ORIGINAL ARTICLE

Randomized double blind trial of intraperitoneal instillation of bupivacaine and morphine for pain relief after laparoscopic gynecological surgeries

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ABSTRACT

Background: Intraperitoneal injection of anesthetic has been proposed to minimize postoperative pain after laparoscopic surgery. So a randomized, placebo-controlled study was conducted to compare the effectiveness of intraperitoneal bupivacaine with or without morphine for postoperative analgesia after laparoscopic gynecological surgeries. **Methods:** A total of 90 ASA I and II female patients scheduled for laparoscopic gynecological procedures were enrolled in the randomized double blind prospective study. The drug was injected intraperitoneally before the removal of trocar at the end of surgery. In group BM (*n*=30): 0.25% bupivacaine 30 ml + 2 mg morphine, in group BO (*n*=30) 30 ml 0.25% bupivacaine and in group C (*n*=30) 30 ml of saline was injected intraperitoneally. Postoperative quality of analgesia was assessed by VAS (0-100), for 24 hours and when VAS >40, rescue analgesic was administered. Total dose of rescue analgesia and side effects were noted. **Results**: Intraperitoneal instillation of bupivacaine and morphine significantly reduces immediate postoperative pain (VAS: 23.33±6.04 vs. 45.5±8.57). It also reduces pain at 4 hours after surgery in the BM group (VAS 24±12.13 vs. 41.17±7.27 in the BO group). The time of administration of first rescue analgesic was significantly higher in the BM group (6.15 hours) compared to the BO group (4.51 hours). The total dosage of rescue analgesic was more in the BO and C groups compared to the BM group. **Conclusion:** Addition of morphine to local anesthetic significantly prolonged the time to first rescue analgesic requirement and the total consumption of rescue analgesic in 24 hours without any significant increase in adverse events.

Key words: *Bupivacaine, intraperitoneal instillation, morphine, postoperative analgesia*

INTRODUCTION

Laparoscopic operative procedures revolutionized surgery with many advantages and smaller and more cosmetic incision, reduced blood loss, reduced postoperative stay, and pain, which cut down on hospital cost. However, patients undergoing laparoscopic procedures experience postoperative pain especially in the abdomen, back, and shoulder region which require proper attention. Pain intensity usually peaks during the first postoperative hours.[1]

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There are three components of pain after laparoscopic surgeries:

1. Visceral pain results from the stretching of the intraabdominal cavity and peritoneal inflammation.
2. Shoulder pain results from phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity.
3. Parietal pain due to surgical incision which is much less in intensity by virtue of its small size.[2]

The fact that pain comprises several components, providing adequate postoperative analgesia in women after operative laparoscopy while meeting the criteria for discharge within a reasonable time continues to be a challenge.

Recently peripheral use of local anesthetics for postoperative pain relief has become a popular practice after laparoscopic surgery. Intraperitoneal instillation of local anesthetic has been most promising to minimize postoperative pain after laparoscopy surgery. Several reports are available on the efficacy of intraperitoneal administration of

local anesthetic for analgesia after laparoscopic surgery. Combinations of intraperitoneal local anesthetic with many opioids have been studied in the past.[2] This prospective study was conducted to evaluate the analgesic efficacy of intraperitoneal bupivacaine and morphine after laparoscopic gynecological surgeries. To improve the reliability of results we have compared the main group, i.e., bupivacaine plus morphine with two other groups, one where bupivacaine was alone instilled and the other control group where saline was instilled.

METHODS

A total of 90 ASA I and II patients between ages 20 and 50 years scheduled for laparoscopic gynecological surgery were enrolled in a randomized double-blind prospective study after the hospital ethics committee approval and written informed consent. 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.

A conventional balanced general anesthesia was administered. The induction protocol was standard for all patients and consisted of intravenous administration of glycopyrrolate (0.2 mg), fentanyl (2 μg/kg), thiopentone sodium (5-7 mg/kg), succinylcholine (1.5 mg/kg), and vecuronium (4 mg). Anesthesia was maintained with a mixture of nitrous oxide and oxygen, isoflurane and supplements of vecuronium. Ventilation (tidal volume 8-10 mg/kg) was adjusted to maintain end-tidal carbon dioxide between 35 and 40 mmHg. Patients were placed in trendelenburg position during laparoscopy, intraabdominal pressure was maintained between 12 and 14 mmHg. At the end of the procedure, those patients who were allocated to group BM received 30 ml of 0.25% bupivacaine and 2 mg morphine intraperitoneally. A total of 7 ml each was instilled on the inferior aspect of each diaphragm and remaining 16 ml on the operative site via the umbilical port site with patient in antitrendelenburg position (after peritoneal wash and suctioning). In those allocated to group BO, 30 ml of 0.25% bupivacaine was instilled in the same pattern and in the placebo group 30 ml of saline was instilled. CO_2 was then evacuated from the peritoneal cavity and skin incision was sutured.

Anesthesia was discontinued and neuromuscular blockade was reversed with inj. neostigmine (0.05 mg/kg) and inj. Glycopyrrolate (0.004 mg/kg). Patients were extubated and shifted to the postanesthesia care unit.

Patients were randomized into one of the three groups by the closed envelope technique. A drug solution was prepared by a doctor who had not participated in the study, and drug was filled in precoded syringes and given to the surgeon. The surgeon and anesthetist in the postanesthetic care unit (PACU) were unaware of the treatment for which the patient was randomized.

Before induction of anesthesia patients were instructed how to use a 100 cm visual analog scale (VAS-0 with end-point labeled "no pain" and 100 to "worst conceivable pain"). The degree of postoperative pain was assessed at 0, 1/2, 1, 4, 8, 12, 16, 24 hours using the VAS score. Post-op analgesia regimen was standard in all groups. When the VAS score was greater than 40, patients were given inj. diclofenac sodium (75 mg IV). The time to first analgesic and total analgesic requirement during 24-hour post-op period were recorded and occurrence of adverse events was also recorded.

Statistical data

For statistical analysis, SPSS version 12.0 was used. Data were presented as mean±SD or proportion (%). Statistical analysis was performed with an ANOVA test and a $P<0.05$ was considered significant.

Observations

All three groups were similar for age, weight, duration of surgery, and type of operative procedures [Tables 1 and 2]. Mean pain scores were significantly lower in the group BM when compared to the controlled group during the entire duration of the study, while between groups BO and C the mean pain score were significantly lower in the BO group in all time intervals except in the fourth hour when the pain score was significantly higher in group BO [Table 3].

Regarding the pattern of pain, it was predominantly of generalized abdominal type among all groups [Table 4],

Table 1: Demographic and surgical data

Group	Age	Weight	Duration
BM	35.63±9.28	56.6±12.02	115.33±19.61
BO	34.3±9.26	54.63±10	114.7±40.88
C	33.7±7.69	53±6.1	115.3±16.28
P value	0.687	0.36	0.99

Table 2: Operative procedures

	Group BM	Group BO	Group C
Operative laparoscopy for ovarian cyst	19	21	21
Laparoscopic assisted vaginal hysterectomy	11	9	9

Table 3: Visual analogue scale pain score

Group	Visual analog						
	1/2	1	4	8	12	16	24
BM	21.33±6.04	23.33±7.99	24±12.13	23.66±12.65	23.83±10.30	23.66±4.07	24±3.96
BO	23.33±4.53	24.66±10.24	41.17±7.27	23±11.52	26.83±11.51	26.33±11.90	23.83±7.03
C	45.1±7.94	46.5±8.57	36.17±6.15	44±8.41	36.17±12.29	46.17±8.72	31±2
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

followed by incisional pain. None of the patients complained of shoulder pain.

Time to requirement of first dose rescue analgesia was longer in the BM group than in the group BO and was minimum in group C, indicating better and longer pain relief in the BM group compared to groups BO and C. The difference was also statistically significant among all the three groups [Table 5]. Total analgesic consumption was maximum in group C and minimum in group BM [Table 5].

Four patients in group BM and three patients in groups BO and C had complained of nausea and vomiting. There was no incidence of pruritus, excessive sedation, drowsiness or dryness of mouth in group BM patients [Table 6]. There was statistically significant difference in heart rate, systolic and diastolic BP between group BM and group C during the 24-hour period [Tables 7-9].

Intraperitoneal instillation of morphine (2 mg) with bupivacaine (0.25% 30 ml) significantly reduces immediate post-op pain (VAS 21.33±6.04 vs. 45.1±7.4. 4) [Figure 1]. It also reduces the intensity of pain even after 24 hours (VAS 24±3.96 vs. 31±2). Total analgesic consumption was also less in group BM (0.73 mean total dose vs. 2.57 mean total dose) compared to group C. The incidence of nausea and vomiting was similar and there was no significant difference among the three groups.

Table 4: Pattern of pain

Types of pain	Group			*P* value
	BM (%)	BO (%)	C (%)	
Incisional	6 (20)	9 (30)	7 (23)	0.656
Generalized abdominal	13 (43)	19 (63)	23 (77)	0.029
Perineal	1 (3)			0.364
Shoulder	0	0	0	
Total	20 (66)	28 (93)	30 (100)	

Table 5: Analgesic requirement

Types of pain	Analgestic profile		
	No. of pts given rescue analgesia	Mean time for the first dose (hours)	Mean total dose
BM	20 (66%)	6.15	0.73
BO	28 (93%)	4.51	1.43
C	30 (100%)	1.25	2.57
P value	<0.0001	<0.0001	<0.0001

Table 6: Post-operative complaints

	BM	BO	C	*P* value
Nausea/vomiting	4	3	3	0.894
Pruritus	0	0	0	
Excessive sedation	0	0	0	
Dryness	0	0	0	

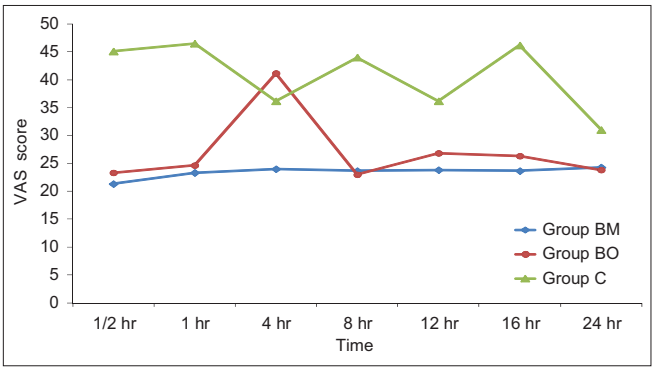

Figure 1: Comparison of visual analog scale between groups

DISCUSSION

Laparoscopic gynecological surgery being a minimally invasive procedure offers many potential advantages to the patients and hospital services. It reduces the hospital stay, expenses, and cosmetic disfigurement. Previous studies agree that postoperative pain from laparoscopy consists of three components, visceral, parietal, and referred shoulder pain distinguishing from each other in the intensity, latency, and duration.[2]

Different regimens have been proposed to relieve pain after laparoscopy surgery such as NSAIDS, opioids, local wound infiltration, intraperitoneal saline, and opioid. Opioid provides effective analgesia but can increase the incidence of nausea and vomiting after surgery and produces excessive sedation which can delay the discharge. NSAIDS may provide a rational approach not only because they avoid the side effects of opioid, but also because of observation of peritoneal inflammation after pneumoperitoneum. Infiltration of local anesthetics

Table 7: Post-operative vitals – Heart rate

Group	Heart rate at intervals (hours)						
	1/2	1	4	8	12	16	24
BM	83.76±5.28	82.73±6.27	83.66±5.93	85.23±5.98	85.06±5.50	83.86±4.70	84.6±3.23
BO	83.6±3.36	84.26±3.71	88.9±5.03	83.13±5.83	86.1±5.29	86.1±6.17	82.86±3.25
C	90.83±6.73	95.73±6.08	84.33±6.51	82.76±6.94	85.2±5.94	85.4±6.15	82.4±6.07
P value	0.77	0.12	0.002	0.276	0.746	0.31	0.13

Table 8: Post-operative vitals – Systolic BP

Group	Systolic BP at intervals (hours)						
	½	1	4	8	12	16	24
BM	126.66±7.63	126.2±8.72	125.33±8.63	129.33±7.47	127.13±7.84	122.2±7.04	122±7.02
BO	126.73±4.94	127.31±7.47	135.26±7.18	126.93±5.93	126.07±17.79	128.13±7.30	124.87±5.05
C	126.06±11.41	131.73±9.49	126.76±9.14	133±7.97	128.73±9.46	134.87±8.65	127.93±5.52
P value	0.94	0.03	0.00003	0.007	0.716	<0.0001	0.025

Table 9: Post-operative vitals – Diastolic BP

Group	Diastolic BP at intervals (hours)						
	1/2	1	4	8	12	16	24
BM	74.86±6.84	76.73±7.45	79.53±8.3	80.08±8.41	81.73±6.62	79.93±5.25	77.4±5.06
BO	79.73±5.67	81.06±6.17	86.4±4.74	81.26±5.35	83.2±5.40	82.06±4.93	80.8±4.91
C	80.46±7.87	84.13±7.26	79.2±7.47	84.93±6.31	81.53±7.56	86.13±6.36	81.2±5.02
P value	0.004	0.001	0.0002	0.02	0.57	0.0002	0.008

decreases scapular pain. Visceral pain has its maximum intensity during the first hour and is exacerbated by coughing, respiratory movements, and mobilization.[2]

Intraperitoneal local anesthetic (IPLA) have been used as "visceral blocks" since as early as 1950 and IPLA has been used to reduce shoulder tip pain, overall pain, nausea and vomiting, and hospital stay.[3] Recently peripheral use of local anesthetics for postoperative pain relief has become a popular practice after laparoscopy surgery. Among the several local anesthetic techniques for pain relief that are currently in practice like dipping local anesthetic solution into the fallopian tube, transcervical injection, mesosalpingeal, and rectus sheath blockade, the instillation of local anesthetic intraperitoneally has been most promising.[4]

Intraperitoneal instillation of 20 ml of 0.5% bupivacaine provides effective analgesia with plasma concentration below toxic levels (0.92-1.14 μg/ml). Several reports have shown that the range of mean plasma concentration after intraperitoneal administration of plain bupivacaine 100-150 mg. is well below toxic concentration of 3 μg/ml.[1,5] Narchi *et al.* showed that intraperitoneal instillation of 100 mg bupivacaine did not cause toxicity. This technique is safe with good pain relief in initial few hours.[6]

The rationale for choosing the intraperitoneal route is to block the visceral afferent signaling and potentially modifying visceral nociception and provides analgesia. The local anesthetic inhibits nociception by affecting nerve membrane associated proteins and by inhibiting the release and action of prostaglandins and other agents that sensitize or stimulate the nocicepters and contribute to inflammation.[4] However, absorption from large peritoneal surface may also occur, which may be a further mechanism of analgesia.

We chose bupivacaine for our study because of its potency and prolonged duration of action. The half-life of bupivacaine is between 5 and 16 hours.

We have used 75 mg bupivacaine in our study; none of our patient developed any signs of toxicity. In addition to this, we added 2 mg of morphine to 30 ml of 0.25% bupivacaine which further increased the efficacy of intraperitoneal bupivacaine after laparoscopic surgery. In a similar trial using pethidine performed by O Hanlon, it was found that intraperitoneal pethidine analgesia was superior to an equivalent dose of IM pethidine for the postoperative pain relief in patients undergoing laparoscopy cholecystectomy.[7] Intraperitoneal pethidine may have the potential to provide additional analgesic benefits because of the combined opioid agonistic and local anesthetic properties.[7] Two different studies on the effect of IP instillation of opioid showed that morphine was ineffective in providing

analgesia while meperidine achieved adequate pain relief. This may be because the intact peritoneum preventing the entry of hydrophilic morphine molecules and blocks their access to the neural receptors. Inflammation disrupts the peritoneal barrier and consequently the access of opioid agonists to the sensory neurons is facilitated producing analgesia only in swollen tissue.[5] Since meperidine is a lipophilic opioid, it can provide better analgesia. The effect of meperidine appears to be produced by its action on to independent pathways-opioid receptor pathway which subserve analgesic action and sodium channel which subserve local anesthetic action.[5] Administration of lipophilic opioid (Fentanyl or Meperidine) in the peritoneal cavity provides better analgesia.[2]

By using IPLA it may be possible to modulate peritoneal and visceral signaling to the brain, thereby attenuating the metabolic impact of visceral surgery. There is a blockade of free afferent nerve endings in the peritoneum. Systemic absorption of local anesthetic from the peritoneal cavity may also play a part in reduced nociception. The local anesthetics have antiinflammatory actions and mechanisms of these effects may be prostaglandin antagonism, inhibition of leukocyte migration, and lysosomal enzyme release, all effects seen *in vitro* and animal studies. A proinflammatory cytokine cascade in the peritoneal cavity, with direct action on the visceral afferents and the vagus as a major vehicle, is a feasible contributor to postoperative visceral pain perception and the "sickness response." By using IPLA it may be possible to modulate peritoneal and visceral signaling to the brain, thereby attenuating the metabolic impact of visceral surgery. Metaanalysis by Kahokehr revealed an overall reduction of pain, opioid analgesia use, need for rescue analgesia, postoperative cortisol, and glucose response.[8] Kahokehr *et al*. investigated the effects of intraoperative instillation and postoperative infusion of IPLA ropivacaine after colectomy improves early surgical recovery.[9]

On analyzing the VAS scores for pain the mean pain score of the control group at initial ½ hour of postoperative period was 41 + 5.4. This suggested that the postoperative pain of laparoscopic surgeries can be significant and residual analgesic effect of fentanyl given at the time of induction was not satisfactory in the immediate postoperative period.

On analysis of the VAS score for pain, it was shown that group BM had better pain relief than the control group at all time intervals and this difference was also statistically significant ($P<0.05$). Chudrigar *et al*. had done the same study in laparoscopic cholecystectomy and he found less VAS score in study group patients for 3 hours.[10] On comparing the VAS score of the BO group and control group, the BO group showed statistically significant reduction in pain scores at all time intervals except in the fourth hour. Pain scores of group BO are higher than the C group in the fourth hour. This may be due to the combined effect of wearing off of the effect of bupivacaine and modification of the pain score of the C group by rescue analgesic.

In our study, there was no shoulder pain in patients because the residual intraperitoneal CO_2 was emptied carefully by the surgeon. Hernandez *et al*. found a low incidence of shoulder pain in all groups.[2]

Among the two treatment groups significant difference in pain scores exists only in the fourth hour, where the mean pain score of group BO and group BM was 41.2±7.27 and 24±12.13 respectively. This difference is suggestive of prolongation of duration of analgesia by combining intraperitoneal morphine with bupivacaine.

Patric Narchi *et al*. have reported that intraperitoneal infiltration of both bupivacaine and lignocaine are effective in reducing postoperative shoulder pain for 24 hours.[6]

Studies conducted by Chundrigar *et al*. and Szem *et al*. showed similar results with mean duration of analgesia lasting for 2-8 hours only, which is in concordance with pharmacological profile of the drug also.[10,11] Malhotra *et al*. found that 100 mg of intraperitoneal bupivacaine provides pain relief for a longer duration (8 hours) compared to 50 mg of drug (4-6 hours). Analgesic requirement was also less in the 100 mg group after laparoscopy gynecological surgery.[12]

Comparing the analgesic requirements revealed that a number of patients who received rescue analgesia is significantly lower in the BM group compared to group BO and group C. Time for the first analgesic dose was significantly prolonged in group BM than in other two groups; and also the total analgesic doses required was significantly less in group BM. These findings suggest that the addition of morphine to intaperitoneal bupivacaine significantly prolongs the duration of analgesia. Sallyann and colleagues observed that the combination of intraperitoneal bupivacaine plus meperidine provided better pain relief than combination of intraperitoneal bupivacaine plus intramuscular meperidine following laparoscopic tubal ligation and they suggested that the analgesia observed may be produced by the local anesthetic effect of meperidine seen both *in vitro* and *vivo*.[13] In our study, the duration of analgesia prolonged by combining morphine to intraperitoneal bupivacaine. We believe that the effect might be due to a mild degree of inflammation that might set in within few hours of surgery which facilitates the action of morphine on visceral nociceptive receptors.

Regarding adverse effects, only nausea and/or vomiting was

there in 10 out of 90 patients and was equally distributed in all groups. There was no pruritus, excessive sedation or dryness of mouth in the BM group patients. This may be explained as the dose of morphine used in our study for intraperitoneal instillation was significantly less to produce systemic side effects.

Vital parameters like HR, BP, and SPO2 are important indicators of patient comfort as the values correlated well with high vas scores.

CONCLUSION

Intraperitoneal instillation of local anesthetic and opioid is an easy, cheap, and noninvasive method which provides good analgesia in the immediate postoperative period after laparoscopic surgery. The combination of intraperitoneal bupivacaine with morphine is superior to the plain bupivacaine for the relief of postoperative pain in patients undergoing laparoscopic gynecological surgery without any significant increase in adverse events. This peripheral action of opioid particularly in inflamed tissue provides support for the existence of peripheral opioid receptors and gives a new approach to pain management which may have great clinical benefits.

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