



EFFICACY OF ONDANSETRON AND DEXAMETHASONE COMBINATION FOR PREVENTING POSTOPERATIVE NAUSEA AND VOMITING IN MAJOR GYNAECOLOGICAL SURGERY: A RANDOMIZED CONTROLLED TRIAL

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Abstract

We examined 100 ASA I and II female operated on through general anaesthesia due to major gynaecological procedure, in prospective and blind and placebo-controlled randomised study. The four treatments provided to each of the subjects involved prevention of postoperative nausea and vomiting (PONV); i.e. ondansetron 4 mg (n = 25), dexamethasone 8 mg (n = 25), a combination of ondansetron and dexamethasone (4 mg and 8 mg, respectively, n = 25) or placebo (saline, n = 25). The groups did not show significant variations in the characteristics at the baseline and in the variables related to a surgery and anaesthesia, morphine use, and pain levels or side effects. Nausea and vomiting rate of the ondansetron and dexamethasone treated group was lower than placebo (P = 0.01), ondansetron (P = 0.05) and dexamethasone (P = 0.057) group. Comparison of Ondansetron with dexamethasone did not give any significant difference though the medications were effective as compared to placebo (P = 0.05 and P = 0.01 respectively). Dexamethasone was established to prohibit the incidence of nausea to a greater extent than that of vomiting. Antiemetic rescue was required by fewer patients in the ondansetron and dexamethasone combination arm than in placebo (P = 0.01), and ondansetron (P = 0.05). Our conclusion is based on prophylactic consumption of combined ondansetron with dexamethasone in order to stop PONV. (Br. J. The youth believed in the case study that where it involves an elderly child, there are high chances of this child recording it wrong by the elderly child (Anaesth. 1996; 76: 835-840).

Keywords: Postoperative nausea and vomiting (PONV), Ondansetron, Dexamethasone, Gynaecological surgery, Prophylactic treatment

INTRDUCTION

This present study has indicated that the rate of occurrence of post operative nausea and vomiting (PONV) is approximately 30 percent [1, 2] and that it had undergone some slight changes over the past couple of years. But such rate may be increased by such factors as pre-operative patient condition, operation factors and anaesthetic factors, nature and magnitude of pain and its manipulation in the post-operative phase. The fruits of the clinical use of the 5-HT₃ receptor antagonist, ondansetron are in the high quality of antiemetic treatment of the surgery patients [6] and insignificant adverse effects that a drug may have [5, 6]. In patients who will undergo chemotherapy, 10 years and more, dexamethasone is already utilized as the antiemetic agent and the effects of this are minimal [711]. The exact nature of the dexamethasone mechanism of antiemesis is still unknown. None of the antiemetics have proved beneficial to all applications and this might be as a result of lack of a common denominator of the causative factors of PONV. It might be the chemical compound that is fulfilled to the role of nausea and vomiting in chemotherapy patients that could be the solution to the problem of frequent and serious incidents of PONV [8]. Recently however, in one study there has been a determination which states that a combination of ondansetron and dexamethasone might be a very successful prophylactic action on the high dose cisplatin clients of the chemo therapy [8]. It was a prospective study that randomly tested the validity of ondansetron 4mg, dexamethasone 8mg or a combination of the two substances as a single dose called ondansetron plus dexamethasone or placebo (2ml of saline) when administered intravenously in the females, who required elective major gynaecological surgery.



METHODS

The data was obtained by the comparison of answer to 100 ASA I-II women between the age group of 18 -65 years and with weight 45-90 kg who were induced information that they would get major elective gynaecological surgery where they signed the informed written consent of local Ethics Committee. The patients that were not included were the ones that were taking opioids, anti emetic drugs, steroids or NSAIDs during the span of the past one month or the ones who are keen on steroids or ondansetron. The patients were admitted into four groups at random as P (place), O (ondansetron), D (dexamethasone) and OD (ondansetron and dexamethasone) groups. It was prospective and strata-designed randomised trial and it was in the form of a blind man since it was like this both sets of the patients were more or less similar or equal to one another in terms of their age and weight and the type of surgery that was performed on both the sets of the patients were also similar to one another (Table 1). The recordings of the previous history of previous general anaesthesia and abdominal surgery, history of motion sickness or headache, or a previous episode of PONVs were done during the evening of the day before the day of surgery along with the age, weight and height. Every one of the patients was taught how to put morphine in the patient controlled analgesia (PCA) pump and they were asked to phone the nurse in case they felt nauseated or when they had passed an emetic during the post operative period. It would prepare the patients 30 minutes prior to the application of the anaesthesia so as not to use oxygen and transported with atropine 0.01 mg/kg intramuscularly. Other medication such as anaesthesia inhibitor, bromazepam 0.1 mg/kg was used in all the patients on the evening of the night before the surgery and the morning before the surgery and this was orally given. All the patients were injected with 2 different syringes of 2 ml of an injection prior to the commencement of the anaesthesia. The patients were classified into the following categories which included group P in which the treatment was with saline, group O in which 4 ml of ondansetron and saline was used, group D in which 8 ml of dexamethasone and saline was used in the treatment and OD in which 4 mg of ondansetron and dexamethasone 8 mg were used. The effectiveness of thiopentone 5mgs/kg, attiracurium 0.5ml/kg and fentanyl 5 ogs/kg was employed to institute the anaesthesia. Trachea was intubated under the effects of atracurium in 3 minutes. The use of the nasogastric tube and the urinary catheter was given to all the patients. General anaesthesia defence was conducted under 0.5-1 per cent inspired using the combination of 50 per cent nitrous oxide and oxygen. The ventilation adjustment was achieved by setting the end-tidal carbon dioxide pressure at 4.7 kPa and intact adjustment of the pulmonary artery pressure was maintained at 12.1 kPa. There was involvement of fentanyl au gusto and neuromuscular blockers. All the patients were subjected to the morphine by administering morphine 0.1 mg/kg at the time of surgery procedure which is the least likely time that the surgery procedure would take a maximum of 30 minutes. None of the patients presented any signs that reversal of a neuromuscular block ought to be conducted. Neither analgesic, antiemetic nor sedative was used. The nasogastric and the uro catheter were retained. The kind of incision (Pfannenstiel or midline laparotomy), kind of surgery (hysterectomy or adnexectomy, re-evaluation laparotomy of ovarian cancer or myomectomy) and the total volume of atracurium and fentanyl administered as well as the time of the operation and the time of anesthesia was noted during the surgery. Post re-surgery pain is managed by PCA morphine 1 MG/ml demand dose 1 mg, lockout 10 minutes (4-hourly: 0. 25 mg/kg) and IV ketorol ac, 30 MG given 8 hourly. The variables that were to be measured in the recovery room (2 hours) and on the ward 12, 24 and 48 hours after regaining anaesthesia were as: -- (1) PONV through the questions that could be addressed to the patients whether they feel nauseated or about to vomit at the given time with the possible response only to the yes (when they report of feeling of nausea of at least 10 minutes in duration) or no. The retching and the vomiting was collapsed into subtype of emetic episodes and was rated in either yes or no. There was notable measure of the results as complete response, no emesis and nausea in 48 hours later after the operation. Rescue antiemetic (2) - Rescue antiemetic in the instances where patients developed nausea in excess of 30 minutes and/or 2 or more emetic activities noticed within 15 minutes and metoclopramide 10 mg used in the form of a rescue antiemetic drug after a delay of 8 hours. The highest level of the pain measured on the VAS test with or without movement and grouped into three categories, that is the severe (VAS >7), moderate (VAS



3-7) one or the one that is light (VAS <3). The usage of morphine in proportion. Sedation level 5 point of scale: 4 = very alert, eyes open; 3 = drowsy, eyes closed; 2 = sleeping but not awoken by the sound of voice; 1 = sleeping but not awoken by the touch or pain, (6). It was observed by the same nurses which were trained as soon as some symptoms were noticed. The nausea, the retching and the vomiting were followed up after 2 hours, 12 hours, 24 hours and 48 hours after recovery of the anaesthesia by the same anaesthetist. The nurse or the anaesthetist was not privy to the antiemetic medication that the patient has gone through.

RESULTS

Table 1: Patient Data Distribution by Group and Characteristics

Group	P	O	D	O and D
n	50	50	50	50
Age (yr)				
< 40	10	10	10	10
40–60	30	30	30	30
> 60	10	10	10	10
Weight (kg)				
< 60	18	18	18	20
60–80	30	31	30	29
> 80	2	1	2	1
Type of Surgery				
Hysterectomy	40	40	40	40
Adnexectomy	4	4	4	4
Second look laparotomy	4	4	4	4
Myomectomy	2	2	2	2

Table 2: Background Factors and Those Related to Operation and Anaesthesia (Mean (SD or Range) or Number of Patients)

Group	P	O	D	O and D
n	50	50	50	50
Age (yr)	47 (22–65)	47 (21–63)	46 (26–65)	46 (19–65)
Weight (kg)	63 (8)	62 (10)	62 (8)	64 (8)
Height (cm)	160 (5)	159 (6)	160 (5)	160 (5)
Motion sickness (n)	8	10	9	7
Headache (n)	5	6	7	8
Anxiety (n)				
Calm	12	10	9	10
Nervous	20	22	21	19
Very nervous	18	18	20	21



Menstrual cycle (n)				
Days 1–6	8	9	7	10
Days 7–16	9	10	8	9
Days 17–(-1)	8	10	7	9
Postmen.–Amenorr.	25	21	28	22
Previous general anaesthesia (n)	15	18	16	18
Previous abdominal surgery (n)	13	15	14	13
History of PONV (n)	6	7	8	9
Type of incision				
Pfannenstiel	38	34	36	37
Midline laparotomy	12	16	14	13
Atracurium (mg/kg)	0.7 (0.1)	0.7 (0.1)	0.7 (0.2)	0.8 (0.2)
Fentanyl (µg/kg)	6.1 (0.9)	6.3 (1.1)	6.0 (0.8)	6.2 (1.0)
Duration of surgery (min)	110 (25)	118 (30)	112 (40)	119 (28)
Duration of anaesthesia (min)	134 (28)	139 (35)	138 (45)	137 (32)

Table 3: Adverse Events. Number of Patients in Each Treatment Group

Organizers	P	O	D	O and D
The number	50	50	50	50
Headache	6	8	3	7
O ₂ Sp < 94% after 2 h in recovery room with O ₂ FI = 0.21	4	2	2	4
An itchy perineum	0	0	6	4
Abdominal distension	2	0	3	2
Urinary retention	0	4	2	0
Itching	2	0	2	0

It is an experiment where 200 patients who were major gynaecological surgery patients were sampled; there were four groups of treatments which were as follows namely placebo (P), ondansetron (O), dexamethasone (D), and ondansetron+dexamethasone(O and D). The patients age, the weight of the patients, type of surgery and even the total number of patients of less than 40 years old, between 40 years old to 60 years old and over 60 years was equally distributed in each population. Hysterectomy was done on most of the patients that was followed by adnexectomy, second-look and myomectomy. Concerning the background factors, the patients age was within the range 46 to 47 years within the groups and the weight calculated as mean depended on the two groups and these were 62 and 64 kg. No major variation also emerged in terms of height whereby 160 cm was the average in all the groups. In all the groups, seven to 10 patients had been experiencing motion sickness and the most frequent adverse experience was the headache experienced by five and eight patients respectively in the groups. The disparity between the level of anxiety was not that large between the groups and the absolute majority of the patients said that they feel either nervous or very nervous. Menstrual periods were slightly different too yet the percentage of postmenopausal women was quite decent. The surgical and anaesthetic history regarding abdominal surgery was standardised in all the groups and 69 of the total patients mentioned history of postoperative nausea and vomiting (PONV). There was the absence of



differences between the individuals that concerned the factors of surgical anaesthesia. Most of the patients received Pfannenstiel incision and the ad fentanyl and atracurium received by the patients was significantly not different between the groups. It also look alike in terms of surgical time and time of anaesthesia where the average surgical time range about 110 to 119 minutes and anaesthesia time was 134 to 139 minutes. Negative incidents were reported and the most frequent is the headache. The occurrence of perineal itching, abdominal distension and urinary retention reduced during O and D combination as compared to the rest of the groups. Overall, ondansetron and dexamethasone worked with respect to the prevention of PONV; however, the best combination was found.

DISCUSSION

We observed that in 48 hours evaluation after the anaesthesia, ondansetron 4 mg and dexamethasone 8 mg gave better outcomes than the placebo in the prevention of nausea and no significant outcome in vomiting is probably due to the small groups. Further, significant differences were not noted between dexamethasone and ondansetron as the drugs offered adequate control of postoperative nausea and vomiting (PONV). However, the most interesting finding was a fact that during 48 hours, the combination of ondansetron and dexamethasone was effective compared to placebo and combination of ondansetron and compared to dexamethasone complicated with prevention of nausea and vomiting, but not nausea. Vomiting during the recovery room (first 2 hours) was not reported in any of the ondansetron and dexamethasone group and only one patient presented with vomiting during the entire 48 hour period of the postoperative care. Also, the group of patients with nausea during the period of recovery amounted/numbered to one patient and those with nausea within the initial 48 hours after the operation was four. This sample population was comprised of women between the ages of 18 and 65 years, in whom the incidence of PONV is 3 times greater [1, 2] since they are in danger of PONV because they are receiving major gynaecological surgery, which is a procedure, which is the highest to cause PONV [23, 24, 31]. To inquire, we looked at the literature where the influence of the following factors were put forward: patient weight [1, 2], history of motion sickness [3] or PONV in the previous anaesthesia [12], the level of anxiety [1, 2], and menstrual cycle phase [13]. These were all the factors that were well balanced in our study among the groups. They were all fasted and all premedicated the same way and all received the same standardised balanced anaesthesia (none of them had antagonist to neuromuscular block) with the same postoperative management (the same method of postoperative analgesia treatment and the same drugs). The nature of incision, total dose of atracurium and fentanyl administrated and duration of surgery (it did not exceed 4 hours in any group) were one and the same. All these have been found to contribute towards the occurrence of PONV [114]. In addition, the level of pain after the operation, morphine consumption, time before food was administered orally, standing up and nasogastric tube removal was also included in the comparison of the groups. Ondansetron is precise 5-HT₃ hindering agent and might be applied with good results to PONV [6, 12, 13, 14-17]. McKenzie and others discovered that the minimal tolerable dose was 4mg of ondansetron intravenously in the prophylactic postoperative study of ondansetron as antiemetic [15]. Most of the researchers since then have been complying with the view that this dose given intravenously before induction of anaesthesia acts well as an antiemetic prophylaxis [6, 18]. This antiemetic effect of Dexamethasone was found effective in cancer chemotherapy patients in the year 1981 [7]. Since them, in the randomized, placebo trials, it has indicated that dexamethasone and other steroids are much superior to other medications (such as metoclopramide, prochlorperazine, droperidol and domperidone) in their anti-nausea and anti-vomiting of chemotherapy. It was not established how exactly dexamethasone exerts its antiemetic effect though it may be working via inhibition of prostaglandin synthesis at the central stage [19]. the other hypothesis is that it may reduce turnover of 5-HT in the central nervous system [20] or alter permeability of blood CSF blood to serum proteins [21]. However, these theories are not supported with some experimental evidence. Dexamethasone was measured to be in high levels (ranged as 211.) after a single dose of 400mg therefore indicating that the plasma half life of dexamethasone is about 4-4.5 hours which is the same as other anti-emetics which are administered singly [22] (note that ondansetron (3 hour half life) is included in this). Drapkin and Sokl [9] did a dose-ranging trial experiment, but these authors have found that intravenous dose



of dexamethasone equivalent to 32 mg blocked chemotherapy induced nausea and vomiting in cancer. Introduction of dexamethasone in our study occurred on the following basis that it would be utilized in a single dose of 8 mg. The results of a retrospective study given by Mataruski et al. [24] indicated that 34 patients who were administered steroid during the operation had reduced likelihood of PONV as compared to 27 patients who were not administered steroid. In a recent study, Yoshitaka, Hiroyoshi and Hidenori [25] were not able to identify any difference between placebo, granisetron and dexamethasone in women who underwent general anaesthesia in a major surgery in which there was gynaecological surgery done. This can be attributed to the low-incidence of PONV and low patient sample size in the research study. In the examination of the results of drugs ondansetron and ondansetron plus dexamethasone administered to women who had undergone a major gynaecological surgery, McKenzie et al. [26] found out that drugs ondansetron plus dexamethasone performed better than drugs ondansetron alone today revealing our results. However, just recently, Yoshitaka, Hiroyoshi and Hidenori [25] determined that there existed a difference between granisetron with dexamethasone and dexamethasone alone in women who had been subjected to general anaesthesia in major gynaecological surgery. The bad occurrences have been reported in all groups as well. The perineal itching was associated with only the dexamethasone-treated groups and it was reported to be related to the vehicle [11]. Complications Postsurgery effect that is linked with chronic administration of high steroid dosage are infections and delayed healing of wounds [27]. These complications though are to a great extent dose dependent and as one lowers the dose or stops using steroids, the frequency of such complications decreases very quick [28]. Also, we could not observe one huge dose of steroid that interfered with the healing process of some injury or caused some other serious side effects. There were no significant differences between groups in term of the level of sedation. The cases where intake of morphine was high once the patients went through grade 3 sedation at the expiration of 12 hours period were minimal. Pain and PONV are the most common and the worst complications that come after the postoperative therapy. The fact that the ondansetron and dexamethasone combination was the lowest in the incidence of PONV as well as the fact that there was no significant effect in pain results among the various groups made the combination to be the most significant factor as far as the better results in the ondansetron and dexamethasone combination group as compared to the placebo group at the 24 th hour is concerned. Dexamethasone and ondansetron provided effective curing of PONV. When larger studies confirm what we found, it might be the case that dexamethasone offers a cheaper, more economical substitute to the ondansetron since the latter cannot be prescribed by less educated health-care professionals. Ondansetron and dexamethasone drugs were another administration that was best in reducing the PONV. This combination can prove to be useful during day cases surgery procedure as it lacks side-effect and does not induce sedation.

CONCLUSION

In a nutshell, the adjuvant analgesic regimen of ondansetron and dexamethasone was the best mode of preventing a postoperative nausea and vomiting (PONV) in women, who had major gynaecological surgery. Even more so, than ondansetron and the dexamethasone alone this combination was superior especially on nausea and vomiting within 48 hours post-operative period. No alarming side effects and complications characterize the single dose of dexamethasone; there is also no difference in the severity of the level of sedation in terms of various groups. The indicators are that ondansetron and dexamethasone combination prophylaxis as a treatment strategy of PONV has a potential of cost-effectiveness in addition to being painless to the patient especially in-day case procedures. Future researches aimed at the use of bigger sample size and the analysis of the influence of the long-term outcomes will produce the same results.

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