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Research Article

Postoperative nausea and vomiting management in maxillofacial procedures: Dexamethasone combined with metoclopramide

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Abstract *Background:* Efficient prevention and management of postoperative nausea and vomiting (PONV) continues to be a concern that needs to be addressed. There was a persistently high incidence of PONV despite prophylaxis with, metoclopramide, droperidol, dimenhydrinate or ondansetron when each was used alone in 'at risk' patients. Dexamethasone was also used as a stand alone drug in patients undergoing surgery. However, the current opinion questions the role of monotherapy. Drug combinations are deemed to be more useful for balanced anti-emesis. The aim of this study was to evaluate the prophylactic antiemetic effects of the combination dexamethasone–metoclopramide in patients undergoing maxillofacial procedures.

Patients and methods: In this placebo-controlled, double-blind study, 208 outpatients under standardized anesthetic technique were randomized to receive dexamethasone 8 mg before anesthesia

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induction and metoclopramide, 10 mg at the end of surgery (Group A), dexamethasone 8 mg before anesthesia induction and placebo at the end of surgery (Group B), placebo before anesthesia induction and metoclopramide, 10 mg at the end of surgery (Group C) or placebo before anesthesia induction and at the end of surgery (Group D). Complete response to prophylactic antiemetic medication was defined as no vomiting, no sustained moderate nausea and no requesting of antiemetic drug.

Results: During predischarge period, the number of patients with complete response to prophylactic antiemetic medication was significantly higher in Groups B (90.4%) and A (86.5%) in comparison with Groups D (55.8%) and C (75%). At the 24 h follow-up evaluation, complete response was higher in Group A (96.2%) in comparison with Groups C (67.3%) and D (78.8%).

Conclusions: Dexamethasone–metoclopramide combination is not more effective than administration of dexamethasone alone in the prophylaxis of (PONV).

1. Introduction

The incidence of PONV has remained static over the last 20 years despite the use of short-acting anesthetics and execution of minimally invasive surgeries, most of those executed in the ambulatory context [1].

The use of prophylactic antiemetic drugs produces greater patient satisfaction than treatment of symptoms of PONV [2–4]. However, it has generated a great controversy regarding antiemetic treatment to be more cost-effective compared to routine prophylaxis because of the introduction of newer, more expensive antiemetic medications (antiserotoninergic and neurokinin 1 antagonist) [5,6]. The results of multifactorial design studies suggest that antiemetics with different mechanisms of action have additive effects on the incidence of PONV [7]. The low cost and excellent safety profile of dexamethasone have been classified as a highly cost-effective strategy in the prevention of this adverse event [7,8]. Metoclopramide is a medication that has been used for 40 years in the prevention of postoperative emesis [9]. It is a very low-cost drug, and dose of 10 mg IV, has a low incidence of adverse events [10]. Despite its limited relevance prophylactic antiemetic (NNT [number needed to treat] = 9.1 and 10 for early postoperative nausea and vomiting, respectively) is the only medication approved by the Mandatory Health Plan as an antiemetic prophylaxis [10].

In order to determine the true benefit of antiemetic prophylaxis with two drugs administered at different times of anesthesia, we designed this clinical study comparing the efficacy of dexamethasone and metoclopramide, each of these medications used individually and with combination in preventing PONV after outpatients' maxillofacial surgical procedures.

2. Patients and methods

After approval being obtained from the Research Committee of the Department of Anesthesiology and the Faculty of Medicine, King Khalid University Hospital, King Saud University in Riyadh, Saudi Arabia 208 patients signed written informed consent, and scheduled electively for maxillofacial surgical procedures (e.g. impacted tooth extraction, jaw reconstruction, removal of cyst or tumor) were enrolled in this randomized clinical, double-blind, placebo controlled trial. Patients between the ages of 20 and 52 years were randomly assigned to one of four treatment groups using a table of computer-generated random numbers:

(A) dexamethasone–metoclopramide group who received dexamethasone before induction of anesthesia and metoclopramide 30 min before the end of surgery, (B) dexamethasone group, who received dexamethasone before induction of anesthesia and 0.9% normal saline 30 min before the end of surgery, (C) metoclopramide group who received 0.9% normal saline before anesthesia induction and metoclopramide 30 min before the end of surgery and (D) placebo group who received 0.9% normal saline both before induction of anesthesia, about 30 min before the end of surgery.

We excluded patients who had received any antiemetic medication or who had experienced emesis or nausea during a period of 24 h before surgery, pregnant, had consumed psychoactive substances for 24 h before surgery, who had received steroids in a period of 6 months prior to surgery and patients with a known allergy to the drugs studied. Also patients with an ASA (American Society of Anesthesiology) class III or higher. Also patients who suffer from any condition that contraindicated steroid administration: hypertension, heart disease, renal failure, peptic ulcer disease, diabetes, Cushing disease, adrenal insufficiency, immunosuppression, recent tuberculosis and cataracts were excluded from study. Detailed medical history was obtained from each patient and also demographic information including age, height, weight, ASA physical status, prior use of drugs, previous history of PONV or vertigo of motion.

Immediately before surgery, all patients were assessed for nausea, anxiety, sedation, dizziness and pain using a 100 mm verbal analog scale (VAS) (0 = none and 100 = maximum pain). The medications were prepared to the study by the head nurse of operating room in two numbered 5 ml syringes, which were identical in appearance. The first syringe (syringe labeled #1), contained dexamethasone 8 mg, or 0.9% normal saline (in a total volume of 5 ml) was administered 3 min before induction of anesthesia. The second syringe (syringe labeled #2), contained metoclopramide 10 mg, or 0.9% normal saline (in a total volume of 5 ml) was administered 30 min before the predicted end of surgery. Patients in Group A received dexamethasone 8 mg in Syringe #1 and metoclopramide, 10 mg in Syringe #2. Patients in Group B received dexamethasone 8 mg Syringe #1 and 0.9% normal saline in the Syringe #2. Patients in Group C received 0.9% normal saline in the Syringe #1 and metoclopramide, 10 mg in Syringe #2. Patients in

Group D received 0.9% normal saline both in the Syringes #1 and #2. In the operating room, patients were monitored conventionally and subsequently received a standardized anesthetic technique consisting of fentanyl, propofol and rocuronium for induction and isoflurane for maintenance after endotracheal intubation. At the end of surgery neuromuscular relaxant was antagonized using neostigmine.

The anesthetic time (from start of induction to discontinuation of the volatile anesthetic), the time of surgery (from the local anesthetic infiltration to the placement of surgical dressings), and eye opening times (from volatile anesthetic discontinuation to eye opening), follow verbal commands (from the discontinuation volatile anesthetic to lift his/her head to the verbal command) and orientation (from the discontinuation of the volatile anesthetic until it was able to give the name and date of birth) were recorded. Length of stay in the post-anesthesia care unit (PACU), and time to unassisted ambulation (from the discontinuation of volatile anesthetics) which meets hospital discharge criteria were recorded.

The standard criteria for hospital discharge included stable vital signs, ability to ambulate without assistance, spontaneous diuresis and absence of severe pain or nausea. One of the investigators blinded to the antiemetic treatment group recorded all intraoperative and recovery variables, including the incidence of PONV and the need for rescue antiemetic medication. An episode of emesis was defined as vomiting or retching or any combination of these events occurring in rapid sequence (<1 min between events). When the interval between episodes of vomiting or retching was >1 min were considered separate episodes. If the patient experienced repeated episodes (two or more) of emesis, or moderate nausea (>40 mm on VAS) held for 15 min or more, or if requested antiemetic, promethazine was administered, 6.25 mg IV. If emesis or nausea persisted for more than 15 min after administration of promethazine, 4 mg IV ondansetron was administered. The primary efficacy outcome in this study was defined as a complete response to antiemetic prophylaxis. This in turn was defined as no vomiting, no moderate nausea sustained for 15 min or more and no application for administration of rescue antiemetic medication.

In all patients, postoperative pain was treated with morphine 1.5 mg IV bolus every 10 min until the patient feels comfortable (<40 mm on VAS). The VAS was used to assess nausea, anxiety, sedation, dizziness and pain immediately before the discharge. We recorded all adverse events and medications used in the PACU.

Patients were contacted within 24 h after surgery by antiemetic blinded investigators. They were asked to report the number of episodes of vomiting and any antiemetic medication taken since patient left the hospital. Similarly, they were asked to rate nausea since they were discharged using a 11-point verbal scale (0 = no nausea to 10 = ''worst imaginable nausea'').

2.1. Statistical analysis

Assuming that 60% of patients undergoing maxillofacial procedures under general anesthesia develop PONV and the incidence of this adverse event in patients treated prophylactically with dexamethasone is approximately 45% in previous studies, was established by an a previous power analysis, 52 patients were needed per group to have 80% chance to detect a 25% reduction of PONV in Group A in relation to the Groups B and C and a reduction of 40% compared with Group D with a significance level ($P = 0.05$). One way analysis of variance series (ANOVA) were conducted to examine differences among the four groups with respect to parametric variables. If there was a significant difference, Student's t-test was used to detect intergroup differences. Categorical variables were analyzed by χ^2 and Fisher test. A $P < 0.05$ was considered significant.

3. Results

The four treatment groups were comparable with respect to sex, age, BMI, menstrual cycle period, prior use of cigarettes,

Table 1 Patient demographic characteristics, preoperative assessment scores, anesthetic and surgical data.

	Group A ($n = 52$)	Group B ($n = 52$)	Group C ($n = 52$)	Group D ($n = 52$)
Age (years)	32 ± 9	30 ± 10	31 ± 9	32 ± 11
Sex (F/M; *n*)	24/28	26/26	22/30	21/31
BMI (kg/m^2)	24 ± 3	24 ± 3	24 ± 3	23 ± 3
History of smoking [*n* (%)]	15 (28.8)	15 (28.8)	11 (21.2)	17 (32.7)
History of PONV [*n* (%)]	5 (9.6)	3 (5.8)	10 (19.2)	4 (7.7)
History of vertigo [*n* (%)]	4 (7.7)	3 (5.8)	8 (15.4)	6 (11.5)
Nausea VAS (0–100 mm)	11	4	0	6
Anxiety VAS (0–100 mm)	34	36	32	35
Sedation VAS (0–100 mm)	0	1	1	0
Vertigo VAS (0–100 mm)	0	0	2	2
Pain VAS (0–100 mm)	3	1	1	1
Propofol (mg)	160 ± 26	160 ± 19	160 ± 29	158 ± 30
Fentanyl (mg)	156 ± 35	156 ± 43	169 ± 49	158 ± 35
Rocuronium (mg)	30 ± 17	28 ± 14	30 ± 15	27 ± 15
Anesthesia time (min)	125 ± 58	121 ± 48	131 ± 63	137 ± 68
Surgery time (min)	113 ± 56	108 ± 46	115 ± 61	124 ± 66
Eye opening time (min)	17 ± 9	17 ± 11	17 ± 8	16 ± 10
Verbal command time (min)	20 ± 10	21 ± 11	19 ± 8	20 ± 11
Orientation time (min)	42 ± 20	41 ± 18	38 ± 12	38 ± 17

Values are mean ± SD, numbers (*n*), or percentages (%).
No significant differences between groups.
F/M = female/male, BMI = body mass index, PONV = postoperative nausea and vomiting, VAS = verbal analog scale.

Table 2 Incidence of nausea and vomiting (moderate > 40 mm on VAS) persisting for 15 min or more, and response to treatment.

	Group A (n = 52)	Group B (n = 52)	Group C (n = 52)	Group D (n = 52)
n (%) (95% CI)				
Vomiting (PACU)	6 (11.5) (3–20)[a]	4 (7.7) (5–14)[bc]	13 (25) (13–37)	20 (38.5) (25–52)
Nausea (PACU)	4 (7.7) (4.5–14)[bc]	2 (3.8) (1–9)[dc]	13 (25) (13–36)	21 (40.4) (27–54)
Rescue treatment (PACU)	3 (5.8) (5–12)[dc]	2 (3.8) (1–9)[dc]	13 (25) (13–37)	19 (36.5) (23–49)
Failed treatment (PACU)	7 (13.5) (4–23)[bc]	5 (9.6) (2–17)[dc]	13 (25) (13–37)	23 (44.2) (22–49)
Failed treatment (24 h)	2 (3.8) (–0.14–9)[bc]	6 (11.5) (3–20)[d]	16 (30.8) (20–45)	11 (21.2) (10–32)

The values are numbers (n) or percentages (%) and confidence intervals (CI) 95% of the percentages.
[a] $P < 0.05$ compared with Group D.
[b] $P < 0.05$ compared with Group C.
[c] $P < 0.01$ compared with Group D.
[d] $P < 0.01$ compared with Group C.

Table 3 Time profiles of intermediate and late recovery and verbal scores on scales similar to hospital discharge.

	Group A (n = 51)	Group B (n = 51)	Group C (n = 51)	Group D (n = 51)
Nausea VAS (0–100 mm)	8[a]	27[b]	46	77
Anxiety VAS (0–100 mm)	17	4	15	27
Sedation VAS (0–100 mm)				
Vertigo VAS (0–100 mm)	33	33	17	31
Pain VAS (0–100 mm)	7	4	10	32
PACU stay time (min)	9	10	9	12
Ambulation time (min)	30 ± 6[a]	25 ± 5[a]	39 ± 4	54 ± 6
Tolerance to liquids (min)	193 ± 66[ac]	187 ± 76[ac]	278 ± 155	267 ± 146
Work return (days)	350 ± 178[ad]	351 ± 132[ad]	424 ± 176	478 ± 245
	4 ± 1	4 ± 1	5 ± 1	4 ± 1

Values are mean ± SD, numbers (n).
VAS: visual analog scale.
[a] $P < 0.01$ compared with Group D.
[b] $P < 0.05$ compared with Group D.
[c] $P < 0.01$ compared with Group C.
[d] $P < 0.05$ compared with Group C.

and history of previous PONV or vertigo of motion. There were no differences in preoperative assessment for patients regarding verbal scales of nausea, anxiety, sedation, dizziness and pain. The doses of fentanyl, propofol, rocuronium, neostigmine and atropine were similar in all groups, like the time of anesthesia and surgical time of eye opening, and command guidance (Table 1).

During pre-hospital discharge, the number of patients experiencing full prophylactic treatment response was significantly higher in dexamethasone Group (B) and dexamethasone metoclopramide (A) when compared with placebo (D) and metoclopramide alone (C). Complete response was similar among patients who received dexamethasone alone (Group B) and dexamethasone–metoclopramide combination (Group A) and those who were given metoclopramidealone (Group C) and placebo (Group D) (Table 2). Also Table 2 shows the incidences of PONV persisted for 15 min or more and request for antiemetic therapy in each group.

In a post hoc analysis on the use of postoperative analgesia, the dose of morphine was significantly lower in Group A [(dexamethasone–metoclopramide) 10.4 ± 3.2 mg] and Group B [(dexamethasone) 10.3 ± 3.6 mg] with respect to Group D [(placebo) 17.7 mg ± 5.6 mg] ($P < 0.05$). One patient in Group A was hospitalized for intractable pain. Evaluations carried out with verbal scales similar to hospital discharge revealed no differences in anxiety, dizziness, sedation or pain. However, nausea scores were significantly higher in Group D compared with Groups A and C (Table 3). Patients who received dexamethasone–metoclopramide and dexamethasone alone had a shorter stay in the PACU and met the hospital discharge criteria significantly faster than patients who received metoclopramide or placebo. Similar results were obtained with the time interval to achieve the real output of unassisted ambulation and oral tolerance to liquids. These variables also did not differ between dexamethasone–metoclopramide and dexamethasone alone groups and between metoclopramide and placebo groups (Table 3).

The assessment that carried out at 24 h showed that the proportion of patients with complete response in this period was significantly higher in the dexamethasone–metoclopramide group compared with metoclopramide alone and placebo groups and similarly in the dexamethasone alone compared with the metoclopramide alone groups. The proportion of treatment failures in the metoclopramide and placebo groups were similar (Table 2).

There were no differences in the time of reinstatement work (Table 3) and there was no evidence of surgical wound infection in any of the 208 participating patients.

4. Discussion

This study demonstrated that administration of dexamethasone as a single medication, is equally effective like the combination of dexamethasone–metoclopramide to prevent PONV in outpatient maxillofacial procedures. This means that the addition of metoclopramide does not confer any additional benefit in the prevention of secondary event. It also shows that metoclopramide administered as single prophylactic antiemetic agent is comparable to placebo.

This study found that dexamethasone administered before induction of anesthesia was associated with a reduction in the incidence of failed prophylactic antiemetic therapy in 35% (incidence of treatment failure of 44.2% vs. baseline 9.6% in the dexamethasone group) and 31% when metoclopramide was added. This reduction is greater than 26% reported in a multifactorial study which included multiple risk factors for PONV and surgical procedures [7].

Our study also found an incidence of 44.2% PONV in the placebo group, which was lower than the incidence that demonstrated by Apfel (59%) among those patients not receiving prophylactic antiemetic therapy and who received volatile anesthetic, nitrous oxide and fentanyl [7]. It should be noted that in that study, the ENT procedures had the highest incidence of PONV (14.3%) [11–13]. That is why our study population represents a clinically relevant baseline risk of PONV as the maxillofacial surgeries is not considered one of the high risk surgeries for nausea and vomiting. Surprisingly, our incidence of nausea in the PACU was similar to that of emesis, unlike what usually reported [12,14].

Dexamethasone has proved more effective as a prophylactic antiemetic when administered during anesthesia induction [8,15,16]. There are several reasons why this time of implementation seems to be especially effective for reducing emetic symptoms; is associated with pre-incisional reduced levels of 5-hydroxytryptophan in neural tissue by depleting its tryptophan precursor (16), the anti-inflammatory properties of corticosteroids before the surgical incision can prevent the release of serotonin in the gastrointestinal tract [17], and it is possible that early administration of dexamethasone may potentiate the effects of other antiemetics by sensitizing pharmacological receptors [18].

There is indirect evidence that metoclopramide may be more effective as a prophylactic antiemetic when administered at the end of surgery [19]. Ferrari and Donlon found that 0.15 mg/kg of metoclopramide upon arrival at the PACU was an effective prophylactic antiemetic in children born to adenoidectomy [20]. In contrast, Furst and Rodarte failed to demonstrate antiemetic effect when 0.5 mg/kg of metoclopramide was administered immediately after induction of anesthesia [21]. The behavior of metoclopramide as a prophylactic antiemetic in this study is consistent with results of previous study: a dose of 10 mg IV antiemetic effects has no clinical relevant [10]. It is likely that the dose used in this study (which is routinely used in clinical practice) is big [22]. Its effect on 5-HT3 receptors appear to be dose dependent and the lowest dose to block these receptors is suspected [23]. Therefore there is a require for further evaluation to determine the optimal dose of metoclopramide in combination with dexamethasone for the prevention of PONV without any improper blocking dopamine receptors, the situation which is associated with the presentation of the undesirable extrapyramidal effects.

This study evaluated the treatment outcomes in two different time periods. The short-term efficacy is primarily an economic impact in the ambulatory area [12]. The long-term positive results are the best indicators of the antiemetic activity and patient's welfare [23].

The present study confirms the early and late antiemetic efficacy of dexamethasone when compared to placebo that reported in a recent systematic quantitative review [8]. However, so far no results have been reported about the efficacy of dexamethasone–metoclopramide combination in the prophylaxis of PONV. By contrast, the use of this addition is purely anecdotal, and has in fact been adopted in antiemetic prophylaxis protocols in some anesthesiology departments.

5. Conclusion

In conclusion, the combination of dexamethasone with metoclopramide was not significantly more effective than single administration of dexamethasone in the prophylaxis of PONV in patients undergoing maxillofacial surgery. Therefore other antiemetic agents such as haloperidol and antiserotoninergic, added to dexamethasone may be considered for increase antiemetic prophylactic effectiveness [12,24]. Metoclopramide at doses of 10 mg IV has no prophylactic antiemetic effects, the fact that this is the only medication approved by the prophylactic antiemetic Compulsory Health Plan must be reconsidered.

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