Original Article

Postoperative Nausea and Vomiting in Diagnostic Gynaecological Laparoscopic Procedures: Comparison of the Efficacy of the Combination of Dexamethasone and Metoclopramide with that of Dexamethasone and Ondansetron

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Abstract:

BACKGROUND AND OBJECTIVE: This study was conducted in a tertiary hospital with the aim of comparing the efficacy of a combination of dexamethasone and metoclopramide with dexamethasone and ondansetron for the prophylaxis of postoperative nausea and vomiting [PONV] after diagnostic gynaecological laparoscopic procedures. SUBJECTS AND METHODS: In this prospective, randomised, double-blind study, 120 women received either saline I.V. [Group I, n=40]; a combination of dexamethasone [8 mg] with metoclopramide [10 mg] [Group II, n=40]; or a combination of dexamethasone [8 mg] with ondansetron [4 mg] [Group III, n=40] prior to induction of general anaesthesia. PONV was evaluated at regular intervals. The results were analysed using one-way ANOVA, post-hoc, Chi-square, Kruskal-Wallis tests and Z test for proportions where appropriate through a SPSS V.9 package. RESULTS: The 3 groups were well matched for demographic characteristics. The incidence of nausea and emesis was significantly lower in Group III {[17.5%, *P <0.02*] and [10%, *P <0.01*] respectively}. Nausea scores were also lower in Group III *[P <0.02]*. Rescue anti-emetic requirements were higher in Group I *[P <0.05]* as compared to Groups II and III. CONCLUSIONS: A combination of dexamethasone and ondansetron was more efficacious as compared to that of metoclopramide and dexamethasone. The combination of metoclopramide and dexamethasone seems to offer no additional benefit as compared to saline placebo. **(J Postgrad Med 2003;49:302-6)**

Key Words: Postoperative nausea and vomiting, Anti-emetics, Dexamethasone, Metoclopramide, Ondansetron.

Efficient prevention and management of postoperative nausea and vomiting [PONV] continues to be a concern that needs to be addressed.[1] The incidence of PONV in patients undergoing gynaecological procedures is estimated to be in the range of 56-93%.[2,3]

There was a persistently high incidence of PONV despite prophylaxis with dimenhydrinate,[1] metoclopramide,[4] droperidol,[5] or ondansetron[5] when each was used alone in 'at risk' patients. Dexamethasone was also used as a stand alone drug in both paediatric and adult patients undergoing surgery.[6-8] However, the current opinion questions the role of monotherapy.[9]

PONV is still an unresolved problem. The incidence of PONV after gynaecological laparoscopic surgery is high and its control remains a difficult task.

Drug combinations are deemed to be more useful for balanced anti-emesis. A combination of ondansetron and dexamethasone for instance, is supposed to be quite effective.[10,11] However, the high cost of ondansetron has been a major constraint in its routine prophylactic use.[6]

This placebo-controlled, randomised double-blind study was conducted in search of an economical and efficacious combination of drugs for regular clinical use in the prevention of PONV in routine gynaecological diagnostic laparoscopic surgery. We also ventured to test the hypothesis of a likely synergistic effect between dexamethasone [which has been reported to be better in preventing nausea,[11] and which supposedly decreases 5-HT levels in the central nervous system,[12,13]] and the prokinetic drug metoclopramide [which has a dose-dependent action on central dopaminergic D_2 receptors, central and peripheral 5-HT_3 receptors, peripheral 5 HT_4 receptors,[4] thereby combining theoretically some of the anti-emetic properties of droperidol and ondansetron[14]].

Subjects and Methods

Subsequent to the institutional review board approval and after obtaining an informed consent, 120 women posted for diagnostic gynaecologi-

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cal laparoscopic procedures were randomised into 3 groups using the table of random sampling numbers. Those administering the interventions, and those assessing the outcomes were blinded to group assignment for the duration of the study.

Exclusion criteria included women above the age of 60 yrs, ASA class higher than II, those with significant medical diseases, those who received anti-emetics 24 hrs prior to surgery, and those women with a history of motion sickness or previous PONV. A PONV incidence of about 39% was predicted as female gender and non-smoking status were the two of the four risk factors (as identified by Apfel[15]) which were common to all the three groups. We did not categorise women according to the phase of the menstrual cycle at the time of operation, as many had irregular periods or dysfunctional uterine bleeding. Depending upon the group assignment, subjects received 4 ml saline [placebo] [Group I, n=40]; 4 ml of a combination of dexamethasone [8 mg] with metoclopramide [10mg] [Group II, n=40]; or 4 ml of a combination of dexamethasone [8 mg] with ondansetron [4 mg] [Group III, n=40], two-three minutes prior to the induction of anaesthesia.

The syringes containing the drugs were coded. The anaesthetist and the investigator were blinded to the drugs administered. All 120 women were premedicated with tab. midazolam 7.5 mg orally about 30 minutes prior to surgery. General anaesthesia was induced with thiopentone 4-6 mg kg^{-1}, fentanyl 2 mcg kg^{-1}, and atracurium 0.5 mg kg^{-1}. This was followed by endotracheal intubation and intermittent positive pressure ventilation with O_2, N_20 67% and isoflurane 0.5-2%. No nasogastric tube was left *in situ* during the procedure. Prior to the completion of the procedure, inj. diclofenac 75 mg was given IM. CO_2 (3-4 l) was used as the insufflating gas at a pressure of 20 mm Hg. After completion of the procedure, residual neuromuscular blockade was reversed with inj. atropine and inj. neostigmine. All women were extubated in the operating room. Patients were observed in the recovery room until they were haemodynamically stable, fully conscious and comfortable. Means and Standard Deviations [SD] were calculated for age, weight, duration of operation and stay in the recovery room in each group. The primary outcome measure was to assess the incidence of PONV in the first 24 hours and its amelioration with the two drug combinations. All the other parameters recorded were secondary outcome factors.

The simplified Apfel score is a useful tool for assessment of the risk of PONV. The primary end points of this study were the incidence of PONV in the first 24 hours and its amelioration with two drug combinations.

The patient was evaluated for PONV every hour postoperatively for the first 6 hours, every 2 hours for the next 6 hours and every 4 hours for the next 12 hours. The women were evaluated for a total period of 24 hours postoperatively. The incidence of nausea and emesis in each group was noted separately. The absence of any emesis or nausea was recorded as complete response. Retching was recorded as emesis. The incidence of emesis at 6 hours postoperatively in each group was also noted. The nausea score was evaluated using an 11-point numerical visual analogue scale [VAS <5= mild, 5 = moderate and >5 =severe, where 0= no nausea and 10= nausea as bad as can be].[12]

The severity of emetic episodes in terms of number of episodes per patient in each group was tabulated. The number of episodes per patient was classified as mild [< 2 episodes], moderate [= 2 episodes], and severe [> 2 episodes].[12] Ondansetron (1 mg) was administered as a rescue anti-emetic when the patient had more than two episodes of vomiting.[9]

Pain was measured on an 11-point numerical visual analogue pain scale [0-10; 0: no pain; 10: most severe pain possible].[7] The mean pain score was calculated based on the number of women with a VAS > 5. Rescue analgesic [Inj. propacetamol 2 gm IV] was given if the VAS exceeded a score of 5. No other opioid or sedative drug was given postoperatively.

Statistical Analysis

A pilot study performed at our institute revealed a PONV incidence of 60%, in patients undergoing diagnostic gynaecological laparoscopic procedures where no exclusion criteria were implemented. A power analysis based on this showed that a sample size of 40 patients would be required in each group to have a 95% chance [$(1-\pm) = 1.65$] with a one-sided test of detecting a 50% relative reduction in PONV with 80% power [$(1-^2) = 0.84$] and with an expected 10% [0.1] dropout rate.

An SPSS V.9 package was used for statistical analysis. The demographic data, the incidence of nausea, emesis and the frequency of complete response were analysed by one-way ANOVA test. The post-hoc test was used for the incidence of nausea and emesis [95% confidence interval]. The Chi-square test was also used to evaluate the incidence of nausea and emesis as well as complete freedom from nausea and emesis. Kruskal-Wallis [K-W] test was used for assessing nausea scores. The Z Test for proportions was used to evaluate the incidence of the severity of emetic episodes and for the usage of rescue anti-emetics and analgesics [95% confidence intervals]. A *P value* less than 0.05 were taken as significant.

Results

There was no statistical difference among the three groups as regards the demographic data (Table 1). The incidence of nausea was significantly less in Group III when compared to Groups II and I. The incidence in Groups I and II was similar and was close to the predicted PONV values. Nausea scores were lower in Group III as compared to Group I and II. The frequency of emesis was also significantly reduced in Group III as compared to Groups I and II (Table 2).

The frequency and severity of the episodes of emesis were highest in Group I as compared to Groups II and III. Subjects enrolled in Group I also required rescue anti-emetics more

frequently than their counterparts in the other groups [Table 2]. The incidence of mild to moderate episodes of emesis was higher in Groups I and II as compared to Group III. During the 24-hr observation period, the incidence of complete response was higher in Group III as compared to the other two groups (Table 2). Two patients in Group III had emetic episodes beyond 6 hours postoperatively as compared to 6 patients in Group I and 4 patients in Group II *[P =NS]*. The mean pain scores as well as the requirements for rescue analgesics were similar in the 3 groups (Table 3). None of the patients experienced any side-effects related to dexamethasone [facial flushing or hyperglycaemia], metoclopramide [extra-pyramidal symptoms, sedation, drowsiness or dizziness] or ondansetron [headache or abdominal pain].

A combination of dexamethasone and ondansetron, though not the 'gold standard' in PONV prophylaxis, proved to be more efficacious than the less expensive and easily available drug combination of dexamethasone and metoclopramide.

Discussion

As the three groups were well matched, the difference in the incidence and severity of PONV among the groups should be attributable to the effects of the anti-emetics administered. The aim of this study was to find a viable alternative to the combination of dexamethasone and ondansetron.[10,11] The study could not justify the hypothesis that there might be a beneficial effect if dexamethasone[11-13] is combined with metoclopramide.[4] We accept that the premises were based on the general sites of action of both the drugs and also depended on the doses administered.

We included a placebo group as per the recommendations of Tramer,[9] which gave an insight into the actual incidence of PONV in this subset. It was shown that dexamethasone was most effective when administered at the time of induction of anaesthesia.[6] As for ondansetron, it was suggested that in operative procedures lasting more than 2 hours, it might be more rel-

Table 1: Demographic data

Parameter	Group I (n=40) Mean (SD)	Group II (n=40) Mean (SD)	Group III (n=40) Mean (SD)	F*
Age	30.54 (7.62)	29.3 (7.41)	27.67 (6.31)	3.158
Weight	63.43 (11.59)	63.75 (16.14)	61.25 (8.96)	1.159
Duration of surgery	61.75 (22.34)	63.08 (26.98)	64[24.4]	0.196
Duration of RR stay	44.95(16.41)	44.38 (17.7)	46.45 (11.52)	2.58

* ANOVA test. P=NS

Table 2: PONV episodes, nausea scores, severity of emetic episodes, anti-emetic requirements and incidence of complete response

	PONV episodes		Nausea Scores*			PONV episodes		Severity of episodes of emesis & rescue anti-emetic requirements (No. of Patients)			Complete Response	
Group	Nausea incidence (%)	'P'	Mild VAS <5	Moderate VAS=5	Severe VAS>5	Emesis incidence	'P'	Severe [> 2 episodes]	Mild/ Moderate [= or<2 episodes]	Rescue Anti-emetic requirement [%]	Complete response incidence (%)	'P' (%)
I	18/40 (45.0)	14	4	–	16/40 (40)		6	10	15% [P<0.05]†	22/40 (55.0) [P<0.05]†		
II	16/40 (40.0)		11	5	–	14/40 (35)		1	13	2.5%	24/40 (60.0)	
III	7/40 (17.5)	<0.02‡ <0.02§ [F=3.97]‖	4	3	–	4/40 (10)	<0.01‡ <0.01§ [F=5.42]‖	1	3	2.5%	33/40 (82.5)	<0.02‡ <0.02§ [F=3.43]‖

*Kruskal-Wallis Test between Groups II and I for nausea scores showed no difference *[P=0.67]*. K-W Test showed a significant difference in favour of Group III *[P<0.02]* on comparison of Group III with other groups. † Z test for proportions, ‡ Chi-square test: Group III in comparison with Groups I & II, § One-way ANOVA test and post-hoc test for multiple comparisons [Tamhane]: Group III in comparison with others. ‖ F values by ANOVA test

Table 3: Pain scores & analgesic requirements

Group	No. of subjects with VAPS* > 5 requiring additional administration of analgesic agents	Mean Pain Score	Minimum	Maximum
I (n=40)	10 [25]	7.7	6	10
II (n=40)	10 [25]	7.3	6	9
III (n=40)	10 [25]	7.4	6	9
*P**	*NS*	*NS*		

Figures in parentheses indicate percentages, * Visual Analogue Pain Score, ** Chi-square test

evant to administer the drug towards the end of the surgery as the half-life of ondansetron is approximately 3.5-4 hrs in adults.[6,9,10,16] Since the mean duration of the procedure in our study was about an hour, we assume that the timing of anti-emetic administration, whether it was administered at the beginning or towards the end of the surgery, would not have affected the outcome. Dexamethasone has been found to be effective when used alone in several studies.[7,8,17] Despite this, dexamethasone in combination with metoclopramide did not have a beneficial effect in our patients as compared to the placebo group.

The pharmacodynamic half-life appears to be dramatically different and longer than the pharmokinetic half-life for anti-emetics and this is especially true with dexamethasone. With a biological half-life of 36 to 72 hrs[18] dexamethasone should theoretically confer a longer duration of prophylaxis. However, the incidence of emesis beyond 6 hrs was similar in the three groups, indicating that the anti-emetics used in this study were not beneficial in delayed PONV [> 6hrs] prophylaxis. This, as a result, has implications for day-case surgery.

Our study confirms the observation of Henzi et al[4] regarding the poor anti-emetic effect of metoclopramide in the dose of 10 mg IV. Unlike Levitt et al[19] who concluded that the efficacy of a combination of dexamethasone and metoclopramide in controlling nausea and vomiting equalled or exceeded that of ondansetron in patients on chemotherapy for breast cancer, we could not demonstrate any such beneficial effects. This might be due to the fact that the aetiology of nausea and emesis in cancer therapy is clearer unlike the multi-factorial aetiology in PONV.

We could have considered other inexpensive drugs like droperidol[3] and dimenhydrinate[1,20] instead of metoclopramide. Droperidol is no longer available in Oman, where this study was conducted, after the FDA placed a black box warning on its use in December 2001. Dimenhydrinate has unclear dose response, has side-effects and the optimal time of administration is not clearly defined.[1] As there seems to be little to choose between dimenhydrinate and metoclopramide, metoclopramide was selected as one of the constituents in the drug combinations in this study.

The dexamethasone and metoclopramide combination was used earlier for major gynaecological surgery.[21] Our study differs from the above in terms of the surgical setting in that diagnostic laparoscopic surgery, compared to major gynaecological surgery is less traumatic and less time-consuming. The incidence of a complete response in Group II [60%], where we used the dexamethasone and metoclopramide combination, was comparable to the observations of Fuji et al.[21]

Our finding that a combination of dexamethasone and ondansetron is most effective in PONV prophylaxis complements previous studies. Lopez-Olando et al[11] concluded that prophylactic administration of a combination of dexamethasone and ondansetron is effective in preventing PONV in patients undergoing major gynaecological surgery with fewer patients requiring rescue anti-emetics as compared to their other regimens of placebo, ondansetron or dexamethasone. Rajeeva et al[12] also found that a combination of dexamethasone and ondansetron provided an adequate control of PONV in patients undergoing gynaecological diagnostic laparoscopies with an overall incidence of only 8% *[P<0.05]*. They suggested that delayed PONV [2-24hrs] was better controlled with dexamethasone and ondansetron than with ondansetron alone. Contrary to this we found that the incidence of delayed emesis [emesis occurring after 6hrs] was similar among the 3 groups. We concur with Henzi et al,[18] who concluded that the best, currently available prophylaxis for PONV is a combination of dexamethasone with a 5 HT_3 receptor antagonist.

Conclusions

We conclude that a combination of dexamethasone and ondansetron offers better prophylaxis for PONV in patients undergoing diagnostic laparoscopic gynaecological procedures than a combination of dexamethasone and metoclopramide. We did not address the issues of economy and surrogate variables like patient satisfaction, hospital-discharge times, expenses incurred towards treating established PONV etc. and these can be considered as the shortcomings in this study. Metoclopramide, in spite of being combined with dexamethasone, showed no beneficial effect. This is consistent with the suggestion that the addition of metoclopramide to other anti-emetics has rarely been shown to achieve any additional benefit.[21,22] We also suggest that the role of metoclopramide 10 mg, given at the beginning of surgery for PONV prophylaxis, needs reassessment.

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