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Research Article

Evaluation of Intraperitoneal and Port Site Infiltration of Bupivacaine in Combination with Fentanyl for Management of Postoperative Pain following Laparoscopic Cholecystectomy: A Double Blind Randomized Study

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Abstract

Background: Despite the reported advantages of laparoscopic cholecystectomy management of postoperative pain following this surgery still remains a significant clinical challenge. Our study was designed to evaluate efficacy of bupivacaine in combination with fentanyl for intraperitoneal instillation and port site infiltration, for management of postoperative pain in patients undergoing laparoscopic cholecystectomy.

Patient and methods: This was a Prospective, double blind, randomized study. 90 patients undergoing elective laparoscopic cholecystectomy under general anesthesia were randomly allocated into three groups. Group I received 50ml of 0.2% bupivacaine alone. Group II received 50 ml of 0.2% bupivacaine with 50µg fentanyl and group III received 50ml of 0.2% bupivacaine with 100µg fentanyl as intraperitoneal instillation and port site infiltration. In the postoperative period pain, nausea- vomiting and sedation was recorded at 0, 2, 4, 6, 12 and 24 hours.

Results: The three groups were comparable in regards to the demographic profile. In all the three groups VAS was less than 3 at each time interval. None of the patients required rescue analgesia. The intergroup comparison of VAS scores at different intervals showed that group receiving 50ml of 0.2% bupivacaine with 100µg fentanyl had lower VAS score. There was no statistical difference in postoperative nausea and vomiting between the three groups.

Conclusions: Intraperitoneal instillation along with port site infiltration of fentanyl and bupivacaine combinations provides effective and safe postoperative analgesia in patients undergoing laparoscopic cholecystectomy.

Keywords: Intraperitoneal analgesia; Fentanyl; Bupivacaine; Port site infiltration; Laparoscopic cholecystectomy

Introduction

The field of surgery has been revolutionized by the advent of laparoscopic operative procedures. The numerous reported benefits of the laparoscopic procedures like reduced blood loss, lower pain intensity, better cosmesis, and shortened hospital stay have led to its increasing success over the last couple of decade [1,2]. However laparoscopic surgery is not entirely pain free procedure. Variable degree of postoperative pain following laparoscopic surgery has been observed [3,4]. The pain following laparoscopic surgery is a combination of somatic as well visceral pain arising due to surgical incision, stretching of the intra-abdominal cavity, peritoneal inflammation, and phrenic nerve irritation caused by residual carbon dioxide in the peritoneal cavity [4-7].

Various modalities like opioids, non steroidal ant inflammatory drugs (NSAIDS), gabapentin, clonidine, N-methyl D-aspartate (NMDA) receptor antagonist, incisional and intraperitoneal local anesthetics have been used to manage the postoperative pain following laparoscopic cholecystectomy, however management of postoperative pain still remains a significant challenge since pain is the chief reason behind prolonged hospital stay following laparoscopic cholecystectomy in as many as 17-41% patients [7-11].

Few studies have evaluated the combination of both intraperitoneal and port site infiltration of local anesthetic and opioids; however there is a dearth of studies evaluating fentanyl and bupivacaine combination for post laparoscopic cholecystectomy pain. [12-15]. With this in mind the above study was designed a prospective randomized study to evaluate the effect of intraperitoneal and port site infiltration of bupivacaine in combination with fentanyl for management of postoperative pain following laparoscopic cholecystectomy

Materials and Methods

Trial design and procedures

Following approval of the institutional ethics committee, this prospective, double blind, randomized study was performed on 90 American Society of Anesthesia (ASA) grade I and II patients admitted to our institution, undergoing elective laparoscopic cholecystectomy under general anesthesia. Following detailed pre-anesthetic evaluation, a written informed consent was taken from all patients. Patients who were within 16-60 years of age, of either sex or ASA grade I and II were included. Exclusion criteria were patients with age less than 16 years and more than 60 years, patient with history of drug allergy to fentanyl or amide group local anesthetics, patients using non steroidal anti-inflammatory drugs (NSAIDS), opioids or any other analgesic. Cases in which surgery was converted to open procedure were also excluded. Patients were randomly allocated by computer generated random tables to one of three groups comprising 30 patients each.

Group I (group bupivacaine): patients received 50 ml of 0.2% bupivacaine (n=30)

Group II (group bupivaciane + fentanyl 50µg): patients received a combination of 50ml of 0.2% bupivacaine and 50µg fentanyl. (n=30)

Group III (group bupivacaine + fentanyl 100µg): patients received a combination of 50 ml of 0.2% bupivacaine and 100 µg fentanyl. (n=30).

The above mentioned drug solution was prepared by a doctor who had not participated in the study and was unaware of the study protocol. 50/100 µg of fentanyl was added to 20 ml of 0.5% bupivacaine which was further diluted with normal saline to yield a combination of 50 ml of 0.2% bupivacaine with 50/100µg fentanyl. Surgeon and the anesthesiologist were unaware of the drug solution to which each patient was randomized. 10 ml of the above solution was sprayed immediately following the creation of pneumoperitoneum (before starting dissection) by the surgeon into the hepatodiaphragmatic space (between diaphragm and the liver lobes), and 10 ml solution into the area of gall bladder. At the completion of surgery before the trocars were withdrawn, the surgeon sprayed an additional 20 ml solution into the same areas. The remaining 10 ml solution was infiltrated equally in all the four port sites.

Anesthetic Technique

All patients were premedicated with intravenous midazolam 0.03 mg/kg, injection metoclopramide 10mg, tramadol 1mg/kg and pentazocine 0.6mg/kg 10minutes prior to induction of anesthesia. Standard monitors were attached. Anesthetic technique was standardized. Following preoxygenation for three minutes, anesthesia was induced with propofol 2mg/kg. Succinylcholine 1.5mg/kg was used to facilitate endotracheal intubation. Anesthesia was maintained with nitrous oxide 66%, oxygen 33% and halothane 0.5% and vecuronium. After 45 minutes of surgery, injection tramadol 0.5 mg/kg was repeated. Neuromuscular blockade was reversed with neostigmine 5.0 microgm/kg and glycopyrrolate 1.0 microgm / kg.

Surgical technique

All the surgeries were performed by a single team of surgeons with standard surgical technique using four ports. Intraperitoneal access was established through a 2-cm umbilical incision. A carbon dioxide pneumoperitoneum was created using an insufflation pressure of 12 mmHg and a maximum flow of 2L/minute, which was restricted electronically during creation of the pneumoperitoneum and at later stages of the procedure.

In both the groups, postoperative analgesia was standardized. Injection diclofenac 1 mg/kg was started 8 hourly in postoperative ward as per routine analgesic protocol being followed in our institution by surgeons starting from the time when patient has arrived in postsurgical ward from operation theatre. Rescue analgesia was planned using intravenous tramadol 1mg/kg if the VAS was >3. If patient had VAS >3 even 30 minutes after receiving tramadol then fentanyl 2µg bolus was planned to be given intravenously.

In all the groups' presence of pain, nausea and sedation was assessed at 0 hour (time at arousal from anesthesia), 2, 4, 6, 12 and 24 hours after completion of surgery. Time to first rescue analgesia requirement apart from standard postoperative analgesia regimen, total analgesic consumption in the first 24 hours postoperatively, and occurrence of adverse events (e.g. Tinnitus, circumoral numbness, twitching, pruritus, and respiratory depression) were also recorded. All postoperative observations were recorded by investigators and nursing staff, who were blinded for the study protocol.

Pain assessment

Eleven point Visual analogue score (VAS) score (0= no pain and 10= worst possible pain), was used to assess pain at rest, at above intervals..

Nausea and vomiting was assessed on a three point score:

0. No nausea/vomiting

1. Nausea

2. Vomiting

Nausea lasting for more than 10 minutes and vomiting was planned to be treated with intravenous ondensetron 0.1 mg/kg body weight.

Statistical analysis

Statistical analysis was performed using a standard statistical program. All data were analyzed using IBM SPSS Statistics 18.0software. For continuous variable one way ANOVA was used and for non continuous variable chi square test was used. $p < 0.05$ at 95% confidence interval was considered statistically significant. The power of the study was 80%.

Results

There was no difference between the three groups in regards to the demographic characteristics and the duration of surgery (Table 1). In all the three groups the Visual Analog Scale (VAS) score was less than 3 at each time interval (Table 2). None of the patients in either group required rescue analgesia. Intergroup comparison of VAS score at different time intervals showed that the group receiving bupivacaine with 100µg fentanyl had the lowest VAS score at all time intervals however this was statistically significant only at 4 hrs and 6hrs. The incidence of nausea and vomiting at 4 hrs was also highest in the group III (15%) as compared to group I (10%) and group II (7%) , however it was also not statistically significant (Table 3) . There was no sedation and pruritus in patients of any group at any time interval and the three groups were comparable.

	Group	Mean ± SD	F value	Sig
Age (Years) (Mean ± SD)	I	41.96 ± 8.91	1.278	0.284
	II	38.30 ± 10.43		
	III	39.86 ± 7.07		
Weight (Kg) (Mean ± SD)	I	47.20 ± 5.71	1.652	0.198
	II	49.36 ± 6.92		
	III	50.06 ± 6.41		
Height (cm) (Mean ± SD)	I	154.50 ± 5.19	1.582	0.212
	II	154.60 ± 4.38		
	III	156.63 ± 6.02		
Duration(min) (Mean ± SD)	I	65.63 ± 3.93	2.613	0.079

Table 1: Demographic characteristics of the patients in the three groups *all data is expressed in mean ± standard deviation. P<0.05 considered significant SD-standard deviation, M-male, F-female, Group I-patients receiving bupivacaine , Group II- Patients receiving bupivacaine+ fentanyl 50µg, Group III- patients receiving bupivacaine + fentanyl 100µg

VAS	Group	Mean ± SD	F value	P-Value
VAS at 0 hrs	I	0.333 ± 0.479	0.378	0.686
	II	0.266 ± 0.449		
	III	0.233 ± 0.430		
VAS at 2 hrs	I	2.30 ± 0.466	1.759	0.178
	II	2.16 ± 0.461		
	III	2.06 ± 0.520		
VAS at 4 hrs	I	2.40 ± 0.563	4.929	0.009
	II	2.33 ± 0.479		
	III	1.93 ± 0.789		
VAS at 6 hrs	I	1.70 ± 0.595	12.39	0.000
	II	1.06 ± 0.784		
	III	0.83 ± 0.698		
VAS at 12 hrs	I	0.700 ± 0.749	0.160	0.852
	II	0.666 ± 0.660		
	III	0.600 ± 0.674		
VAS at 24 hrs	I	0.366 ± 0.490	1.042	0.357
	II	0.266 ± 0.449		
	III	0.200 ± 0.406		

Table 2: Visual analog scale (VAS) at various time intervals *all data is expressed in mean ± standard deviation P<0.05 considered significant SD-standard deviation, VAS-visual analog scale Group I-patients receiving bupivacaine Group II patients receiving bupivacaine+ fentanyl 50µg, Group III- patients receiving bupivacaine + fentanyl 100µg

	0 hrs			2 hrs			4 hrs			6 hrs			12 hrs			24 hrs		
	Gp I	II	III	Gp I	II	III	Gp I	II	III	100 %	100 %	100 %	100 %	100 %	100 %	10 %	100 %	100 %
0	95 %	94 %	90 %	93 %	80 %	85 %	90 %	93 %	85 %	0%	0%	0%	0%	0%	0%	0%	0%	0%
1	5%	6 %	10 %	7%	20 %	15 %	10 %	7%	15 %	0%	0%	0%	0%	0%	0%	0%	0%	0%
2	0%	0 %	0 %	0%	0%	0 %	0%	0%	0%									
P value	0.756			0.652			0.551											

Table 3: Nausea and vomiting scores in three groups at different time intervals *all data is expressed in mean ± standard deviation P<0.05 considered significant SD-standard deviation, M-male, F-female, N-nausea, V-vomiting, Group I-patients receiving bupivacaine, Group II-patients receiving Bupivacaine + fentanyl 50µg, Group III- patients receiving bupivacaine + fentanyl 100µg

Discussion

Laparoscopic cholecystectomy is one of the most commonly performed day care surgery. However in up to 40% of cases hospitalization following the surgery may be prolonged due to inadequate analgesia [7,8,11]. This study demonstrates effective use of intraperitoneal and port site infiltration of bupivacaine in combination

with two different doses of fentanyl for management of postoperative pain following laparoscopic cholecystectomy.

Local anesthetics have been successfully used in management of pain following Laparoscopic Cholecystectomy due to their ability to block the transmission of nerve signal from traumatized tissue and also reduce neurogenic local inflammation at trauma site [11]. In a meta-analysis conducted by Bisgaard seven out of the eight trials noted by him favored the use of local anesthetics for port site infiltration [11]. In the same meta-analysis however he demonstrated equivocal results in regards to the efficacy of intraperitoneal instillation of bupivacaine for visceral pain. In our study we provided both intraperitoneal and port site infiltration thus targeting both the somatic and visceral origin of pain.

The analgesic effect of additional opioid has also been demonstrated in several studies [12-16] Likar et al. [16] demonstrated that morphine added to a local anesthetic for submucosal infiltration in dental surgery had an improved postoperative analgesia for 24 hours [16]. However the use of intraperitoneal and interpleural morphine by stienber et al. [17] did not result in significant analgesia following laparoscopic cholecystectomy [17]. This was ascribed to the low volume of the injected solution and the hydrophilic nature of morphine, which reduces its ability to cross the intact perineurium. In contrast to morphine fentanyl is a lipophilic opioid and thus may have better action due to easily crossing perineurium. Fentanyl used at a dose of 100μg by Gupta et al. [12] for peripheral analgesia in laparoscopic surgery for intraperitonial instillation, showed better analgesia without any complications and toxicity [12]. Similar results were observed in our study in which there was a significant reduction in postoperative VAS score at 4 and 6 hrs. In our study we used fentanyl in dosage of 50μg and 100μg. A dose of 10μg fentanyl used by Tverskoy et al. [18] failed to reduce the analgesic consumption in patients given fentanyl-lignocaine combination for wound infiltration [18]. A dose of 25μg fentanyl with lignocane utilized by Vijay kumar et al. [19] enhanced the duration of analgesia [19]. In a study conducted by Sharma et al. [20] they compared plain bupivacaine with bupivacaine in combination with 2mcg/kg fentanyl and observed significant reduction in the VAS and also prolonged duration of analgesia [20]. Also they did not observe any significant side effects. Therefore, the doses of 50μg and 100μg fentanyl were chosen in our study along with bupivacaine, a longer acting local anesthetic. In both the groups, we did not observe any complications (respiratory depression, pruritus, sedation) and signs of toxicity of fentanyl or bupivacaine clinically, though we did not measure the serum levels of the drugs.

In a systematic review conducted by boddy et al. [21] they examined the effect of timing of instillation on postoperative pain relief and observed that there was a significantly greater pain relief in the cases where local anesthetic was instilled at the beginning of anesthesia as compared to the cases where local anesthetic was instilled following surgery [21]. The presence of inflammation has been found to enhance the efficacy of peripherally applied opioids. This is because inflammation disrupts the perineurium as well as increases the number of peripheral sensory nerve terminals.

The favorable results in our study may be because of; firstly, we instillated and infiltrated 30 ml of study drug solution (bupivacaine-fatanyl combination) after completion of surgery when inflammatory response may have begun. Secondly, we also instillated 20 ml of the drug solution immediately after creation of peumoperitoneum (before starting dissection), as better analgesia was demonstrated with pre-emptive administration of local aesthetic, in some studies [22,23]. This finding is consistent with the theory that an afferent block is achieved after pre operative administration of local anesthetic before nociceptive stimuli can modify the behavioural response and neuronal sensitization of posterior horn neurons [24].

In the metanalysis conducted by boddy et al. [21] they analyzed 24 studies and observed an overall weighted mean difference in VAS of 9 mm in favour of groups receiving intraperitoneal local anesthetic, however they did not find significant effect of intraperitoneal local anesthetic on the total amount of analgesic delivered in the postoperative period. This might be ascribed to the fact that local anesthetic has its effect only over initial few hours. Similar findings were observed in our study where significant analgesia was achieved only at 4 and 6 hours postoperatively

The complexity of pain following laparoscopic surgery makes the use of multimodal analgesic regimen mandatory. Non steroidal anti-inflammatory drugs (NSAIDs) are effective in relieving post operative pain; as a result, there has been interest in the use of NSAIDs to treat a component of pain after laparoscopic cholecystectomy. Unfortunately NSAIDs alone are insufficient to effectively treat post-operative pain. However, inclusion of NSAIDs in a multimodal approach to pain relief after laparoscopic cholecystectomy has been very successful both in improving the quality of analgesia and reducing side effects [25]. In this study we used intraperitoneal instillation and port site infiltration of bupivacaine and fentanyl combination along with diclofenac sodium in post-operative period, as a part of multimodal analgesia. We used 50μg and 100μg fentanyl and 100 mg bupivacaine which is well within the permissible limit and there was no evidence clinically that the dose of drug used had crossed the toxic levels. Despite our inability to measure plasma concentration of bupivacaine it has been shown that range of mean plasma concentration (0.92-1.14 mcg/ml) after intraperitoneal instillation of 100-150 mg plain bupivacaine is well below the toxic concentration of 3 mcg/ml [26,27]

Conclusions

Intraperitoneal and port site infiltration of bupivacaine in combination with fentanyl may provide an effective method for postoperative analgesia in patients undergoing laparoscopic cholecystectomy. This method of analgesia is minimally invasive, targets the pain at its origin and is virtually free of side effects.

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