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Research Article

COMPARISON BETWEEN INTRAPERITONEAL INSTILLATION OF PLAIN VERSUS CARBONATED BUPIVACAINE AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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A B S T R A C T

Background: Laparoscopic surgeries are becoming more acceptable and many methods are being tried to reduce postoperative pain.
Material and Method: 200 patients divided into: group 1 (BP) patients received 0.5 % plain Bupivacaine and Group2 (BC) patients received Carbonated 0.5% Bupivacaine. Local anesthetic solution was instilled intraperitoneally through infra-umbilical incision before removal of trocar at the end of surgery. Degree of post operative pain was assessed using VAS in case of spontaneous pain and VRS on arrival inrecovery room, immediately after surgery and thereafter 1 hourly till 12 hours postoperatively. Patients having VAS >4 after surgery were administered a bolus of Diclofenac (75 mg) i.v. as rescue analgesic.
Results: VAS scores immediately postoperatively were 4.08±0.78 in BP and 3.54±0.78 in BC [$p<0.05$]. No significant difference in VAS scores from 1hour to 10th hour postoperatively. VAS score at 11th hour were 2.42±0.74 in BP and 2.20±0.51 in BC [$p<0.05$] but no significant difference at 12th hour. Immediate post operative rescue analgesic requirement, was significantly more in BP than in BC patients [$p<0.05$]. From 1st hour to 5th hour analgesic requirement rate was found almost same in both the groups. At 6th hour rescue analgesic requirement was significantly more in BP than in BC [$p<0.05$]. There was no significant difference found in analgesic requirement rate from 7th hour to 12th hour in both the groups.
Conclusion: We concluded that Intraperitoneal instillation of carbonated bupivacaine is superior to plain bupivacaine for the relief of post operative pain in patients undergoing laparoscopic surgery.

INTRODUCTION

Laparoscopic operative procedures have revolutionized surgery with many advantages: a smaller and more cosmetic incision, reduced blood loss, reduced postoperative stay and pain, which cut down on hospital cost. Although, there are clear benefits compared with open surgery, post-operative pain after laparoscopic cholecystectomy remains an issue.

Many methods have been used to reduce postoperative pain including non steroidal antiinflammatory drugs (NSAIDS), local anaesthetics and opiods with varying success. Administration of intraperitoneal local anesthetic (LA), either during or after surgery, is used by many surgeons as a method of reducing postoperative pain. This technique was first evaluated in patients undergoing gynecological laparoscopic surgery by Narchi *et al*[1] Its application in laparoscopic cholecystectomy was initially examined in a randomized trial in 1993 by Chundrigar *et al*[2]. Since then, many trials evaluating the efficacy of intraperitoneal LA in laparoscopic cholecystectomy have been published world-wide. Intraperitoneal administration of local anesthetic has not only proven to be effective in the relief of postoperative pain, but also in nausea and vomiting after laparoscopic operations.[3-7]

Another group also reported that visual analog pain scores and consumption of analgesics were significantly lower in patients receiving intraperitoneal bupivacaine immediately after creation of pneumoperitoneum than at the end of surgery.[8]

It is known that local anesthetic drugs are sold as natrium hydrochloride solution to keep high solubility and stability. But in this case, pH of solution is lower than pKa, so that non-ionized to ionized ratio will move up right. Whereas to penetrate neuron membrane, non-ionized lipid soluble solution is needed. So, local anesthetic drugs need extra cellular depolarization process first to change the ionized form into non-ionized. This process takes time that will lengthen the onset of action. Onset of local anesthetic action reflects

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diffusion of the non ionized lipid-soluble form across nerve membranes. Indeed, local anesthetic with pKa's nearest physiologic pH have the most rapid onset of action reflecting the presence of an optimal ratio of ionized to non-ionized fraction.

Alkalinization of local anesthetic solution was frequently performed by addition of Na-bicarbonate to hasten the onset and increase block potential.[8] It is also hypothetised that alkalization of local anesthetic neutralizes the action of residual carbon-dioxide in the peritoneal cavity.

There are no studies regarding intraperitoneal use of bupivacaine with sodium bicarbonate to reduce post operative analgesia. So this study was planned to show comparative efficacy of bupivacaine [plain] and carbonated bupivacaine in reducing post operative pain after laparoscopic cholecystectomy and also the side effects if any.

MATERIAL AND METHODS

After the study protocol was approved by local ethics committee a double blind randomized controlled trial was carried out on 200 patients in S.S. Hospital, IMS, BHU during November 2013 to June 2015, the patients were divided into two groups: Group 1 (BP) - Patients received 0.5 % plain Bupivacaine in a dose of 2mg/kg diluted in normal saline to make a solution of 50 ml, Group 2 (BC): Patients received Carbonated 0.5% Bupivacaine in a dose of 2mg/kg diluted in normal saline to make a solution of 50ml (Carbonated Bupivacaine was prepared by adding 1 ml of 8.4 % sodium Bicarbonate for each 20 ml of Bupivacaine). Patients aged between 20-70 years, of either sex belonging to ASA physical status I to III with ± 20 % ideal body weight were included in the study. Patients with following underlying co-morbidities were excluded from the study: Patients < 20 yrs and > 70 yrs of age, patients who are taking analgesics, any cognitive impairment, coagulopathy, infection at local site, congestive heart failure, uncontrolled diabetes mellitus, severe respiratory distress, systemic infection, allergic reaction to any of the drugs used, emergency operation, history of malignancy or alcohol or drug abuse, confirmed local anesthetic toxicity and chronic pain syndrome. Patients were examined for airway assessment, blood pressure (systolic, diastolic, mean), heart rate and other relevant systems. Various laboratory investigations including hemoglobin, total leukocyte count, fasting blood sugar, E.C.G. and chest X-ray, were analyzed and recorded. Patient was also informed about the nature of study and that they can be allotted in any of the study groups and a written consent was obtained from them.

In the operating room, base line heart rate, non-invasive arterial blood pressure, oxygen saturation values were recorded.18 G peripheral venous canula was inserted on the dorsal side of patient's left hand and 5ml/kg ringer lactate was given intravenously to all patients before the patients were premedicated. Drug solution was filled in pre-coded 50ml syringe.

Before induction of anaesthesia, the patients were instructed how to use VAS. All patients undergoing laparoscopic cholecystectomy received premedication in the form of glycopyrrolate (0.005mg/kg) and Ondansetron (0.1 mg/kg) intravenously half an hour prior to induction of anaesthesia and fentanyl (3 micro gm/kg) intravenously just before induction. Surgery was carried out under general anaesthesia with propofol (2-2.5 mg/kg) for induction and vecuronium (0.1 mg/kg) to facilitate tracheal intubation. Anesthesia was maintained with 60 % N_2O in oxygen with 0.5 %to 1 % Isoflurane. Adequate muscle relaxation was achieved with intermittent doses of vecuronium bromide (0.01 mg/kg). Ventilation (tidal volume 8 - 10 ml/kg) was adjusted to maintain end tidal carbon dioxide between 35 and 40 mmHg. Patients were placed in 15 - 20 degree reverse trendelenburg position during surgery. During laparoscopy, intra-abdominal pressure was maintained at 12 mmHg. The CO_2 was carefully evacuated at the end of surgery by manual compression of abdomen. The local anaesthetic solution as per protocol was instilledintraperitoneally through the infra-umbilical incision before the removal of trocar at the end of the surgery, in trendelenburg position to facilitate dispersion of drug in sub hepatic region. Patients were shifted to recovery room only after complete recovery from anaesthesia. All patients were administered oxygen therapy and monitored for next 12 hours in post anaesthesia care unit. Non-invasive blood pressure, heart rate and peripheral oxygen saturation were recorded immediate post operatively and then every hour till next 12 hours.

The degree of post operative pain was assessed using the VAS in case of spontaneous pain and VRS on the arrival in the recovery room, immediately after surgery and there after 1 hourly till 12 hours post operatively. Those patients having VAS >4 after surgery were administered a bolus of Diclofenac (75 mg) i.v. as rescue analgesic. A second dose of diclofenac was repeated after 1 hour of the first dose. Ondansetron (0.1mg/kg i.v.) was administered on complaint of nausea.

Time to first analgesic requirement, total analgesic consumption in the first12 hours post-operatively and occurrence of adverse events were also recorded. Patients were regularly asked about pruritis and shoulder pain. Blood pressure was regularly monitored for episodes of hypotension (MAP <60 mmng). Heart rate was regularly monitored for episodes of bradycardia (HR < 60). Total duration of surgery was recorded in all the cases. All observations such as post operative pain intensity on VAS and VRS, analgesic request rate, total analgesic consumption, other adverse effects after local anesthetic infiltration were noted down.

Statistical analysis was performed using SPSS software version 16.0. For comparing two groups of mean student's t-test was used. For categorical data Chi-square test was used. p values <0.05 were considered as statistically significant.

RESULTS

In the present study, a total of 200 patients were taken. Two study groups were made each consisting of 100 patients. The mean age was 50.54±13.98 years in BP group as compared to 52.20±14.14 years in BC group showed no statistically significant difference. Other parameters like sex, weight, ASA grade were also comparable. The laboratory and hemodynamic parameters like haemoglobin, total leukocyte count, fasting blood sugar, heart rate, systolic, diastolic and mean arterial pressure, oxygen saturation and duration of surgery were found to have no statistically significant difference.

The immediate post operative VAS score was significantly higher in BP as compared to BC. VAS scores immediately post operatively were 4.08±0.78 in BP and 3.54±0.78 in BC [p<0.05]. No significant difference was found between BP and

BC in the VAS scores from 1hour to 10th hour post operatively. At 11th hour VAS scores were significantly higher in BP as compared to BC. VAS score at 11th hour were 2.42±0.74 in BP and 2.20±0.51 in BC [p<0.05]. At 12th hour there was no significant difference in VAS scores in both the groups (Figure 1).

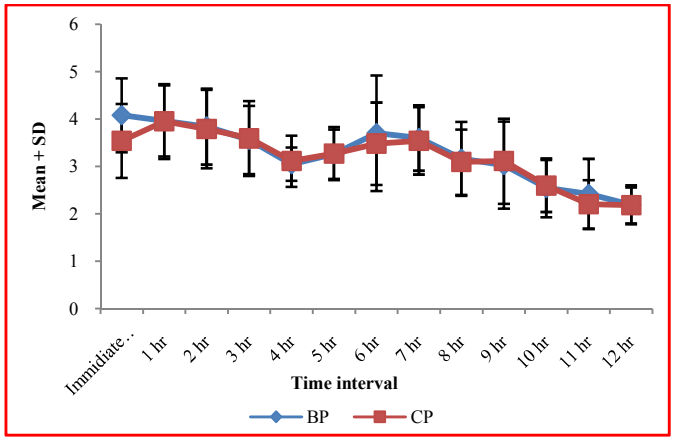

Figure 1 Comparison of Mean VAS score between two groups

Similarly, the immediate post operative VRS scores were significantly higher in BP as compared to BC. VRS score immediately post operatively was 1.21±1.19 in BP and 0.87±1.07 in BC [p<0.05]. No significant difference was found between BP and BC in the VRS scores from 1hour to 12th hour post operatively (Figure 2).

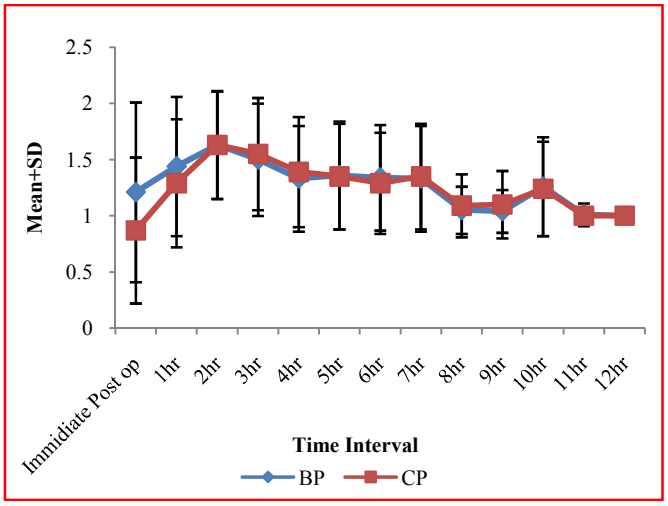

Figure 2 Comparison of Mean VRS score between two groups

The immediate post operative rescue analgesic requirement, was significantly more in BP than in BC patients [p<0.05]. From 1st hour to 5th hour analgesic requirement rate was found almost same in both the groups. At 6th hour rescue analgesic requirement was significantly more in BP than in BC [p<0.05]. There was no significant difference found in analgesic requirement rate from 7th hour to 12th hour in both the groups.

Time to first analgesic requirement was shorter in BP than in BC and total rescue analgesic consumption was significantly more in BP than in BC as shown in table 1. The incidence of pruritis, emesis, hypotension, bradycardia and shoulder pain was almost similar in both the groups (Table 2).

Table 1 Comparison of First Analgesic Requirement and Total Rescue Analgesic consumption between two groups

	BP	BC	p-value
First Analgesic Requirement [in minutes]	96.60±107.16	116.40±101.20	0.181
Total Rescue Analgesic consumption [in mili-gram]	124.50±35.70	103.50±36.58	<0.001

Table 2 Adverse effects

	BP		BC		χ^2	p-value
	No.	%	No.	%		
Pruritus	4	4	1	1	1.846	0.174
Emetic Symptoms	50	50	56	56	0.723	0.395
Hypotension	36	36	33	33	0.199	0.655
Bradycardia	15	15	13	13	0.166	0.684
Shoulder pain	12	12	10	10	0.00	1.00

DISCUSSION

Laparoscopic cholecystectomy is one of the most frequently performed elective general surgical operations. It is performed as a day case or short stay procedure and therefore, the provision of adequate postoperative pain relief is of considerable importance. Patients usually experience postoperative pain, especially in the upper and lower abdomen, back and shoulder region.[9]Pain intensity usually peaks during the first few postoperative hours and is maximum in first 12-24 hours and declines over next two to three days. Postoperative pain is unpredictable, which explains the need for systematic prevention of pain before patient wake up from anaesthesia. Instillation of intraperitoneal LA to reduce postoperative pain has been studied through randomized trials for more than 10 years.[10]

Our study shows that immediate post operative VAS scores was significantly higher in BP as compared to BC. VAS scores immediately post operatively were 4.08±0.78 in BP and 3.54±0.78 in BC [p<0.05]. No significant difference was found between BP and BC in the VAS scores from 1 hour to 10th hour post operatively. At 11th hour VAS scores were significantly higher in BP as compared to BC. VAS score at 11th hour were 2.42±0.74 in BP and 2.20±0.51 in BC [p<0.05]. At 12th hour there was no significant difference in VAS scores in both the groups.

The immediate post operative VRS scores were significantly higher in BP as compared to BC. VRS score immediately post operatively was 1.21±1.19 in BP and 0.87±1.07 in BC [p<0.05]. No significant difference was found between BP and BC in the VRS scores from 1hour to 12th hour post operatively. Above findings suggest that addition of 8.4% sodium bicarbonate fastens the onset of analgesic action of bupivacaine. This rapid onset may be due to more formation of non-ionized form than ionized form of bupivacaine because of alkalinization.[8] As the non ionized form crosses nerve membrane more easily, so blocks the conduction of nerve fibres more rapidly.

A systematic review and meta-analysis[11] has evaluated the intraperitoneal ropivacaine instillation versus no intraperitoneal ropivacaine instillation for laparoscopic cholecystectomy and found that there was no significant difference in the Post-anesthesia care unit (PACU) stay time between the two group.

Oza VP *et al*[12] did a comparative study of postoperative analgesic effect of intraperitoneal instillation of dexmedetomidine with bupivacaine and bupivacaine alone after laparoscopic surgery and

concluded that intraperitoneal instillation of dexmedetomidine with bupivacaine prolongs the duration of postoperative analgesia as compared to that with bupivacaine alone. And also there is less number of rescue analgesics that are required postoperatively when dexmedetomidine is supplemented as an adjuvant to bupivacaine.

A study done by Refaie *et al*[13] concluded that intensity of pain is reduced with bupivacaine than normal saline group. Gupta *et al*[10] also showed that intraperitoneal instillation of fentanyl [100 microgm] along with bupivacaine significantly reduces immediate postoperative pain.

Newcomb *et al*[14] and Sheinin B *et al*[15] studied the effect of intra-peritoneal bupivacaine on postoperative pain in patients undergoing elective laparoscopic cholecystectomy. They concluded that the use of intraperitoneal instillation of bupivacaine did not decrease postoperative pain as compared to placebo.

Upadya M *et al* did Comparison of intra-peritoneal bupivacaine and intravenous paracetamol for postoperative pain relief after laparoscopic cholecystectomy. They concluded that although local anesthetic infiltration and intra-peritoneal administration of 0.5% bupivacaine decreases the severity of incisional, visceral and shoulder pain in the early postoperative period, IV paracetamol provides sustained pain relief for 24 postoperative hours after elective laparoscopic cholecystectomy.[16]

Ramprasad TVS did the study titled efficacy of intra peritoneal and port sites administration of bupivacaine on postoperative pain following laparoscopic cholecystectomy - a randomized clinical trial. He concluded that the installation of 0.25% bupivacaine on the gallbladder bed and infiltration of trocar sites significantly reduces the severity of post-operative pain and analgesic requirement in the postoperative period following laparoscopic cholecystectomy.[17]

A study was done by Marwoto *et al*[8] on patients who would underwent lower abdomen and extremity surgery, with the aim to evaluate the onset of bupivacaine which has been added with sodium bicarbonate on epidural block. Data analysis showed that onset of both motor and sensory block was significantly rapid in treatment group than control group [$p<0.05$]. Our study also revealed that addition of sodium bicarbonate in bupivacaine significantly fastens the onset of action of bupivacaine.[8]

In our study, the immediate post operative rescue analgesic requirement, which is significantly more in BP than in BC patients. In BP, 32% patients required rescue analgesia while in BC only 17% patients required rescue analgesia immediate postoperatively [$p<0.05$]. From 1st hour to 5th hour analgesic requirement rate was found almost same in both the groups. At 6th hour rescue analgesic requirement was significantly more in BP than in BC. In BP, 36% patients required rescue analgesia while in BC only 20% patients required rescue analgesia at 6th hour post operatively [$p<0.05$]. There was no significant difference found in analgesic requirement rate from 7th hour to 12th hour in both the groups. Above findings suggest that addition of 8.4% sodium bicarbonate has better obtundation of factors leading to pain after laparoscopic cholecystectomy. However, this effect does last only about one hour postoperatively. This may be due to neutralization of carbonic acid formed by residual CO_2.

Time to first analgesic requirement was shorter in BP [96±107.16] than in BC [116±101.20] but it was not statistically significant [$p>0.05$]. In a study done by Rafaei *et al*[13] revealed that the number of patients who needed postoperative analgesia in group I (bupivacaine) was significantly lower than group II (control) (7 out of 32 versus 19 out of 31] ($P<0.05$). The time in minutes to first analgesic in patient of group was significantly higher compared with control group ($P <0.05$).

The total rescue analgesic consumption was significantly more in BP than in BC. Total rescue analgesic consumption in BP was 124.50±35.0 and in BC it was 103±36.58 [$p<0.05$]. Pasqualucci *et al* also proved in a study that pain intensity (visual analog and verbal rating scales) and analgesic requirements were significantly less in the group receiving bupivacaine after surgery compared to placebo.[18]In our study rapid onset of analgesic action of bupivacaine occurs in BC patients due to alkalinization of bupivacaine, due to this most of the patients in BC did not need rescue analgesic in immediate post operative period[in contrast to BP patients]. Because of this total consumption of recue analgesic decreased in BC patients.

The incidence of pruritis, emesis, hypotension, bradycardia and shoulder pain was almost similar in both the groups.Incidence of emetic symptom was quite high in both the groups.50% patients in BP and 56% patients in BC developed emetic symptom. In a studyby Goldstein *et al* in 2000 tested the hypothesis that bupivacaine instilled at the end of laparoscopic gynecologic procedures is able to prevent postoperative nausea and vomiting at wake-up and during the first 24 h.[19] In contrast in our study more than 50% patients complained of PONV in both the groups. The retained CO_2 causes intraperitoneal stretching and diaphragmatic irritation and this may cause higher incidence of emetic symptoms.

Shoulder pain is a common outcome after laparoscopic cholecystectomy and can delay return to normal activities, maximum incidence of shoulder pain occurs night after surgery.[20] Incidence of shoulder pain was found 12% in BP and 10% in BC. Study done by Gupta *et al*[10] using bupivacaine and Kim *et al*[22] using ropivacaine showed statistically decreased incidence of shoulder pain 24 hours after surgery [$p<0.05$].

Limitation of this study was that, we measured the pain score only for 12 hours. For more precise results pain score should be measure at least for 24 hours and different pain assessment scales should also be used, for proper assessment of visceral, somatic and shoulder pain.So a study with larger sample and longer duration of monitoring will provide more precise results.

CONCLUSION

We found that intaperitoneal instillation of local anesthetic is an easy, cheap and non invasive method which provides good analgesia in the post operative period after laparoscopy. We concluded that Intraperitoneal instillation of carbonated bupivacaine is superior to plain bupivacaine for the relief of post operative pain in patients undergoing laparoscopic surgery without any significant increase in adverse events. Carbonated bupivacaine not only reduces the intensity of pain but also reduces the total dose of rescue analgesic consumption

as compare to plain bupivacaine. Onset of analgesic action is also rapid with carbonated bupivacaine as compare to plain bupivacaine.

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