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Original Research Article

A randomized double-blind study to evaluate a surgeon-based technique to reduce post-operative pain in minimal gynecological surgery

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ABSTRACT

Background: The study aims to evaluate whether instillation of levo-bupivacaine intraperitoneally decreases post-operative pain after laparoscopic gynaecological surgeries, using VAS pain Scale.
Methods: Randomized placebo controlled double blinded study conducted at tertiary care hospital in New Delhi. 90 ASA I & II women scheduled to undergo elective laparoscopic gynaecological surgeries. 20 ml 0.5% levo-bupivacaine diluted with 40ml normal saline (total 60ml) intraperitoneally at the end of surgery before closure of ports along with port site infiltration of levo-bupivacaine (3-5 ml) in intervention group and 60 ml normal saline intraperitoneally in control group.
Results: Mean pain scores were significantly lower ($p<0.01$) in the intervention group when compared to the control group for initial 4 hours of the study after that mean pain score was lower in intervention group than control group but it was statistically not significant. The requirement of rescue analgesia was also significantly lesser in intervention group compared to control group.
Conclusions: Levo-bupivacaine is an easy, cheap and non-invasive method which provides good analgesia in the immediate postoperative period after laparoscopic gynaecological surgery, without adverse effects, especially in the early postoperative period. This improves patients experience and should be made an integral part of all minimal gynaecological endoscopic surgery.

Keywords: Levo-Bupivacaine, Intraperitoneally, Rescue analgesia, Laparoscopic surgery, Rescue analgesia, Post-operative pain relief

INTRODUCTION

Laparoscopic operative procedures have revolutionized gynaecological surgery. It offers many advantages like smaller and more cosmetic incision, reduced post-operative stay, reduced blood loss, and pain, which cut down on hospital cost. However, patients undergoing laparoscopic procedures in spite of smaller incision experience postoperative pain especially in the abdomen, back, and shoulder region which require proper attention. Pain intensity usually peaks during the immediate postoperative hours when patient has just come out of anaesthesia.[1] To improve patient's, experience after surgery adequate analgesia has to be given at this time. Three components of pain after laparoscopic surgeries are; Visceral pain, Shoulder pain and Parietal pain.[2] Scapular

pain secondary to peritoneal insufflation, especially when shoulder holders and exaggerated Trendelenburg position are used, tends to increase after the eighth post-operative hour, appears during the night after surgery and hinders sleep. Infiltration of local anaesthetics decreases scapular pain.[3,4] The postoperative pain comprises of several components hence warrants the necessity of multimodal analgesic techniques to provide effective postoperative analgesia.[5]

By evaluating the pathophysiology of pain, it is hypothesised that we can prevent or reduce pain by blocking the nociceptors before their stimulation by use of local anaesthesia.[6] Several reports are available on the efficacy of intraperitoneal administration of local anaesthetic for analgesia after laparoscopic surgery particularly laparoscopic cholecystectomy. Bupivacaine is one such local-anaesthetic agent. It has good safety profile, is long acting and free from side effects like gastritis due to NSAIDS, nausea and vomiting and fear of drug dependence as in opioid. However, only a few reports are available on the efficacy of intraperitoneal local anaesthetic administration for analgesia after laparoscopic gynaecological surgery.[5-11,18] The safety and efficacy profile of levo-bupivacaine is better than bupivacaine, and numbers of studies available on the efficacy of levo-bupivacaine (local anaesthetic) for analgesia after laparoscopic gynaecological surgeries are even less, hence we did this study. Laparoscopy is currently being done as a day care procedure. Post-operative pain management is important element to achieve this goal. In case the patient is pain free, she may be discharged the same day. We conducted a prospective, randomized, placebo-controlled, double-blind study to see the efficacy of levo-bupivacaine in post-operative pain management in laparoscopic Gynaecological surgeries.

METHODS

Study design, settings and participants

It was a hospital based prospective randomized placebo controlled double blinded study conducted over a period of one year from June 2017 to May 2018 in Department of obstetrics and Gynaecology at a tertiary care hospital in New Delhi, India. A total of 90 ASA I and II patients between ages 18 to 70 years scheduled for laparoscopic gynaecological surgery constituted the study population. The study exclusion criteria included use of opioid during 24 hours prior to the study, drug or alcohol abuse and H/O allergy to any of the study drug, chronic pain syndrome where pain evaluation was judged unreliable because of neurological disease or treatment with steroids prior to surgery, diagnostic laparoscopy without surgical procedure. Trial (CTRI) Reg. No: CTRI/2019/07/020152.

Procedure

After taking written informed consent, a detailed pre-anaesthetic check-up was done in all patients. Prior to operations, investigations like CBC, KFT, BSR, viral markers, urine examination, chest X-ray, ECG were done. All patients were shown the VAS pain scale so that they are familiarized with it prior to surgery. VAS pain score used consisted of 10 cm line, one end of which represents no pain and the other end represents maximum imaginable pain. Patients were asked to indicate on the line, the intensity of pain, and the length of line was measured in cms as pain score. Sample of 90 patients were randomly assigned into two groups by draw of lots. Randomization was done by the operating surgeon in Operation Theatre and kept as record, secret from the investigator. The operating surgeon instilled 60 ml of the solution intra-peritoneally according to the group to which the patient was assigned. The operating surgeon had no further role into the investigation of the study. Thus, the principal investigator was unaware about the assignment of the patients into either of the groups. Group (I): 45 patients received 20ml 0.5% levo-bupivacaine diluted with 40ml normal saline (total 60ml) intraperitoneally at the end of surgery before closure of ports. Patient were placed head-up position on OT table before installation of levo-bupivacaine. Also, local port site infiltration was done with 3-5ml of 0.5% levo-bupivacaine. Group (II): 45 patients were given 60 ml normal saline intraperitoneally at the end of surgery before closure of ports. The anaesthetic procedure, except for the test drug which was put intraperitoneally, was similar in both the groups and an attempt was made to minimize or exclude other factors which might have affected the post-operative pain response to surgery. Both groups were given Diclofenac 75 mg twice a day intravenously as post-operative analgesia. Immediately starting in post-operative period, pain of the patient was assessed by VAS pain scale and whenever VAS >4 cm rescue analgesia was given. In our study, Tramadol 50 mg intravenously (opioid analogue) was used as a rescue analgesia. Pain scoring was done by VAS at 1, 2, 3, 4, 6, 8, 12 & 24 hr for pain at rest. The heart rate, Blood Pressure, Respiratory rate were assessed at above mentioned time intervals. Post-operative nausea and vomiting (PONV) and need for rescue analgesia with dose and time of administration was documented in Performa. Ondansetron 4 mg was given intravenously for vomiting and nausea.

Sample size justification

The sample size calculation had been done with the view to detect a difference of atleast 4 points on average in the VAS pain score in the case and control group from the study reported by Butala et al using the statistical formula:[10]

$$n = \frac{(\sigma_1^2 + \sigma_2^2)(Z\alpha_{/2} + Z_\beta)^2}{\delta^2}$$

Where: σ_1 =7.27, σ_2=6.15, $Z_{\alpha/2}$ = 1.96 (for 5% level of significance), Z_β = 0.84 (for 80% power), δ=4 (minimum clinical difference), n = 45, Thus, the sample size was taken as 45 for each case and control group.

Statistical analysis

Data were analysed and statistically evaluated using SPSS software, version 17 (Chicago II, USA). Quantitative data was expressed in mean, standard deviation while qualitative data were expressed in percentage. Statistical differences between the proportions were tested by chi square test or Fisher's exact test while difference between mean were tested by student 't' test or Man Whitney U test. 'p' value less than 0.05 was considered statistically significant.

RESULTS

The groups were similar for age, weight, BMI and mean duration of surgery (Table 1).

Table 1: Comparison of demographic and surgical data in both groups.

Parameters	Control group (N=45)	Intervention group (N=45)	P value
Age (years)	38.42±10.61	41.98±11.76	0.13
Weight (kgs)	61.91±11.86	66.46±12.96	0.08
BMI (kg/m^2)	25.05±3.94	26. 84±5.06	0.06
Duration of surgery (minutes)	116.82±36.23	127.33±32.64	0.15

Table 2: Operative procedures in both groups.

Parameters	Control group (N=45)		Intervention group (N=45)	
	N	%	N	%
LAP Adhesiolysis	1	2.2	2	4.4
TLH	20	44.4	29	64.4
LAP Ovarian cystectomy	14	31.1	7	15.5
LAP Ovarian cystectomy+myomectomy	2	4.5	0	0.0
LAP myomectomy	4	8.9	4	8.9
LAP Salpingectomy	4	8.9	2	4.4
LAP removal of rudimentary horn of uterus	0	0.0	1	2.2

Most common operative procedure in both the groups was TLH (44.4% in control group and 62.2% in intervention group) followed by LAP ovarian cystectomy (Table 2). Mean pain scores were significantly lower (p<0.01) in the intervention group when compared to the controlled group for initial 4 hours of the study after that mean pain score was lower in intervention group than control group but it was statistically not significant (Table 3, Figure 1). None of the patients complained of shoulder pain after operative procedure till 8 hours in intervention group and after that only 2 patients complained of pain at 12 hours and 24 hours.

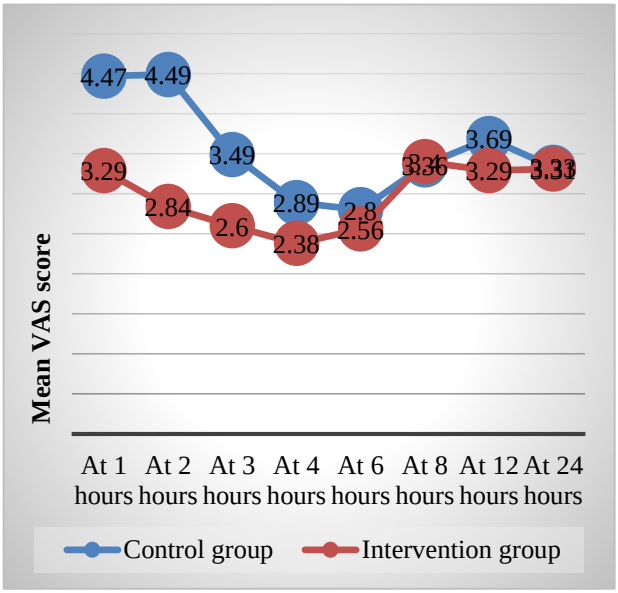

Figure 1: Comparison of VAS pain score at different time period in both groups.

Table 3: Comparison of VAS pain score at different time period in both groups.

VAS score	Control group (N=45)	Intervention group (N=45)	P value
At 1 hours	4.47±1.39	3.29±1.16	<0.001
At 2 hours	4.49±1.53	2.84±0.85	<0.001
At 3 hours	3.49±0.87	2.60±0.69	<0.001
At 4 hours	2.89±0.74	2.38±0.57	<0.01
At 6 hours	2.80±0.87	2.56±0.75	0.18
At 8 hours	3.36±0.98	3.40±1.13	0.92
At 12 hours	3.69±1.08	3.29±0.66	0.09
At 24 hours	3.33±0.67	3.31±0.70	0.97

For control group, 13 patients complained regarding shoulder pain at 6 hours, 29 at 8 hours, 32 at 12 hours and 33 at 24 hours. The difference was statistically significant at 6, 8, 12 and 24 hours (p<0.001) (Table 4, Figure 2). After 2 hours of operative procedure, 15 patients in control group and six patients in intervention group had complained of post-operative nausea and vomiting (PONV) while at 3 hours, 10 patients in control group complained of nausea and vomiting but in intervention group none of the patients complained. The difference was statistically significant (p<0.05). As time passed, cases of

PONV were reduced in both groups for entire duration of surgery and the difference was statistically un-significant (Table 5).

Table 4: Comparison of postoperative Shoulder pain at different time period in both group.

Shoulder pain	Control group (N=45)		Intervention group (N=45)		P value
	N	%	N	%	
At 1 hours	0	0.0	0	0.0	-
At 2 hours	0	0.0	0	0.0	-
At 3 hours	1	2.2	0	0.0	0.98
At 4 hours	1	2.2	0	0.0	0.98
At 6 hours	13	28.9	0	0.0	<0.001
At 8 hours	29	64.4	0	0.0	<0.001
At 12 hours	32	71.1	2	4.4	<0.001
At 24 hours	33	73.3	2	4.4	<0.001

Table 5: Comparison of postoperative nausea vomiting (PONV) at different time period in both groups.

Postoperative nausea vomiting (PONV)	Control group (N=45)		Intervention group (N=45)		P value
	N	%	N	%	
At 1 hours	4	8.9	6	13.3	0.50
At 2 hours	15	33.3	6	13.3	0.02
At 3 hours	10	22.2	0	0.0	<0.01
At 4 hours	0	0.0	0	0.0	-
At 6 hours	2	4.4	0	0.0	0.49
At 8 hours	1	2.2	1	2.2	-
At 12 hours	4	8.9	1	2.2	0.36
At 24 hours	1	2.2	0	0.0	0.98

For entire duration of study, 33 patients (73.3%) in control group required rescue analgesia but in intervention group only 11 patients (24.4%) needed rescue analgesia. The difference was highly significant (p<0.001). Mean analgesic requirement was significantly higher in control group (50.00±36.92 mg) compare to intervention group (12.22±21.73 mg) (p<0.001) (Table 6). On comparing VAS pain scores in similar surgical procedures (TLH), mean pain scores were significantly lower (p<0.01) in the intervention group when compared to the controlled group for initial 3 hours of the study after that mean pain score was lower in intervention group than control group but it was statistically not significant (Figure 3). When port site pain score was compared in both groups, it was observed that the score was significantly lower in intervention group compared to control group for entire duration of study (p<0.001).

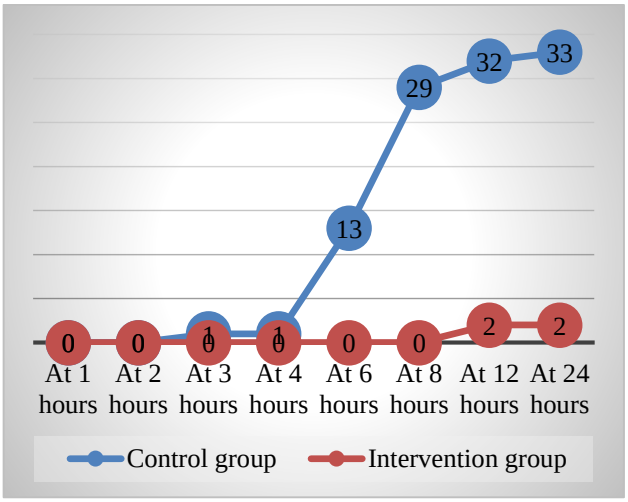

Figure 2: Comparison of postoperative Shoulder pain at different time period in both groups.

No significant difference was observed in heart rate, systolic and diastolic BP between control and intervention group during the 24-hour period. There was no adverse event related to intraperitoneal or port-site instillation of levobupivacaine.

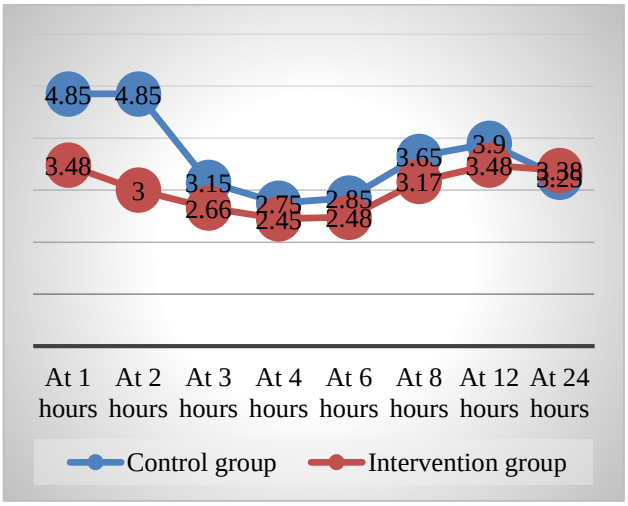

Figure 3: Comparison of VAS score at different time period in both group with TLH procedure.

Table 6: Comparison of total no. of patients given rescue analgesia in both groups.

Rescue analgesia	Control group (N=45)		Intervention group (N=45)		P value
	N	%	N	%	
Yes	33	73.3	11	24.4	<0.001
No	12	26.7	34	75.6	

DISCUSSION

Present study was conducted to evaluate whether instillation of levo-bupivacaine intraperitoneal decreases post-operative pain after laparoscopic gynaecological surgeries, using VAS pain Scale. The study also aimed to assess requirement of rescue analgesia in post-operative periods and incidence of PONV (post-operative nausea and vomiting) in both groups. Narchi et al showed that intraperitoneal instillation of 100 mg bupivacaine did not cause toxicity.[8] This technique is safe and with good pain relief in initial few hours. We chose Levo- bupivacaine for our study because Levobupivacaine (100 mg), an isomer of racemic bupivacaine, has been presented as a safer LA with a reduced risk of systemic toxicity and with long action.[12,13] Only few studies have been done evaluating the effect of intraperitoneally administered levobupivacaine while majority have evaluated bupivacaine. Louizos and colleagues used 0.25% levobupivacaine 20 ml intraperitoneally following the removal of the gallbladder.[14] The group having combination of pre-incisional local infiltration and intraperitoneal instillation of levobupivacaine had pain scores lower than in the other groups during rest, cough, and movement ($p<0.05$) which collaborate with our study. They also determined lower VAS pain scores like those in our study, even though their doses of levobupivacaine was half as compared to dose used in our study. While Alper et al used 0.25% levobupivacaine 40 ml intraperitoneally following laparoscopic cholecystectomy.[15] It was observed that postoperative pain scores were significantly lower only in the first half an hour in the Levo-Bupivacaine group than in the normal saline group ($p<0.05$). This could be because of total volume of solution used by us was more hence the spread to the effected site would be better and because of timing of instillation. Cunningham et al used 40 ml of 0.25% levobupivacaine intraperitoneally following laparoscopic gynaecological surgeries.[18] There was significant reduction in shoulder tip pain at 3 hours (this significance was lost in later hours) and also wound pain at 8 hours and day 4 (significance lost at 3 hour). There was no significant difference in pelvic pain and use of post-operative analgesia. Our study showed better results in mean pain reduction, shoulder pain and significant reduction in post-operative analgesia requirement than them, most probably because volume of solution used by us was more hence more spread to effected site. Study by Ismail et al has similar findings as in our study but had significant prolonged decrease in VAS pain scores than our study probably because pain associated with laparoscopic ovarian drilling was very minimal.[11]

Gluck et al used a total of 9 ml of Bupivacaine 0.5%, or Sodium-Chloride 0.9% (placebo), injected subcutaneously to the trocar sites (3 ml to each trocar site), prior to skin incision.[19] In addition, 10 ml of Bupivacaine 0.5%, diluted with 40 ml of Sodium-Chloride 0.9% (a total of 50 ml solution), or 50 ml of Sodium-Chloride 0.9%, (placebo), were injected intraperitoneally at the end of the surgery. They concluded that application of subcutaneous and/or intraperitoneal local anaesthetic is not effective in reducing pain after gynaecological operative laparoscopy contrary to the results of our study. The reasons for these different results with respect to pain intensity are thought to be related with the time and the site of administration as well as the type, dose and concentration of LA used in the different groups but all above studies more or less collaborated with results of our study in decreasing the post-operative pain and VAS pain scores.

In our study total 33 (73.3%) patients required rescue analgesia but in intervention group only 11 patients (24.4%) needed rescue analgesia. Also, the total mean analgesic doses required was significantly less in Levo-bupivacaine group than control group ($p<0.001$).[17] Finding of our study were corroborated by Govil et al, the total analgesic consumption was maximum in placebo group than in Levo-bupivacaine Group and was minimum in Levo-bupivacaine along with clonidine group and this difference was statistically significant ($p<0.01$) among all the three groups. Similar kind of results were also observed by study of Papagiannopoulou et al, Ismail and colleagues, Alper et al in which the consumption of analgesics and rescue analgesia were significantly lower in the Levobupivacaine group.[11,13,15,17] In present study, after 2 hours of operative procedure, 15 (33.3%) patients in control group and six (13.3%) patients in intervention group had complained of nausea and vomiting while at 3 hours, 10 patients in control group complained of nausea and vomiting but in intervention group none of the patients complained. The difference was statistically significant ($p<0.05$). As time passed, cases of PONV were reduced in both groups for entire duration of surgery and the difference was also seen as statistically non-significant. We think that increased incidence of PONV in control group is because of more pain than intervention group and more use of rescue analgesia (tramadol) in control group which has a side effect of nausea and vomiting. Contrary to our study, Alper et al did not find significant difference in incidence of nausea between the Levobupivacaine group (45%) and the Normal saline group (65%).[15] Alper et al also found a statistically significant increase in vomiting in the normal saline group versus the Levobupivacaine group (8 vs. 0 patients, $p<0.05$).[15]

CONCLUSION

The study concluded that 20 ml of 0.5% levo-bupivacaine diluted with 40 ml of NS (total 60 ml) instilled intraperitoneally at the end of surgery before the closure of ports and port site local infiltration of 3-5 ml 0.5% levo-bupivacaine is an easy, cheap and non-invasive method which provides good analgesia in the immediate postoperative period after laparoscopic gynaecological surgery, without adverse effects, especially in the early postoperative period. There is reduced postoperative rescue analgesic requirement and reduced incidence of postoperative nausea and vomiting (PONV). This improves patient's experience after surgery and also patients can be discharged early. This simple technique

should be made an integral part of all gynaecological laparoscopic surgeries.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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