

A comparison of interpleural bupivacaine and intravenous pethidine for postoperative pain relief following open cholecystectomy

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Abstract

Introduction: Open cholecystectomy is still a fairly frequently performed operation in the developing world. It is more invasive and therefore associated with a greater degree of postoperative pain. The purpose of this study was to compare the efficacy of a single dose of 20 ml 0.5% interpleural bupivacaine with a single 1 mg/kg bolus of intravenous pethidine for postoperative pain relief following open cholecystectomy.

Material and methods: The study consisted of 100 randomly selected ASA physical status I/II male/female adults, aged 30-60 years, diagnosed with chronic cholecystitis and scheduled for surgery. Group I received a single 20 ml 0.5% bolus of bupivacaine into their interpleural space ($n = 50$). Group II received a single bolus of 1 mg/kg body weight of intravenous pethidine ($n = 50$). Visual analogue scale (VAS) scores, pulse rate (PR) and mean arterial pressure (MAP) were recorded and compared between and within study groups at pre-induction, immediately after administration of study drugs at time increments of 5, 15, 30, 60, 120, 240 and 360 min.

Results: Lower VAS scores, longer duration of analgesia (4 h 37 min), significant attenuation of hemodynamic responses, and no incidence of complications were observed among patients who received interpleural bupivacaine.

Conclusions: Interpleural bupivacaine is a better choice than intravenous pethidine for post-operative pain relief following open cholecystectomy. Further studies should be conducted with a special attention to long-term side effects and complications with respect to their routes of administration. The knowledge of open cholecystectomy and its postoperative profile remains vital to the knowledge base of physicians, particularly, in the developing world.

Key words: cholecystectomy, hemodynamic response, interpleural bupivacaine.

Introduction

Cholecystectomy is one of the most common operations performed worldwide [1]. Cholecystectomy is performed by two basic techniques – laparoscopic cholecystectomy (LC) and open cholecystectomy (OC), each with its pros and cons. Laparoscopic cholecystectomy is considered the “gold standard” for treatment of systemic gallbladder disease [2, 3]. It is less invasive than open cholecystectomy, and thus results in less pain

and shorter postoperative hospital stays and sick leave [4-6]. Although recent innovations have made laparoscopic cholecystectomy more prevalent in developed countries [7, 8], open cholecystectomy continues to be widely used in many developing countries [8, 9]. Despite the obvious benefits of the laparoscopic procedure, the high cost of conversion inhibits its widespread availability and use in the developing world [9, 10]. Open cholecystectomy is also used in rare cases in which laparoscopic surgery is contraindicated [3, 4, 6, 10]. Thus, knowledge of open cholecystectomy and its postoperative profile is vital to the knowledge base of physicians worldwide [3].

Open cholecystectomy, on the other hand, is more invasive and associated with a greater degree of postoperative pain, which is often quite severe [5]. It normally results in hospital stays that range from 6.1-10 days and a recommended sick leave of 4-6 weeks [4]. Efficient pain relief is crucial in these cases because postoperative pain can lead to complications including pulmonary dysfunction, physiological changes caused by endocrine, metabolic and inflammatory responses and their associated hemodynamic changes, spinal reflex spasms and diaphragmatic dysfunction [11, 12]. Therefore adequate analgesia immediately following abdominal surgery is essential for the well-being of the patient. However, the best technique used in the management of postoperative pain remains unclear [11].

Several methods may be used to prevent and treat established pain after cholecystectomy. The benefit of using interpleural local anesthetics, such as bupivacaine, has been proven for some time now [11, 13-15]. However, several studies do not confirm the findings [16-18]. In addition, intravenous administration of pethidine has also been studied for postoperative analgesia in patients undergoing open and laparoscopic cholecystectomy [19]. However, the debate regarding the benefit of using this opioid is still very much alive [20, 21]. To further explore this controversy regarding the best method and suitable analgesics, we designed a randomized, double-blind study to compare the efficacy and complications of interpleural bupivacaine and

intravenous pethidine for postoperative pain relief following open cholecystectomy.

Material and methods

This study was undertaken at K.R. Hospital, Government Medical College, Rajiv Gandhi University of Health Sciences (Karnataka state, India). Ethics committee approval and institutional approval were granted for the protocol of this prospective study and informed consent was obtained from all participants. The study population consisted of 100 patients, randomly selected ASA physical status I/II male/female adults, aged 30-60 years, diagnosed with chronic cholecystitis and scheduled for elective open cholecystectomy. There were no statistical demographic differences observed with respect to the number of patients in each group ($n = 50$), age or weight (Table I). Patients aged less than 30 or greater than 60 years old, those having pre-existing systemic disorders, hypertension, ischemic heart disease, diabetes mellitus, COPD and bronchial asthma and those with sensitivity to bupivacaine were excluded from the study. All patients were educated on postoperative pain and the need to alleviate it in the same manner. Before induction of anesthesia, patients were explained about interpleural block and instructed on the use of a visual analogue scale (VAS: with end points 'no pain' and 'worst point') for measurement of pain severity.

Study design

Each patient was randomly assigned to one of two double-blind study groups: group 1 received a single 20 ml 0.5% bolus of bupivacaine into their interpleural space ($n = 50$). Interpleural bupivacaine was given as follows: following open cholecystectomy before extubation, skin was painted on the right side of the thorax and the right sixth intercostal space was identified from the sternal angle. At the sixth intercostal space in the midaxillary line, at the upper border of the lower rib, a skin puncture was made with a loaded syringe of bupivacaine and the needle with the syringe was advanced into the above space, until there was a popping sensation or giving way of resistance. This heralded the entry of the needle into the pleural space by piercing the parietal pleura. Mechanical ventilation was momentarily interrupted, and after negative aspiration of blood, 20 ml of 0.5% bupivacaine was injected into the interpleural space. Group 2 received a single bolus dose of 1 mg/kg intravenous pethidine, following open cholecystectomy and extubation ($n = 50$). The time of onset of analgesia as well as the duration of analgesia was recorded for each patient. The quality of pain relief was assessed

Table I. Patient demographics in the two groups

Characteristics	Group 1 (bupivacaine)	Group 2 (pethidine)
Patients	$n = 50$	$n = 50$
Age [years]	45.68 ± 7.93	45.72 ± 7.12
Sex (M/F)	21/29	20/30
Weight [kg]	53.06 ± 4.71	53.38 ± 5.56
Duration of surgery [min]	74.00 ± 9.64	71.80 ± 8.50

using the visual analogue scale (VAS) [22] at various intervals postoperatively. Pulse rate (PR) and mean arterial pressure (MAP) were recorded for each patient prior to administration of the study drug, at pre-induction (baseline), just before administration of the drug, immediately after administration of the study drug and at time increments of 5, 15, 30 min, 1, 2, 4 and 6 h.

Protocol

The day prior to surgery each patient underwent a thorough pre-anesthetic evaluation with special consideration to elicit any history of hypertension, diabetes mellitus, chest pain, dyspnea, convulsions, wheezing, myocardial infarction, as well as previous anesthetic history and drug sensitivity. Patient information collected during the pre-anesthetic evaluation also included nutritional status, weight, airway assessment by the Mallampatti scoring system [15], and a detailed examination of the cardiovascular, respiratory and central nervous system, which included measured hemoglobin (Hb%), bleeding and clotting time, urine analysis, blood sugar FBS/RBS, blood urea, serum creatinine, ECG, chest radiography, and blood/Rh typing. Patients were advised to fast the night prior to surgery and were premedicated with a single oral dose of 150 mg ranitidine and 0.5 mg alprazolam the night before surgery.

Premedication, for all patients in both groups on the day of surgery, consisted of single injections of 0.5 mg atropine, 1.0 mg midazolam and 15 mg pentazocaine given intramuscularly 30 min prior to surgery. In the operating room, an 18-gauge intravenous cannula was inserted and an infusion of dextrose with normal saline was started. Pulse rate, mean arterial pressure, SPO₂ and ECG were recorded continuously by means of a Siemens SC-7000 multi-channel monitor. Pre-oxygenation was accomplished with 100% O₂ for 3 min, followed by induction with thiopentone (5 mg/kg) and suxamethonium (2 mg/kg). Patients were intubated with an appropriately sized oral endotracheal tube after vocal cords were sprayed with 2 ml 4% lignocaine. The endotracheal tube was fixed and the patients mechanically ventilated using the Bain system. Anesthesia was maintained using 66% nitrous oxide and 33% oxygen. Neuromuscular blockade was maintained with 0.5% halothane and 0.06 mg/kg vecuronium bromide. Anesthesia was reversed with 0.05 mg/kg neostigmine IV bolus and 0.02 mg/kg atropine IV bolus. Immediately following surgery, the study drugs were administered as explained above in the study design section. In a few cases, where the patients experienced more pain, an NSAID such as diclofenac sodium (75 mg) was administered intramuscularly.

Data analysis

Summary statistics of patient gender, age and weight for both group 1 and group 2 are reported as means \pm standard deviation (Table I). Intra- and inter-group analysis for mean VAS score, mean HR and mean MAP were statistically evaluated by *t*-test using both StatPlus™ v2, and Minitab™, where $p < 0.05$ was considered significant, and $p < 0.001$ highly significant. Baseline HR and MAP were also statistically evaluated against HR and MAP after administration of drugs at various time increments using *t*-test.

Results

The demographic characteristics of the patients in each group were similar. There were no statistically significant differences observed with respect to number of patients, age, weight and duration of surgery (Table I). The effectiveness of these two drugs was evaluated by three parameters: mean VAS scores, mean arterial pressure, and mean pulse rate.

Visual analogue scale scores

Visual analogue scale scores were used to determine the degree of pain felt by the patients after drug administration. Group 1 (interpleural bupivacaine) and group 2 (intravenous pethidine) did not significantly differ ($p > 0.05$) with respect to mean VAS scores (Figure 1) at 5, 10, 15, 20 and 25 min after drug administration. However, at 30 min, group 2 had a significantly higher mean VAS score ($t = 2.6, p < 0.01$). As is apparent from Figure 1, this trend became more distinct as time increased. At every time interval from 30 to 360 min after drug administration, the group that received intravenous pethidine consistently exhibited significantly higher mean VAS scores ($p < 0.001$). It is evident from the data that the difference in mean VAS score became especially marked at 120 min and after.

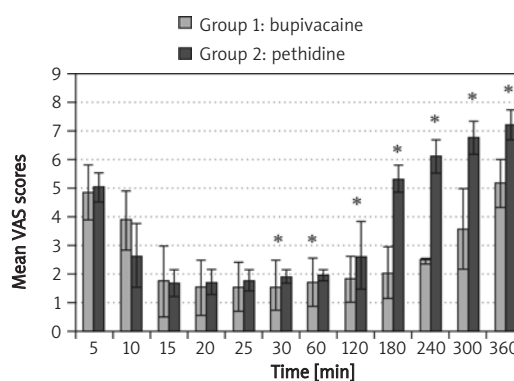


Figure 1. Postoperative mean VAS scores at different intervals

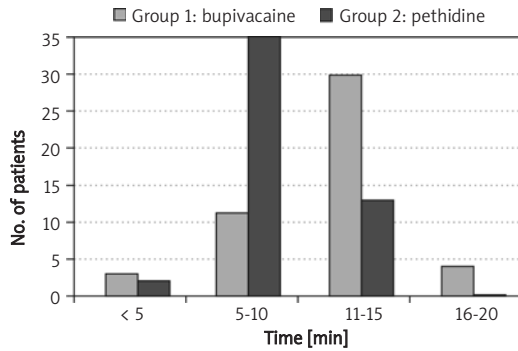


Figure 2. Onset of analgesia

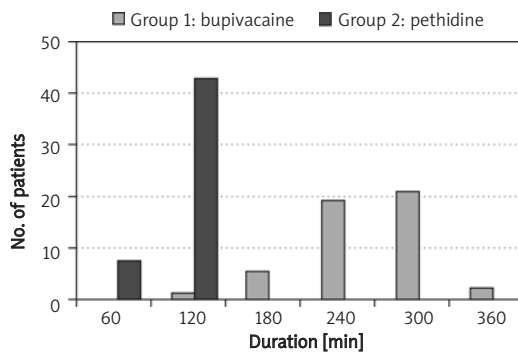


Figure 3. Duration of analgesia

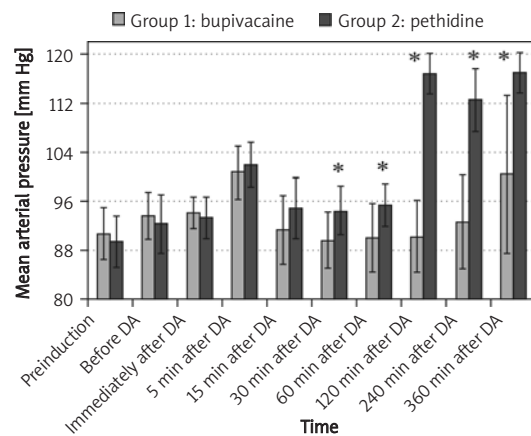


Figure 4. Mean arterial pressure (MAP) at different time intervals

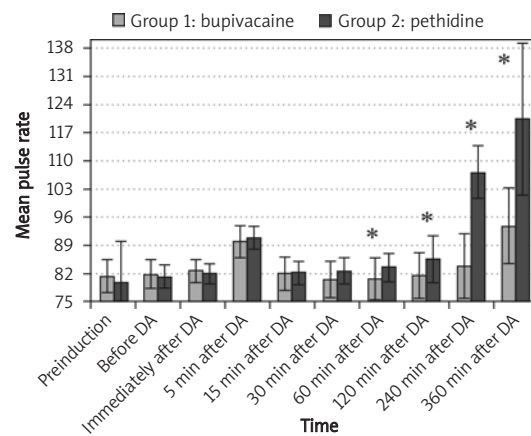


Figure 5. Mean pulse rate at different time intervals

Onset and duration of analgesia

A significant difference in the onset of analgesia ($n = 100, t = 4.13, p < 0.001$) was observed between the patients in group 1 compared to patients in group 2 (Figure 2). In this study, onset of analgesia referred to the time from extubation to the time when the VAS scores dropped to three or below. In group 1, the average time for onset of analgesia was 13.64 min and the majority of patients achieved it in 11 to 15 min. In group 2, the average time for onset of analgesia was 11.10 min and the majority of patients had a range from 5 to 10 min. However, the mean duration of analgesia (4 h 37 min) in group 1 was significantly higher (Figure 3) than that of group 2 (1 h 86 min) ($n = 100, t = 20.03, p < 0.001$). The duration of analgesia referred to the time from onset of analgesia to the time when the VAS scores reached three or higher.

Mean arterial pressure

Mean arterial pressure (MAP) was one measure of hemodynamic response assessed during the study. Group 1 and group 2 did not significantly differ in their mean MAP values at pre-induction (baseline) through 15 min after the administration of drugs ($p > 0.05$) (Figure 4). However, patients receiving pethidine (group 2) recorded significantly higher MAP values at 30 min ($t = 6.13, p < 0.001$), 60 min ($t = 7.73, p < 0.001$), 120 min ($t = 28.2, p < 0.001$), 240 min ($t = 15.2, p < 0.001$) and 360 min ($t = 7.75, p < 0.001$) compared to patients in group 1 at respective time intervals. The difference between group 1 and group 2 in mean arterial pressure was especially marked at 120, 240 and 360 min. In group 1, there was no significant difference observed between the pre-induction values and the mean MAP values from 15 min through 240 min ($n = 50, p > 0.05$). In contrast, group 2 had significantly higher mean MAP values compared to mean baseline values from 15 min through 360 min ($p < 0.001$).

Mean pulse rate

Mean pulse rate was used as another indicator of hemodynamic response. Group 1 and group 2 did not significantly differ in their mean pulse rate values at pre-induction (baseline) through 30 min after the administration of drugs ($p > 0.05$) (Figure 5). However, patients receiving pethidine (group 2) recorded a significantly higher mean pulse rate at 60 min ($t = 2.42, p < 0.05$), 120 min ($t = 3.54, p < 0.01$), 240 min ($t = 15.76, p < 0.001$) and 360 min ($t = 6.66, p < 0.001$) compared to patients in group 1 at respective time intervals. In group 1, there was no significant difference observed between the pre-induction and the mean pulse rate values from 5 min through 240 min ($n = 50, p > 0.05$). In

contrast, group 2 had a higher mean pulse rate compared to baseline pulse rate at 5, 60, 120, 240 and 360 min.

Discussion

In this study, we compared the pharmacodynamics of two common drugs and their effectiveness *via* two different routes of administration for pain management. Our results clearly indicated that patients who received interpleural bupivacaine experienced more effective post-operative pain relief. This is in agreement with several previous studies [23-25]. In general, patients in this group scored much lower on the VAS score index compared to that of patients who received intravenous pethidine. The interpleural route of administration was chosen for bupivacaine because of its lipophilic properties and cardiotoxic behavior [18, 26, 27]. Interpleural blockade produces pain relief by spread of local anesthesia bilaterally to block the sympathetic chains as well as splanchnic nerves. Interpleural block, such as with bupivacaine, when used in situations where analgesia is contraindicated, has no clinically significant adverse effect on respiratory muscle function and is more than likely to be beneficial in the presence of painful conditions compromising pulmonary function [23, 26, 27]. This finding is supported by the incidence of complications observed in this study. In the first group where bupivacaine was administered interpleurally, none of the patients had any clinical complications. However, in the second group where pethidine was given intravenously, 18% of the patients developed post-operative nausea and vomiting. These complications were treated with ondansetron 4 mg intravenously.

Intravenous route of administration was chosen for pethidine since it is a well known systemic analgesia. The average onset of analgesia in group 2 that received intravenous pethidine (11.10 min) was significantly lower compared to group 1 (13.64 min). This can be explained by the fact that the intravenous route of administration provides 100% drug bioavailability, hence all drug molecules are available to interact with pain receptors in a short period of time and induce analgesia. The analgesic effect of pethidine was detectable after 10 min following administration, and peaked in about 50 to 100 min. On the other hand, patients who received bupivacaine experienced a significantly longer duration of analgesia (4 h 37 min), that extended well beyond its half life ($t_{1/2} = 210$ min), than patients who received pethidine, resulting from slower drug diffusion following interpleural administration. In addition, the ability of bupivacaine to cause vasoconstriction decreased its rate of absorption, localizing

the anesthetic at the desired site and allowing its metabolism rate to be at pace with the rate at which it is absorbed into the circulation [21, 26, 27]. In the case of pethidine, 100% of the drug was available at once for liver metabolism and therefore its duration of action was shorter. Our study further suggests that a considerably small quantity of bupivacaine is sufficiently effective in pain relief after open cholecystectomy. Bupivacaine was given as 20 ml of 0.5% (equivalent to 0.01 mg/patient), while pethidine was administered as 1 mg/kg body weight (equivalent to 53 mg/patient). Despite the significant difference in the administered dose, bupivacaine produced a much more potent analgesia in our open cholecystectomy cases. The hydrophobic nature of bupivacaine led to increase in both its potency and duration of action by enhancing its partitioning to the hydrophobic sites and thereby decreased its rate of metabolism by plasma esterases and hepatic enzymes [21].

Measurements of cardiac stress – namely mean arterial pressure and mean pulse rate – indicated that patients who were given interpleural bupivacaine experienced significantly lower cardiac stress at and 30 min after drug administration and the trend became more pronounced as time elapsed. This further signifies that interpleural bupivacaine was more effective for post-operative pain relief following open cholecystectomy than intravenous pethidine. Bupivacaine decreased electrical excitability, conduction rate and force of the contraction of the myocardium [21], which ultimately resulted in a lower pulse rate and mean arterial pressure among patients in this group. On the other hand, patients who received pethidine (group 2) recorded significantly higher mean arterial pressure and pulse rate. This can partially be explained by the fact that pethidine is known to stimulate the release of histamine, which in turn produces a marked increase in pulse rate and vasoconstriction illustrated as elevated mean arterial blood pressure.

In conclusion, given the longer duration of analgesia, better pain relief and less systemic side effects, interpleural bupivacaine has proven to be a better choice than intravenous pethidine for post-operative pain relief following open cholecystectomy. Further studies should be conducted with special attention to long-term side effects and complications with respect to their routes of administration in the near future. In general, although open cholecystectomy has largely fallen out of favor with the advent of laparoscopic cholecystectomy, there are certain circumstances in which it is advisable to use the procedure [2, 3, 7, 8]. This is particularly true in the developing world, where open cholecystectomy is common even today [8, 9]. Due to the high cost of conversion

from open to laparoscopic cholecystectomy, it seems quite likely that open cholecystectomy will continue to be quite common in the developing world [9, 10]. Moreover, open cholecystectomy is also used outside the developing world when laparoscopic cholecystectomy is contraindicated or when circumstances necessitate the conversion from the latter to the former during the operation [3]. Therefore, knowledge of open cholecystectomy and by extension post-operative pain relief following the surgery itself is vital information. The aim of this study was to provide such information.

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