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Comparative study of Oral Vs IV Ondansetron for reducing PONV in patients undergoing laparoscopic surgery under General anesthesia

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Abstract *: Objective: Primary objective of our study was to study efficacy of ondansetron by two different routes i.e. oral vs i.v.in preventing PONV in patients undergoing laparoscopic surgery under general anesthesia. Patients and methods: 80 ASA grade I and II patients undergoing laparoscopic surgery under general anesthesia were randomly divided in two groups- Group A (recieved mouth dissolving placebo tablet 1 hour before induction and 4mg i.v. ondansetron just before induction (n=40), Group B (recieved 8 mg oral ondansetron mouth dissolving tablet one hour before induction and 2 ml saline just before induction) Standard anesthesia using thiopentone sodium, succinyl choline, midazolam, fentanyl , vecuronium and Isoflurane aws used. Diclofenac sodium was used for postoperative analgesia. Incidence of nausea nad vomitting was noted during first six hours; and during next 18 hours. Rescue antiemetic was given when patient complained of nausea and vomiting. Results: The demographic profile was similar in both the groups. We found that complete responce was seen in 92.5% patients in first six hours and 87.5% patients in next 18 hours in i.v. ondansetron group.complete responce was seen in 92.5% patients in first six hours and 90% patients in next 18 hours in oral ondansetron group. Both forms of ondansetron were well tolerated. None of the patients in either of the groups developed any side effects. Conclusions: The effect of oral 8 mg ondansetron was comparable to i.v. ondansetron 4 mg in preventing PONV in patients undergoing laparoscopic surgery under general anesthesia. Oral ondansetron prophylaxis may be a practical and cost effective alternative to i.v. administration.*

I. INTRODUCTION

In recent years, laparoscopic surgery has become a common clinical practice as it results in multiple postoperative benefits including less trauma, less pain, less pulmonary dysfunction, quicker recovery, and shorter hospital stay. Post-operative nausea and vomiting (PONV) is one of the most common side effects (40 – 75 %) associated with laparoscopic surgical procedures.[1] It can be very distressing for patients. It can lead to medical complications like wound disruption, esophageal tears, gastric herniation, muscular fatigue, dehydration and electrolyte imbalance. Patient may aspirate the vomitus leading to pulmonary complication. PONV may increase patient's anxiety about undergoing further surgery. Additional expenditure may occur due to delayed recovery, delayed discharge [2] and increased medical care. Nausea and vomiting is one of the most common postoperative complaints following general anaesthesia, second only to pain. [3] Perioperative use of ondansetron, a 5-HT_3 antagonist, appears to be helpful in the prevention and treatment of PONV. [4] Intravenous route is used commonly during perioperative period. Oral ondansetron is used postchemotherapy [5], acute gastroenteritis [6] and sometimes in perioperative period. [7] Oral antiemetic prophylaxis may be a practical and cost-effective alternative to intravenous administration in perioperative period. Hence we decided give ondansetron using two different routes i.e. i.v. and oral. Primary objective of our study was to study efficacy of ondansetron by two different routes, i.e. oral and IV, in preventing PONV in patients undergoing laparoscopic surgeries and compare the efficacy. Secondary objective was to study side effects of the study drugs.

INCLUSION CRITERIA

ASA Grade 1 and 2 patients of either sex of age group 18 – 65 years undergoing elective laparoscopic surgical procedures under general anesthesia.

EXCLUSION CRITERIA

1. H/o preoperative nausea or vomiting
2. H/o PONV after previous anesthesia
3. H/o motion sickness
4. Patient having diseases prolonging gastric emptying like diabetes mellitus, intestinal obstruction, hiatus hernia, obese patient (BMI > 30)

5. Known allergy to study drug or their constituents.
6. Pregnant and lactating mothers.
8. Patients on other antiemetic medications, opioids or hormonal therapy

II. MATERIALS AND METHOD

This randomized double blind prospective study was conducted in a teaching institute. After getting approval from the Hospital Ethics Committee and obtaining written informed consent, 80 patients, ASA 1 / 2, aged 18-65 years, undergoing elective laparoscopic surgery under general anaesthesia were selected. Patients were randomized into two groups using serially numbered, opaque, sealed envelopes.

Group A received mouth dissolving placebo tablet 1 hour before induction and 4 mg IV Ondansetron just before induction (n = 40).

Group B received 8 mg oral Ondansetron (mouth dissolving tablet) 1 hour before induction (n = 40) and 2ml saline IV just before induction.

Study drugs were administered by person not involved in postoperative outcome assessments. After confirming overnight fasting, Cardioscope, NIBP and Pulsoxymetry were attached. All the patients were premedicated with ranitidine 50 mg intravenously in the operating theatre. Then midazolam 0.03mg/kg amd Inj fentanyl 2mcg/kg was administered intravenously. Anaesthesia was induced with thiopentone sodium 5 mg/kg and tracheal intubation was facilitated by succinyl choline 1.5mg/kg. Following tracheal intubation vecuronium 0.1mg/kg was given. Anaesthesia was maintained with Isoflurane with 33% oxygen in nitrous oxide and the lungs were ventilated to maintain an end-tidal carbon-dioxide 35–45 mmHg. After intubation, nasogastric tube was inserted in all the patients and suction applied to empty the stomach of air and secretions. Before tracheal extubation, the nasogastric tube was suctioned and removed. Intravascular diclofenac (AQ) 75 mg was administered for postoperative analgesia 30 minutes before anticipated end of procedure. At the end of the procedure, neuromuscular blockade was reversed pharmacologically with neostigmine (50 mcg/kg) and glycopyrrolate (8mcg/kg). The trachea was extubated on return of consciousness with adequate muscle tone and patients were shifted to the post anaesthesia care unit. Duration of anaesthesia was noted. Postoperatively, diclofenac 75 mg was administered 8-hourly as i.v. infusion for analgesia. Inj paracetamol (1%) 100 ml i.v. was used as rescue analgesia.

In the postoperative period, nausea and vomiting were assessed in two epochs of 0–6h and 6–24 h by an anaesthetist who was unaware of the group allocations.

Following scores were used to assess nausea, vomiting and retching.

Nausea, defined as subjectively unpleasant sensation associated with awareness of the urge to vomit, was recorded on 11 point rating scale from 0 to 10 with 0 representing no nausea and 10 representing the worst imaginable nausea.

11 point scale was subsequently graded into 4 levels.

Severity of nausea	Scale
None	0
Mild	1- 3
Moderate	4- 6
Severe	7- 10

Emetic episodes were recorded as retching or vomiting.

Vomiting was defined as the forceful expulsion of gastric contents from the mouth.

Retching was defined as the labored, spasmodic, rhythmic contraction of the respiratory muscles without the expulsion of gastric contents.

If the events of vomiting or retching were separated by more than 1 min, they were considered as separate episodes.

Efficacy of the study drug was evaluated as

Complete response: no emetic episode / no nausea

Moderate response: 1-2 emetic episodes / mild to moderate nausea

Failure of response: > 2 emetic episodes / severe nausea

Patients complaining of severe nausea and having >2 episodes of vomiting were given Injection metoclopramide 0.15 mg/kg intravenously as rescue anti-emetic.

III. STATISTICAL METHODS

Sample size was calculated as follows: the reported incidence of PONV in laparoscopic surgeries has been 40–70% [1]. To detect a 30% reduction in the incidence would require at least 33 patients in each group to achieve 80% power at 5% Type I error if the incidence of PONV is 50%. A total of 80 patients were recruited taking into account possible inadvertent data attrition. All analyses were performed using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA) and a p value < 0.05 was taken to be significant.

IV. RESULTS

Table 1 Demographic data and duration of anesthesia. All values except gender are expressed as mean +_SD. Gender is expressed in numbers.

	Intravenous ondansetron(n = 40) Mean +_SD	Oral ondansetron (n = 40) Mean +_SD
Age; years	43.5+_15.4	44.7+_13.5
Gender; M:F	7:33	9:31
Weight; kg	52.2+_12.03	50.2+_11.14
Duration of anesthesia; min	87.7+_4.12	89.3+_5.23

Demographic data and duration of anesthesia were comparable in both the groups.

Table 2 Incidence of postoperative nausea and vomiting. The values are expressed as numbers (%)

		Intravenous ondansetron (n = 40)	Oral ondansetron (n = 40)	p value
0–6 h	Nausea	3 (7.5%)	2 (5%)	0.222
	Vomiting	1 (2.5%)	2 (5%)	0.474
	Rescue antiemetic	2 (5%)	2 (5%)	0.608
6–24 h	Nausea	5 (12.5%)	4 (10%)	1.000
	Vomiting	2 (5%)	2 (5%)	0.608
	Rescue antiemetic	3 (7.5%)	2 (5%)	0.222

Table 3 Efficacy of the study drugs. The values are expressed as numbers (%)

		Intravenous ondansetron (n = 40)	Oral ondansetron (n = 40)	p value
0–6 h	Complete response	37 (92.5%)	37 (92.5%)	0.608
	Moderate response	2 (5 %)	2 (5%)	0.608
	Failure of response	1 (2.5 %)	1 (2.5 %)	0.608
6–24 h	Complete response	35 (87.5%)	36 (90%)	0.568
	Moderate response	4 (10%)	3 (7.5%)	0.456
	Failure of response	1 (2.5%)	1 (2.5%)	0.608

V. DISCUSSION

Postoperative nausea and vomiting (PONV) are common and distressing complications and are the main concern of 40–70% of patients after laparoscopic surgery [1]. In ambulatory surgery setting, 0.1%-0.2% patients need unanticipated admission due to PONV. [8] Patient concerns regarding PONV are often greater than their concern for avoidance of postoperative pain [9]. Ondansetron, a 5-hydroxytryptamine subtype 3 (5-HT3) receptor antagonist, has been documented to be an effective anti-emetic in preventing and treating PONV with few side effects [10]. Orally disintegrating ondansetron has been shown to be effective in preventing chemotherapy induced nausea and vomiting [11] and in acute gastroenteritis. It is tried in perioperative period as well [7]. The oral route of drug administration is simple, cheaper, painless and hence acceptable to most of the patients. Orally disintegrating tablet of ondansetron easily disintegrates on the tongue and is well absorbed from the gastrointestinal tract [11].

We hypothesised that oral Ondansetron is as effective as IV Ondansetron. Primary objective of our study was to study efficacy of Ondansetron by two different routes, i.e oral and IV, in preventing PONV in patients undergoing laparoscopic surgeries and compare the efficacy. Secondary objective was to study side effects of the study drugs. Though it has been recommended that PONV studies should be placebo controlled, considering high likelihood of developing PONV without prophylaxis in patients undergoing laparoscopy surgeries, we did not consider it ethical to include placebo arm in the study. There were no significant differences between the two groups with respect to age, height, weight, operative time. (Table 1). There is increased incidence of PONV in females throughout life, even after menopause, which obviates any role of estrogen as a factor. [3] Comparable sex distribution in both the groups avoids this bias.
History of previous PONV or motion sickness increases the risk for PONV by two to three times. History of motion sickness suggests a more susceptible vestibular component. This factor has been reported as a strong predictor of PONV [12] hence we excluded these patients from our study.

Factors such as premedication, type of anaesthesia, intraoperative anaesthetic drugs and preoperative antiemetic drugs can affect the incidence of PONV. Patients receiving general anaesthesia are more likely to experience PONV than those receiving regional anaesthesia [13] hence to avoid variation; we selected patients undergoing surgery under general anaesthesia only.
Opioids have well established emetogenic potential, the degree of risk is predicted on the total dose administered, not on the particular agent. [3] But for providing good analgesia all the patients received fixed doses of fentanyl intraoperatively. Propofol decreases postoperative nausea and vomiting when it is used for induction of anaesthesia, compared with thiopentone [13] hence to avoid any change in incidence of PONV due to propofol, we used thiopentone sodium for induction of anaesthesia. There have been conflicting reports regarding the effect of nitrous oxide on PONV. It has been reported that nitrous oxide produces a greater incidence of vomiting [14] and that omission of nitrous oxide reduces the incidence of vomiting [15], but only if the baseline risk of vomiting is high in the patient population [16]. However, there are also reports showing no reduction in the incidence of nausea when nitrous oxide was omitted [16]. Omitting nitrous oxide to reduce PONV may increase the risk of intraoperative awareness [16] hence we included nitrous oxide in all the patients.

Inhaled agents also have emetogenic potential. We used Isoflurane in all the patients to avoid any bias though the differences in the incidence of PONV with isoflurane, desflurane and sevoflurane are not well documented. It is commonly thought that the use of antagonists of neuromuscular block anticholinesterases such as neostigmine for the reversal of non-depolarising neuromuscular blocking drugs can increase the incidence of PONV [17] due to the muscarinic actions on the gastrointestinal tract. Some authors reported no significant difference in PONV between those who received a reversal agent and those who did not [18]. We have used Neostigmine with glycopyrrolate in all the patients.
Pain can increase the incidence of PONV [19] by prolonging gastric emptying time. Use of postoperative opioids can increase PONV. Hence Diclofenac Sodium was used to manage postoperative pain. [20] Tramadol was avoided because of its emetogenic property. The study protocol used predefined doses of opioids and NSAIDs for intra-operative and postoperative analgesia equally in both the groups. This may help to eliminate the variations in the incidence of nausea or vomiting caused by pain and opioids.

The use of 5-HT3 receptor antagonists is popular as the drugs have shown good efficacy in preventing PONV. These drugs act by two mechanisms: firstly, by blocking the 5-HT3 receptors in the area postrema and the nucleus tractus solitarius and secondly, by blocking peripherally afferent vagal impulses originating from 5-HT3 receptors in the mucosa of the gastrointestinal tract. The intravenous route conventionally has been used for prophylaxis in the perioperative period. Tramer reported optimal prophylactic intravenous dose of ondansetron was likely to be 8 mg for long-term efficacy [21]. Watcha and White re-analysed data used by Tramèr et al and found that the absolute success rates for prophylaxis with ondansetron 4 and 8 mg i.v. did not significantly differ for the separate incidences of nausea and vomiting [22]. Hence we used a 4-mg dose of IV ondansetron.

Previous studies have shown oral ondansetron to be effective in preventing chemotherapy induced nausea and vomiting [23], acute gastroenteritis [6] and perioperatively. Bioavailability of oral ondansetron is 56% [11], hence 8-mg tablet appears equivalent to 4 mg of intravenous ondansetron. When the oral tablet is administered pre-operatively there is no risk of accidental aspiration of the tablet because patient is conscious and the interference in absorption due to altered gastrointestinal motility would be minimal during this time. Peak plasma concentrations occur at approximately 1.7 hours after oral administration. Despite the plasma half life of approximately 3 to 4hours efficacy is 24 hours [24]. Hence single dose of 8 mg was administered orally one hour prior to operation.

Orally disintegrating tablets (ODT) of ondansetron, which disperse rapidly when placed on the tongue, have been used to treat radiotherapy- and chemotherapy-induced nausea and vomiting [23, 25]. We preferred using this formulation of ondansetron instead of traditional oral medication because of need for preoperative fasting. The ODT form of ondansetron seems to offer important advantages for anesthesia practice, as it avoids IV injection while maintaining the desired preoperative fasting state. Another important advantage of this formulation of the drug is that it can be used in ambulatory surgery after patient discharge.
Gastric distension due to gases entering stomach during positive pressure ventilation through facemask has been associated with increased PONV [26]. Routine aspiration of gastric contents via orogastric suctioning does not decrease postoperative nausea and vomiting [27]. Still nasogastric tube was inserted after intubation, in all the patients and suction was applied to empty the stomach of air and secretions immediately after insertion. At the end of operation, before tracheal extubation, the nasogastric tube was suctioned. Presence of a nasogastric tube during postoperative period may stimulate the gag reflex [27], hence the tube was removed before extubation. This was done in all the patients to avoid any bias.

Our results showed that orally disintegrating ondansetron (8 mg) was as effective as intravenous ondansetron (4 mg) in preventing PONV during the first 24 h in patients undergoing laparoscopic surgery under general anaesthesia. Three patients in the intravenous as well as oral group vomited after the first 6 h.

Arash et al found no significant difference in Ondansetron, Orally Disintegrating Tablets Versus Intravenous Injection for Prevention of Intrathecal Morphine-Induced Nausea, Vomiting, and Pruritus in Young Males with respect to incidence or severity of PONV. [28]

J. H. Raphael found that 82% patients had no nausea or vomiting after receiving IV ondansteron after laparoscopy [29] as against 92.5% in first 6 hours after IV ondansetron in our study.

For the 24-hr recovery period after surgery, the percentage of emesis-free patients was 65.5%, after intravenous ondansetron group in patients undergoing laparoscopic cholecystectomy in a study done by Mohamed et al. [30]

We found that complete response was seen in 92.5% patients in first 6 hrs and 87.5% patients in next 18 hours in IV ondansetron group. Also complete response was seen in 92.5% patients in first 6 hours and 90% patients in next 18 hours in oral ondansetron group Our results have shown that pre-operative oral ondansetron is equally efficacious as intravenous ondansetron in preventing PONV after laparoscopic surgery. Oral ondansetron is a viable alternative to IV ondansetron in treating PONV in first 6 hours. The patients usually tolerate oral intake by this time and can be administered another dose of oral ondansetron if the need arises postoperatively. Both forms of ondansetron were well tolerated. None of the patients in either of the groups developed headache, cardiac dysrhythmias, or extrapyramidal signs. Freedman SB reviewed cardiac arrhythmias with ondansetron and found no reports describing arrhythmia associated with single dose oral ondansetron. But 60 reports of arrhythmias were identified with IV Ondansetron administration. [31] We did not measure postoperative pain in detail, which could affect the incidence of PONV and we acknowledge this as a shortcoming of the study. Also, further studies are required to evaluate the efficacy of oral dispersible ondansetron in other types of procedures and anaesthesia. Ondansetron gel is being evaluated for transdermal delivery, with penetration enhancers camphor and isopropyl-myristate. Skin pretreatment with a micro-needle roller may improve the delivery of the gel. This may be the future route for ondansetron administration. [32]
From the findings of our study, we conclude that orally disintegrating ondansetron is an effective alternative to intravenous ondansetron in preventing postoperative nausea and vomiting in patients undergoing laparoscopic surgeries under general anaesthesia. Ondansetron is tolerated well by both the routes without any difference in side effects.

REFERENCES

[1] *Koivuranta MK, Laara E, Ryhanen PT . Antiemetic efficacy of prophylactic ondansetron in laparoscopic cholecystectomy. A randomized, double-blind, placebo controlled trial. Anaesthesia 1996; 51: 52–5.*

[2] *Chung F, Mezei F. Factors contributing to a prolonged stay after ambulatory surgery. Anesth Analg 1999;89:1352–9.*

[3] *Nausea, Vomitting, and hiccups: A Review of Mechanisms and Treatment, Daniel E. Becker, Anaesth Prog, 2010 Winter; 57(4): 150-157.*

[4] *McKenzie R, Kovac A, O'connor T, Duncalf D, Angel J, Gratz I, Tolpin E, McLeskey C, Joslyn A.: Comparison of ondansetron versus placebo to prevent postoperative nausea and vomiting in women undergoing ambulatory gynecologic surgery. Anesthesiology 78(1) 1993.*

[5] *Khamales S, Bethune-Volters A, Chidiac J, Bensaoula O, A randomized, double-blind trial assessing the efficacy and safety of sublingual metopimazine and ondansetron in the prophylaxis of chemotherapyinduced delayed emesis. Anti-Cancer Drugs 2006; 17: 217–24.*

[6] *Golshenkan K, Badeli H, Rezaieian S, Mohammadour H, Hassanzadehrad A. , Effect of ondansetron on decreasing vomiting associated with acute gastroenteritis in Iranian children. Iran J Pediatr, 2013, Oct; 23(5): 557-63*

[7] *Lahsaei SM, Amini A, Tabatabei SM, Mehrabani G, A comparison between cetrizine and ondansetron in preventing postoperative nausea and vomiting in adults. J Res Med Sci.2012 Aug: 17(8): 760-3*

[8] *Gan TJ, Meyer TA, Apfel CC, Chung F, Davis PJ, Habib AS, Hooper VD, Kovac AL, Kranke P, Myles P, Philip BK, Samsa G, Sessler DI, Temo J, Tramer MR, Vander Kolk C, Watcha M, Society for ambulatory Anaesthesia. Society for ambulatory Anaesthesia guidelines for management of postoperative nausea and vomiting. Anaesth analg.2007;105:1615-1628.*

[9] *Eberhart LH, Morin AM, Wulf H, Geldner Q. Patient preferences for immediate postoperative recovery. Br J Anaesth 2002; 89:760–1.*

[10] *Pearman MH. Single dose intravenous ondansetron in the prevention of postoperative nausea and vomiting. Anaesthesia 1994; 49 (Suppl.): 11–5.*

[11] *GlaxoSmithKline. Product Monograph on Zofran ODT (Ondansetron Orally Disintegrating Tablets) – Product Information 4137892. Research Triangle Park, NC: GlaxoSmithKline, 2001.*

[12] *Sinclair DR, Chung F, Mezei G. Can postoperative nausea and vomiting be predicted? Anesthesiology 1999; 91:109-18.*

[13] *Myles PS, Hendrata M, Bennett AM, Langley M, Buckland MR. Postoperative nausea and vomiting. Propofol or thiopentone: does choice of induction agent affect outcome? Anaesth Intensive Care 1996; 24:355-9.*

[14] *Hartung J. Twenty-four of twenty-seven studies show a greater incidence of emesis associated with nitrous oxide than with alternative anesthetics. Anesth Analg 1996; 83:114-6.*

[15] *Tramer M, Moore RA, McQuay HJ. Meta-analytic comparison of prophylactic antiemetic efficacy for postoperative nausea and vomiting: propofol anaesthesia vs omitting nitrous oxide vs total i.v. anaesthesia with propofol. Br J Anaesth 1997; 78:256-9.*

[16] *Tramer MR, Moore RA, McQuay HJ. Omitting nitrous oxide in general anaesthesia: meta-analysis of intraoperative awareness and postoperative emesis in randomized controlled trials. Br J Anaesth 1996; 76:186-93.*

[17] *Watcha MF, Safavi FZ, McCulloch DA, Tan TSH, White PF. Effect of antagonism of mivacurium-induced neuromuscular block on postoperative emesis in children. Anesth Analg 1995; 80:713-7*

[18] *Haigh CG, Kaplan LA, Durham JM, Dupeyron JP, Harmer M, Kenny GN. Nausea and vomiting after gynaecological surgery:A meta-analysis of factors affecting their incidence. Br J Anaesth 1993; 71:517-22.*

[19] *Kotiniemi LH, Ryh nen PT , Valanne J, Jokela R, Mustonen A, Poukkula E. Postoperative symptoms at home following day-case surgery in children: a multicentre survey of 551 children. Anaesthesia 1997; 52:963-9.*

[20] *Eriksson H, Tenhunen A, Korttila K. Balanced analgesia improves recovery and outcome after outpatient tubal ligation. Acta Anaesthesiol Scand 1996 Feb; 40(2):151-5.*

[21] *Tramer MR, Reynolds JM, Moore RA, McQuay HJ. Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials. Anesthesiology 1997; 87:1277-89.*

[22] *White PF, Watcha MF. Posoperative nausea and vomiting: prophylaxis versus treatment. Anesth Analg 1999; 89:1337-9.*

[23] *LeBourgeois JP, McKenna CJ, Coster B, et al. Efficacy of an ondansetron orally disintegrating tablet: a novel oral formulation of this 5-HT(3) receptor antagonist in the treatment of fractionated radiotherapy-induced nausea and emesis. Clin Oncol (R Coll Radiol) 1999; 11:340–7.*

[24] *Pritchard JF, Bryson JC, Kernodle A, Age and Gender effects on the ondansetron pharmacokinetics: Evaluation of healthy aged volunteers. Clin Pharmacol Ther 51:51-55, 1992.*

[25] *Davidson N, Rapoport B, Erikstein B, et al. Comparison of an orally disintegrating ondansetron tablet with the conventional ondansetron tablet for cyclophosphamide-induced emesis in cancer patients: a multicenter, double-masked study. Clin Ther 1999;21:492–502.*

[26] *Julie Golembiewski, Eric Chernin, Tania Chopra, Prevention and treatment of postoperative nausea and vomiting, Am J Health Syst Pharm, 2005;62(12):1247-1260*

[27] *Tr panier CA, Isabel L. Perioperative gastric aspiration increases postoperative nausea and vomiting in outpatients. Can J Anaesth 1993; 40:325-8.*

[28] *Arash Pirat, Şenay F. Tuncay, Adnan Torgay, Selim Candan, Ondansetron, Orally Disintegrating Tablets Versus Intravenous Injection for Prevention of Intrathecal Morphine-Induced Nausea, Vomiting, and Pruritus in Young Males. Aneastheisa & Analgesia November 2005 vol. 101, no.5, 1330-1336.*

[29] *J. H. Raphael, A. C. Norton. Antiemetic efficacy of prophylactic ondansetron in laparoscopic surgery: randomized, double-blind comparison with metoclopramide Br. J. Anaesth. 1993; 71: 845–848*

[30] *Mohamed Naguib, Abdel Karim El Bakry, Mohammed H. B. Khoshim, Amir B. Channa. Prophylactic antiemetic therapy with ondansetron, tropisetron, granisetron and metoclopramide in patients undergoing laparoscopic cholecystectomy: a randomized, double-blind comparison with placebo. Canadian Journal of Anesthesia. Volume 43, Number 3, 226-231.*

[31] *Freedman SB, Ulervk E, Rumantir M, Finkelstein Y, Ondansetron and the risk of cardiac arrhythmias: A systematic review and postmarketing analysis. Ann Emerg Med, 2014 Jul: 64(1): 19-25.*

[32] *Patel DR, Joshi A, Patel HH, Stagni G, Development and in vivo evaluation of ondansetron gels for transdermal delivery. Drug Dev Ind Pharm, 2014 Jun 12:1-7*