Transdermal Scopolamine Alternative to Ondansetron for Prevention of Early 6 Hours Postoperative Laparoscopic Cholecystectomy Emetic Symptoms

Raghad Hannon Alsudani, Asmaa Khalid Al- Hayali***

ABSTRACT:

BACKGROUND:

Nausea and vomiting are the commonest complication Post-operatively which are usually self-limiting; however, it can cause serious consequences. There are many drugs to manage Post-operative nausea and vomiting.

OBJECTIVE:

Compare the efficacy of transdermal scopolamine versus ondansetron for the prevention of post-operative laparoscopic cholecystectomy emetic symptoms.

PATIENTS AND METHODS:

One hundred patients who were candidate for undergoing laparoscopic cholecystectomy are divided in to two groups each of them have 50 patients, first group received an active TDS patch (containing scopolamine 1.5 mg) 60 min before entering the operating room. The second group was administered ondansetron, 4 mg that was administered I.V near the end of the procedure, and all patients received a standardized general anesthetic technique.

RESULTS:

There were no significant differences in any of the emetic outcomes or need for rescue antiemetics between TDS and ondansetron groups in the first 6 h after surgery.

CONCLUSION:

Premedication with TDS (1.5) mg was as effective as ondansetron (4 mg) in preventing nausea and vomiting in the early postoperative periods. Also less cost with TDS patch.

KEYWORDS: transdermal scopolamine; ondansetron; nausea and vomiting, antiemetic.

INTRODUCTION:

Postoperative nausea and vomiting is persist to be one of the most common complaints following anesthesia administered for surgery, it develops immediately in the postoperative period and may last longer.[1] In adults, Apfel and colleagues identified four highly predictive risk factors for postoperative nausea and vomiting (Post-operative opioid use in a dose-relate manner, patient gender (more for female),motion sickness, and smoking as it decreases the incidence. The presence zero ,one ,two, three or four of these factors paralleled to an incidence of postoperative nausea and vomiting of 10%, 21%, 39%, 61%, and 79%, respectively.2,3 Other risk factors[3,4] are Surgery examples for the surgery that have increased risk of nausea and vomiting breast, ophthalmic (strabismus repair), gynecological, laparoscopic, laparotomy, craniotomy (posterior fossa) orthopedics (shoulder procedures).Premedication clonidine and benzodiazepines decreased the risk of nausea and vomiting, Anesthesia type Volatile anesthesia has greater association with the risk of nausea and vomiting post-surgery, it's dose-dependent.[5]Dehydration and early food consumption rises the risk of nausea and vomiting.

It's known that Laparoscopic cholecystectomy most common patients are female who are also more susceptible to have nausea and vomiting after surgery than male. Post-laparoscopy nausea and vomiting incidence is ranging from 40% to 70%. It was proposed that pneumoperitoneum required for Laparoscopy has got direct consequence on postoperative nausea and vomiting and that happen because of retention of carbon dioxide gas, which acts both centrally on CNS level and peripherally.

Ondansetron:

Has been the most studied. The most common side effects are headache; Dizziness, constipation, and diarrhea. These are usually short term, and only mild to moderate in intensity. Most available Data suggests that these are most effective when administered at the end of surgery [6].

*Baghdad Medical City, Baghdad, Iraq

**Al-Karma Maternity and Emergency Hospital, Al-Anbar, Iraq

Dosage: The recommended adult intravenous dose of ondansetron for prevention of perioperative nausea and vomiting is 4 mg either prior to the induction of anesthesia or at the end of surgery. Postoperative nausea and vomiting can also be treated with a 4 mg dose, repeated as needed every 4–8 hour. Ondansetron undergoes extensive metabolism in the liver via hydroxylation and conjugation by cytochrome P-450 enzymes. Liver failure impairs clearance several-fold, and the dose should be reduced accordingly.[7]

Scopolamine and its quaternary derivatives act as antimuscarinics like ATROPINE, but may have more central nervous system effects. Is a centrally-active anticholinergic drug which has been found to be highly effective the prevention of motion-induced nausea and vomiting. Scopolamine reduces the secretions of certain organs in the body, such as the stomach.[8] Transdermal scopolamine (TDS) has also been reported to be effective in the prevention of postoperative nausea and vomiting. However, concerns have been raised regarding its use for routine antiemetic prophylaxis because of its alleged slow onset of action and side effect profile (e.g., drowsiness, visual disturbances, dry mouth, signs of an allergic reaction: hives; difficulty breathing; swelling of the face, lips, tongue, or throat.).[9] Every single imaginable factor should be resolved before starting salvage antiemetic drugs. Pain, mechanical reasons blood in the throat, intestinal obstruction and utilization of narcotics and different drugs should be considered.

PATIENTS AND METHODS:

this study is prospective randomized clinical trial. It is conducted in the surgical theatre of elective laparoscopic cholecystectomy in Madenat Al-Imamen Al-Khadumain medical Centre in Baghdad, Iraq during a period extending from sixth of March 2018 until fourth of December 2018.The study was approved by the Iraqi scientific council of anesthesia and intensive care, and the consent was obtained from all patients before including them in the study. A detailed history was taken from each patient; a clinical examination was performed pre operatively.

The inclusion criteria:

Patient selected to undergo elective laparoscopic cholecystectomy operation .Age ranges from 18-65 years.ASA 1 and 2

The exclusion criteria:

- Individuals who are hypersensitive to the study medications .If nasogastric tube were expected after surgery.
-Patient refusal.
-Patients who had received an antiemetic medication within the preceding day.
-History of alcohol.

In the preoperative preparing area, approximately 60 min before entering the operating room, a TDS patch containing 1.5 mg scopolamine was applied to a hairless area behind the ear. Before induction of anesthesia, name, age, gender and initial vital signs all were recorded. All the patients were prepared properly to the operation, wide bore IV cannula inserted, lying in supine position, connecting to the monitoring (pulse rate (PR), noninvasive blood pressure, SPO2&ECG). All patients received 50mg ranitidine, and 8mg dexamethasone as pre-induction agent. Anesthesia was induced with 0.5mg/kg ketamine, anesthetizing dose of propofol up to 2.5 mg/kg and tracheal intubation (with size 7.0-8.0 internal diameter endotracheal tube) was facilitated with a muscle relaxants Rocuronium bromide 0.6mg /kg. Anesthesia was maintained with isoflurane with concentration 1.2% in 100% oxygen. Analgesia was maintained paracetamol vial 15 mg/kg and nefopam ampoule 30mg.Ondansetron 4mg was administered IV. Upon withdrawal of the laparoscope. At the end of surgery, the neuromuscular agent was reversed by neostigmine 0.04 mg/kg with atropine 0.02 mg/kg. After adequate and regular ventilation, the endotracheal tube was removed and the patients transferred to postoperative care unit. The frequencies of patient complaints of nausea, vomiting and retching, visual disturbance, dry mouth, drowsiness, and restlessness, were recorded at 2, 4, and 6 h intervals as categorical responses (i.e., existing or lacking) by directly questioning each patient about these adverse effects. The need for rescue antiemetics during these postoperative periods was also noted. Complete responses to the multimodal prophylactic regimens were defined as the absence of protracted nausea (15min) or repeated episodes of vomiting/retching requiring rescue antiemetic therapy during the first 6 h postoperative study period.

Data analysis:

Statistical suite for social science version 20 (SPSS 20) was used for both data entry and data analysis. Continuous parametric data were presented as mean and SD and discrete nonparametric data presented as number (%). T test for independence used to test the significance of association for continuous variable and Chi-square test for discrete variable-value of< 0.05 were considered significant.

RESULTS:

This study included 100 patients, 50 for each group were enrolled and analyzed. The relationship between both gender, age and the occurrence of nausea and vomiting in both sex groups and their response to transdermal scopolamine patches
and ondansetron was analyzed (**Table 1, Table 2**). The incidence of post-operative nausea and vomiting and the need for antiemetic rescue medication occurrence in the first 2, 4, 6 hours respectively was documented for both drugs groups and revealed
no significant differences between them (**Table 3, figure 1, 2, 3)**. The complete response rates did not differ significantly between the two treatment groups (46% and 50% in the ondansetron and Transdermal scopolamine groups, respectively) (**Table 3, figure 1, 2, 3)**.
The incidence of side effects occurrence in both drugs groups and its relationship to the drug (TDS patch group and ondansetron) was calculated. **(Table 4)** and also demonstrated in **(figure 4).**The retail cost of transdermal scopolamine was 9$ per pack that is 3$ per patch while ondansetron ampoule cost a 7$. Fifty patch and 50 ampoules were received so the total cost of 50 patients receiving TDS is 150$. While the total cost of ondansetron was 350$ i.e. Ondansetron to TDS price ratio were 2.3:1.

Table 1: Gender differences between transdermal scopolamine patches and ondansetron group (McNemar test assess ass.between gender and type of drug taken shows significant association).

Drug	Female	Male	Differences
TDS	40 (80%)	10(20%)	McNemar shows significant association: p-value= 0.0001>0.05 Calculated chi2=19.3 Critical chi2=3.8
Ondansetron	43 (86%)	7(14%)	
Total	83(86%)	17(14%)	100(100%)

Table 2: Mean age differences between transdermal scopolamine patches and ondansetron group.

Age (Mean + SD) Years	TDS	Ondansetron
	41 ± 8	40 ± 8
P value =0.9 non-significant in unpaired t test (>0.05)		

Table 3: Postoperative Nausea and Vomiting and the Need for Rescue Antiemetics in the 6hrs. Study Period, as well as Complete Response Rates in the two Antiemetic treatment Groups.

Variables	Transdermal scopolamine	Ondansetron	P value
PONV 2 hr. Nausea Vomiting Rescue antiemetic	 21(42%) 3(6%) 23(46%)	25(50%) 2(4%) 20(40%)	P value=0.68>0.05 Non significant X2=0.75
PONV 4 hr. Nausea Vomiting Rescue antiemetic	 15(30%) 1(2%) 10(20%)	 18(36%) 3(6%) 20(40%)	P value=0.5>0.05 Non significant X2=1.3
PONV 6 hr. Nausea Vomiting Rescue antiemetic	 4(8%) 0(0%) 1(2%)	 5(10%) 0(0%) 0(0%)	P value=0.2>0.05 Non significant X2=1.1
Complete response rate	23(46%)	25(50%)	P value=0.6>0.05 Non significant Fishers extract test

Table 4: Side effects of treatment.

Side effects	TDS	Ondansetron	**association**
Headache	8(16%)	6(12%)	P value=0.5 Which is more than 0.05 X^2=2.2 No significant ass. Between side effect and drugs
Dry mouth	10(20%)	2(4%)	
Restlessness	7(14%)	4(8%)	
Drowsiness	8(16%)	5(10%)	

DISCUSSION:

In this comparative study which enrolled 100 patients divided into two groups, 50 patients each that receive a different antiemetic drug. The patient individual data like (age, gender) for both groups were comparable, P- *value* for age and gender (P value =0.9) which is more than 0.05 i.e., statistically non-significant in independent t test.

The mean age in this study is close to the mean age of study performed by Paul F et al were the mean age 42,5 ± 10.

Regarding to antiemetic efficiency of transdermal scopolamine patches, it didn't significantly differ from ondansetron (4 mg) in preventing of nausea& vomiting in patients having major laparoscopic cholecystectomy when calculated at 2nd, 4thand 6th hours post laparoscopic cholecystectomy; the p-*values* were 0.6, 0.5, and 0.2 respectively). comparable results were proposed by *Paul et a* in a study performed by him which found that transdermal scopolamine patches and ondansetron were very similar in their antiemetic usefulness the full response rates did not vary considerably between the two treatment groups; (51% and 47% in the ondansetron and transdermal scopolamine patches groups, respectively, while in this study the complete response rate were 46% and 50% in the transdermal scopolamine patches and ondansetron groups respectively) and that is statistically not differ significantly between them as the p-value=0.6).

In another study by Tarkkila et al [10]who described that when administered as part of a multidrug prophylactic regimen, Premedication with transdermal scopolamine patches reduced postoperative emesis. When compared with earlier studies in which the transdermal scopolamine patches was applied in the day that precedes the surgery, its application sixty minutes before surgery appears to result in an improved side effect profile.[11]

Although use of the TDS patch was more likely to produce side effects especially a dry mouth in the early postoperative period, the incidence of other common side effects in the TDS group did not differ much from the ondansetron treatment groups. (*P-Value*=0.5).

Transdermal scopolamine side effects had been systematically reviewed by *Kranke et al* as they have used it for the prevention of nausea and vomiting following surgery.[12]He proposed that mouth dryness and blurring of vision were common side effects in patients treated with

TDS. In another study done by *Paul F. White et al*[13], also states that there is an increased incidence of dry mouth with Transdermal scopolamine users in the postoperative period, and the other side effects which are commonly associated with using scopolamine did not differ much from the group who received ondansetron. With respect to additional antiemetics drugs required for the transdermal scopolamine patches getting patients. Contrasting with ondansetron the collective requirement for rescuing antiemetics was diminished from 46% to 20% through the first and second 2 hours after medical procedure individually. Thus, the difference between the two groups neglected to accomplish important statistical significant *(P-value = •.6)*.

The marketing price of TDS found to be significantly less than ondansetron, suggesting that it is a profitable alternative to the popular serotonin antagonist. In this study, the retail cost of transdermal scopolamine was 9$ per pack while ondansetron ampoule cost a 7$. i.e. Ondansetron 2.3 time more expensive than TDS. In a study performed at the University of Texas Southwestern Medical Center, The retail cost of TDS (US $7.75 per 1.5 mg patch), and ondansetron (US $26.80 per 4 mg ampule); the price differences between the two drugs are quite clear.

CONCLUSION:

In summary, this study support the use of TDS as a cost-effective alternative to ondansetron as part of multidrug prophylaxis anti emetic regimen for patients with laparoscopic cholecystectomy.

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