 2.3:2.8). Duration of surgery (min)

was comparable in both groups (IC 83.07 ± 13.759, ICP 80.70 ± 15.139; $P = 0.529$)

VAS score has been calculated at the end of 1, 2, 4, 6, 12, 24, and 48 h. The mean of these scores is calculated for these scores in each group. The "*P*" value is also calculated for each reading in both the group. There are VAS scores significantly less at 1, 2, and 4 h in group ICP as compared with group IC [Table 1]. The rescue was required in only five (16.7%) patients in the ICP, whereas 17 (56.7%) patients required rescue analgesic in only IC group. This difference is significant as $P < 0.05$.

On day one, there was a significant difference in FOB score [Table 2]. The score was significantly better in ICP group. The second day even though the score was still better in ICP group, difference did not reach the level of significance. Day three onward score in both the groups was found to be comparable to each other.

Only nine (30%) patients had nausea in ICP group as against 13 (43.3%) in IC group. Only one (3.3%) patients had vomiting in ICP group as against 04 (13.3%) in IC group. In both, the groups mean duration of surgery is almost same, that is, 83 and 80.7 min. $P = 0.52$ is not significant.

While comparing duration in the recovery room (RR), the mean time taken by patients in ICP is significantly less, that is, 21.3 min as against to 29.9 min in the other group [Table 3] *P*-value (0.001). The mean time taken by patients to walk without support in the ICP group was 9.7 h, whereas in other groups, it was 14.5 h. This difference is significant as $P = 0.01$. The mean time taken by patients for starting daily routine activities in the ICP group was 2.2 days, whereas in other groups, it was 2.4 days. This difference is not significant as $P = 0.053$. The mean time taken to discharge the patients in ICP group was 2.1 days, whereas in other groups, it was 2.27 days. This difference is not significant as $P = 0.098$.

DISCUSSION

Age and sex in both groups were comparable. However, in our study there was female preponderance, F:M was 2.5:1. It could be because of cholelithiasis being more common in females.

Table 1: VAS score at various interval postoperatively

VAS score interval postop (h)	Intra-incisional		Intra-incisional + Intra-peritoneal		*P* value
	Mean and confidence interval	Standard deviation	Mean and confidence interval	Standard deviation	
1	4.13(1.53–6.7)	1.279	1.43 (−0.6–3.43)	1.040	<0.001
2	3.23(2–4.5)	0.626	2.47 (0.93–4)	0.776	<0.001
4	3.33 (2.2–4.4)	0.547	2.80 (1.8–3.8)	0.484	<0.001
6	4.10 (1.8–6.5)	1.185	3.37 (1.1–5.6)	1.129	0.015
12	3.07 (0.73–5.4)	1.172	2.70 (0.9–4.5)	0.915	0.171
24	2.13 (3.7–0.6)	0.776	1.73 (0.8–2.6)	0.450	0.028
48	1.00 (0.1–1.9)	0.455	1.10 (0–2.2)	0.548	0.433

Table 2: Comparison of feeling of well-being scores postoperatively

Day	Intra-incisional		Intra-incisional + Intra-peritoneal		*P* value
	Mean (confidence interval)	Std deviation	Mean (confidence interval)	Std deviation	
1	1.87 (0.11–3.63)	0.881	2.6 (1.35–3.8)	0.621	<0.001
2	2.87 (4–1.73)	0.571	3.17 (1.9–4.5)	0.648	0.062
3	3.63 (2.6–4.6)	0.490	3.73 (2.8–4.6)	0.450	0.414
4	4.07 (2.9–5.23)	0.583	4.0 (2.9–5.1)	0.55	0.999
5	4.77 (3.9–5.6)	0.430	4.83 (5.56–4.0)	0.379	0.527

Table 3: Comparison of recovery parameters

Parameter	Intra-incisional		Intra-incisional + Intra-peritoneal		*P* value
	Mean (confidence interval)	Standard deviation	Mean (confidence interval)	Standard deviation	
Recovery room stay (min)	29.90 (19.7–40.3)	5.189	21.37 (15–27.4)	3.011	0.001
Walking without support (h)	14.57 (7–22.2)	3.794	9.73 (4.7–14.7)	2.504	0.01
Daily routine activities (days)	2.43 (1.4–3.4)	0.504	2.20 (1.4–3)	0.407	0.053
Time to discharge (days)	2.27 (1.37–3.17)	0.450	2.10 (1.5–2.7)	0.305	0.098

We used both instillation and infiltration at the end of surgery. There is collective evidence which suggests that intraperitoneal instillation[4,5] and incisional infiltration[6-8] of local anesthetic at the end of laparoscopic cholecystectomy have better pain relief than at the beginning of surgery.

Etiology of pain after laparoscopic cholecystectomy is multifactorial. Incisional pain, visceral pain, and shoulder tip pain are the various components which have been hypothesized. Few studies state that incisional pain is the most predominant type[9,10] while there are others who believe the shoulder tip is most predominant.[11] Various methods for pain relief have been used for post-operative pain in laparoscopy. Efficacy of intraperitoneal bupivacaine instillation in reducing post-laparoscopic cholecystectomy intra-abdominal pain has been well-established. It has been proposed that intra-abdominal pain after laparoscopic cholecystectomy is caused by the formation of carbonic acid, especially in the subdiaphragmatic area and irritation of the peritoneum due to carboperitoneum.[12] Intraperitoneal instillation of bupivacaine relieves this pain and acts also on the raw area in gall bladder bed. VAS scores of in-group IC for 1st 8 h are significantly more than group ICP which suggests that intraperitoneal bupivacaine reduces the visceral component of post-operative pain significantly. Studies suggest that pain after laparoscopic cholecystectomy peaks around 4–8 h.[12,13] VAS score after 12 h postoperatively was comparable in both the groups. Rescue analgesia requirement was significantly more in group IC. It was maximum in the first 6–7 h postoperatively, coinciding with previous study findings suggesting pain intensity maximum during 4–8 h postoperatively. No side effects or adverse events related to intraperitoneal or intraincisional bupivacaine were noted during this study. By reducing the requirement of rescue analgesia, it further decreases the risk of side effects associated with them. The duration of surgery in our study is group IC and group ICP is 83.07 (13.76) and 80.70 (15.12), respectively. This is significantly longer compared to other studies.[14] Reason behind this finding is our hospital being a state-run teaching hospital with surgeons of varied of the degree of experience in performing laparoscopic cholecystectomy.

In our study, stay in the recovery room in group IC and group ICP is 29.90 (5.12) and 21.37(3.01), respectively, which are comparable to a similar study using ropivacaine.[15] Stay in the recovery room was significantly shorter in group ICP because of better pain relief and lesser incidence of nausea, vomiting.

In our study, we assessed walking without support as a measure of recovery because it reduces the need of attendant and also eases the attendant's burden. This has a huge psychosocial impact on patient's recovery and well-being. Group ICP showed significantly less time to resume walking around without support as compared to group IC. This difference of around 4–5 h is of great financial importance in private hospitals. This can be attributed to better pain relief, less nausea, and vomiting which fastened patient's recovery. Pain is a very important factor affecting patient's sense of well-being and post-operative recovery.[14] Multimodal analgesia is known to result in better pain relief postoperatively,[16] facilitate early recovery, discharge, and early resumption of daily activities;[11,17] earlier resumption of walking around without support, better pain relief, and lesser nausea improve patient's confidence and sense of well-being in the early post-operative period. In our study, on day 1, the sense of well-being was significantly better in group ICP, on day 2, the difference did not reach the level of significance, while day 3–5 were comparable. Pain aggravates nausea and vomiting through neurohormonal mechanisms. It also increases nausea due to the increased consumption of opioids.[11] This explains the significantly more incidence of nausea and vomiting in group IC. There is enough evidence to support that laparoscopic cholecystectomy can be performed as daycare surgery.[18-24] But in a developing country like India patient prefers to stay overnight after surgery. This could be because of psychosocial factors or infrastructure available.[25] In our study, the duration of hospital stay was similar in both the groups. The reason behind this finding is our hospital is a government-run hospital and in our hospital discharge is governed by surgical unit protocol.

Limitation

In our study, we have excluded cases which had surgical complications such as major bleeding or rupture of gall bladder intraoperatively to avoid bias, so the efficacy of a combination of intraperitoneal and incisional bupivacaine needs to be further explored in these scenarios.

CONCLUSION

A combination of intraperitoneal and incisional bupivacaine at the end of the LC results in better pain relief, shorter stay in the recovery room, decreased cumulative analgesic consumption, and decreased incidence of PONV. This also fastens recovery and improves patient's sense of well-being.

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