Effectiveness of Ondansetron to prevent postoperative nausea and vomiting in ambulatory two port needlescopic cholecystectomy: a randomised controlled trial

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Abstract

Aim: To investigate the effectiveness of ondansetron in the relief of post-operative nausea and vomiting in patients following ambulatory two port needlescopic cholecystectomy.

Methods: Consecutive adult patients undergoing ambulatory two port needlescopic cholecystectomy were randomised to receive either a single dose of 8mg intravenous ondansetron or nothing. The primary outcome measure was the degree of post-operative nausea and vomiting (score 1 to 4) at 4 hours after surgery.

Results: Patients' characteristics in the ondansetron (O) group (n=40) and the control (C) groups (n=41) were comparable. There was no significant difference between O and C groups in the incidence of PONV (17.5%versus 22%, p=0.615) and median PONV score (1 versus 1, p=0.226) at 4 hours after surgery. The post-operative pain score, analgesia consumption and post-operative stay were also similar in the two groups. Almost all the patients in both groups (97.5% versus 95.1%) could be discharged on the same day of operation.

Conclusion: The administration of 8mg ondansetron conferred no additional benefit in post-operative nausea and vomiting.

Keywords: Needlescopic cholecystectomy; Post-operative nausea and vomiting.

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Background

Laparoscopic cholecystectomy (LC) has been widely practiced in Hong Kong since 1990 and it is one of the most commonly performed operations in current surgical practice [1]. Although access trauma is much reduced compared with open cholecystectomy that requires a large incision, the conventional four port technique still leaves a patient with significant post-operative discomfort [2,3.4]. The two port LC was devised with the aim to decrease such discomfort, hence a shorter hospital stay and recovery period. Our previous prospective randomized controlled trial comparing two port versus four port LC has demonstrated the benefit of reducing port site wound pain in the two port group while the duration of hospital stay was similar between the two groups [5]. Two port technique is modified using needlescopic instruments, making the port site even smaller [6]. Recent reports in the literature suggest that post-operative nausea and vomiting (PONV) are common distressing complications following LC and it is a major factor in prolonging hospital stay [7,8,9]. Ondansetron is a potent prophylaxis against nausea and vomiting following chemotherapy [10] and its use for PONV has been documented [11,12,13,14]. This study was performed to evaluate the efficacy of ondansetron in preventing PONV following ambulatory two port needlescopic cholecystectomy (NC) in a prospective randomized trial. To the best of our knowledge, this is the first prospective randomized trial comparing antiemetic prophylaxis of PONV following two port NC

Patients and Method

Between August 2003 and May 2004, patients with symptomatic gallstones or benign gallbladder polyp scheduled for elective laparoscopic cholecystectomy were invited to join this study if they fulfilled the following specified criteria: (1) clinically and radiologically symptomatic gallstone disease, or gallbladder polyps smaller than 1cm, (2) American Society of Anaesthesiologists (ASA) grade I and II, (3) age between 18 and 70 years old, (4) post-operative home assistance was available. Patients were excluded in the study according to the following exclusion criteria: (1) body mass index greater than 28 [15], (2) history of upper abdominal surgery, (3) impaired liver function test, (4) suspected biliary tree obstruction, (5) concomitant pathology requiring additional surgical intervention, (6) allergic to ondansetron, (7) two port NC was unsuccessful and it included the addition of ports or conversion to open surgery. The study protocol obtained approval from the local ethics committee and written informed consent was obtained from all patients enrolled in the study.

Randomisation was carried out at the end of the operation at the time of gallbladder retrieval by computer generated random number inside a numbered, sealed, opaque envelope. Patients were randomly allocated to receive either a single dose of ondansetron 8mg given intravenously or nothing immediately after randomisation.

All patients received a standardised anaesthetic technique using isoflurane in the two hospitals. Under general anaesthesia and after administration of intravenous prophylactic antibiotic (cefuroxime 1.5gm), surgery was performed with a standard two-port needlescopic technique. In short, a 12 mm supra-umbilical port

and a 3 mm subxiphisternal port were created. 10mm operating telescope and 3mm needlescopic instruments were used for dissection. The cystic duct and artery were controlled with double Tayside extracorporeal knots before division[6]. At least one specialist surgeon who was familiar with the technique scrubbed up in the operation theatre and was in charge of the whole operation. The operating surgeon could decide on the use of additional ports or conversion as appropriate. Each surgical wound was infiltrated with 0.25% bupivacaine at the conclusion of surgery.

Post-operatively, a team of surgeon and nursing staff who were blinded to the study was responsible for managing these patients in the day surgery centres. Oral dologesic, ibuprofen or intramuscular injection of pethidine as required could be given for pain control. An intravenous injection of metoclopramide at 10mg per dose every eight hours could also be given for PONV as requested by the patients. The independent surgeon could discharge the patients on the same day when they were ambulatory and tolerated a normal diet. Those patients who could not meet the discharge criteria were admitted to hospital for further observation and management. All patients discharged on the day of operation received a telephone interview by an independent nurse one day after the operation. Any major complications were recorded and appropriate medical advice would be given to them if necessary.

The primary outcome measure was the degree of post-operative nausea and vomiting at 4 hours after the operation. PONV was scored according to a PONV scale from one to four (1= no symptoms, 2= symptoms not requiring pharmacological treatment, 3=symptoms relieved by pharmacological treatment and 4= symptoms not relieved by pharmacological treatment). Post-operative pain at 4 hours was scored using an unscaled 0-10 visual analogue scale (VAS) where 0 and 10 represent no pain and the most severe pain respectively. Other outcome measures including the length of post-operative stay and patient's overall satisfaction with the surgery were also recorded. Patient's satisfaction was rated by a 1-4 satisfaction score(1= very unsatisfied, 2= unsatisfied, 3=satisfied and 4= very satisfied).

Statistics

Several randomised prospective trials have studied the incidence of PONV after LC. The incidence in the placebo arm varied from 46 to 72% [13, 16, 17]. It was estimated that a sample size of around 40 patients in each group was required if the expected difference in the incidence of nausea and vomiting between the two groups was at least 30 %, with a power of 80% at the 0.05 level of significance. Categorical data were analysed with the chi square test or Fisher's exact test as appropriate. Continuous data were analysed by student's t-test if normally distributed or Mann-Whitney U test otherwise. All data were analysed by Statistical Package for the Social Science for Windows (SPSS version 10.0).

Results

81 patients were enrolled in the study from August 2003 to May 2004. Their ages ranged from 22 to 68 year old. 40 patients were randomized to the ondansetron group (O) and 41 patients were randomized to the control group (C). Demographically, there was no statistically significant difference between the 2 groups (Table 1). The incidence of PONV at 4 hours with a score greater than or equal to 2 (i.e symptoms that might or might not require pharmacological treatment) were 27.5% in the ondansetron and 39.0% in the control group respectively (p=0.271). 7 patients (17.5%) in the ondansetron group and 9 patients (22%) in the control group experienced vomiting (p=0.615). Among those patients who experienced PONV, only 5 patients (12.5%) in the ondansetron group and 5 patients (12.2%) in the control group required pharmacological treatment. The median PONV score at 4 hours was 1 (range: 1-4) in both groups and no significant difference was detected between the two groups (p=0.226). Both groups also had comparable mean operation times (54.3+/-19.9 minutes in O group versus 57.9+/-23.3minutes in C group; p=0.46). The mean post-operative pain score at 4 hours was also similar in both groups (3.8+/- 2.1 in C group versus 3.9+/- 1.9 in O group respectively (p=0.774). The need for post-operative

Table 1 Comparison of baseline characteristics and outcomes between ondansetron group and control group.

	Control group N=41	Ondansetron group N=40	P value
Male : Female	13: 28	15: 25	0.584
Age – years Mean (SD)	49.2 (8.6)	48.6 (10.9)	0.760
Incidence of PONV with score >or =2 (%)	16/41 (39.0)	11/40 (27.5)	0.271
No. of patients with vomiting (%)	9 (22)	7 (17.5)	0.615
PONV score at 4 hours Median (range)	1 (1-4)	1 (1-4)	0.226
Pain score at 4 hours Mean (SD)	3.8 (2.1)	3.9 (1.9)	0.774
Need for post-operative Analgesia (%)	17/41 (41.5)	15/40 (37.5)	0.715
Operation time (minutes) Mean (SD)	57.9 (23.3)	54.3 (19.9)	0.460
Satisfaction score Median (range)	4 (1-4)	4 (1-4)	0.996
No. of patients needing overnight hospital	2 (4.9)	1 (2.5)	1.000

analgesia was also comparable in both groups (37.5% in O group and 41.5% in C group, p=0.715). Most patients in both groups were highly satisfied with the operation and the median satisfaction score was 4 in both groups (range 1-4; p=0.996). All patients except 3 were discharged on the same day of operation (1 in O group and 2 in C group). One patient in the ondansetron group had significant post-operative pain in the day surgery centre and was observed overnight. He was discharged the next day. One patient in the control group had persistent low blood pressure and another patient had mild wheezing after the operation. Both patients could be discharged the next day after conservative management. No patients were readmitted. No other major post-operative complication was detected in our study.

Discussion

With the increase in popularity of minimally invasive surgery in past two decades and the constraints of tight budgeting in medical care today, there is a tremendous growth in ambulatory surgery in developed countries. However, it is estimated that about 30% of patients will have post-operative nausea and vomiting [18,19] and this is the major factor in prolonging hospital stay in ambulatory surgery [7,8,9]. The aetiology of PONV is multifactorial and it includes patient factors, anaesthetic factors and post-operative care [20]. In fact, laparoscopic surgery itself is a main risk factor for PONV and its incidence can be as high as 72 % [17]. For laparoscopic cholecystectomy, PONV may be associated with stretching of the peritoneum due to CO2 pneumoperitoneum and the gallbladder surgery itself [2]. Routine prophylaxis for PONV remains controversial. One recent large and multicentre European randomised controlled trial of post-operative nausea and vomiting (n=5199) has recommended single antiemetic prophylaxis in moderate risks patients and multiple antiemetics prophylaxis for high risks patients for the prevention of PONV [21].

Among the antiemetic prophylaxis used worldwide, droperidol, dexamethasone and ondansetron are the 3 commonly used drugs in recent published English literature. Ondansetron is a highly selective 5-HT3 receptor antagonist and it is also a very potent antiemetic drug with few side effects. Its effectiveness in prevention of PONV following chemotherapy [10], surgery [11] and LC [12,13,17] is well documented. Our previous prospective randomised controlled trial [5] comparing two port versus four port LC has demonstrated the benefit of reducing port site wound pain in the two port group while the duration of hospital stay was similar in both groups. In order to minimise the effect of PONV, we used ondansetron as the antiemetic prophylaxis to conduct the first prospective randomised study comparing PONV in two port NC. There are some limitations in this study. We have tried to minimise the impact of patient factors in PONV by setting out the inclusion criteria and only good risk patients are recruited for ambulatory surgery. Patients could enter the randomisation process only if successful two port NC was performed. Patients with extremes of age and high body mass index (>28) were excluded from this study. In reality the surgery is usually performed for a heterogeneous group of patients especially the obese patient who has a higher incidence of symptomatic gallstone. Patient history of motion sickness is not recorded in this study and this is one of the important factors affecting PONV. Although we have standardized the anaesthetic technique using isoflurane, there may be minor differences in practice of the anaesthetic technique in the two hospitals as 2 groups of anaesthetists were involved in this study.

Based on the results of published ondansetron trials for LC [13,16,17,22], the incidence of PONV has ranged from 46 to 72 % in control groups and 32 to 64% in ondansetron groups. In our study, our reported incidence of PONV is low compared with other studies. The incidence of PONV at 4 hours after surgery was 27.5% in the ondansetron group and 39.0% in the control group. The incidence of PONV requiring pharmacological treatment was even lower with12.5% in ondansetron group and 12.2% in the control group. The median PONV score at 4 hours was 1 (range 1-4) in both groups. Hence no beneficial effect was observed in the ondansetron group for prevention of PONV. We speculate that this may be due to the short duration of operation time which can effectively reduce the incidence of PONV. The median post-operative hospital stay in this study was even better than that (1 Vs 2 days) reported in our previous study [5] using a similar 2 port technique for LC. The reason behind this may be due to better patient selection in this study. Our results suggest that this is a negative antiemetic prophylaxis trial. Both groups of patients have similar demographics. However, there was no significant difference in the incidence of PONV, PONV score, pain score, need of post-operative analgesia, operative time and patient satisfaction score. Moreover, almost all the patients (78/81) in both groups could be discharged on the same day of operation. In conclusion, the prophylactic administration of 8mg ondansetron following 2 port needlescopic cholecystectomy confers no additional benefit in good risk patients in terms of post-operative nausea and vomiting. Moreover ambulatory 2 port NC can be performed in good risk patients with high patient satisfaction.

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