NALOXONE VERSUS METOCLOPRAMIDE FOR THE TREATMENT OF ESTABLISHED POSTOPERATIVE NAUSEA AND VOMITING IN PATIENTS FOLLOWING GENERAL ANESTHESIA WITH FENTANYL SUPPLEMENTATION

- PILOT STUDY -

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Introduction

Postoperative nausea and vomiting (PONV) remains a common adverse event associated with surgery and anesthesia. Despite significant advances in the area of PONV and the introduction of new antiemetic agents, the overall incidence of PONV is currently estimated to be around 20 to 30%[1].

PONV can cause prolonged post anesthesia care unit (PACU) stay and unanticipated admissions following ambulatory surgery, therefore increasing medical costs[1]. Nausea and vomiting are also among the most unpleasant experiences associated with surgery and one of the most common reasons for poor patient satisfaction rating in the postoperative period[2]. Because PONV is multi-factorial and several neurotransmitters are involved in the emetic response, effective management remains challenging.

Intraoperative opioids are considered one of the anesthesia related factors for PONV[3-5]. In a review of 27,626 patients admitted to the PACU, administration of opioids during surgery increased the risk of PONV four folds[6]. Roberts et al[7] also confirmed that incidence of nausea and vomiting both increased in a dose dependent manner by the amount of opiate administered postoperatively. Prophylactic administration of an antiemetic had no influence on the risk of PONV in the PACU related to opioids[6].

Low dose naloxone infusion (0.25mcg-1mcg/kg/hr) has been shown to decrease epidural and patient controlled analgesia (PCA) opioid related side effects (nausea, vomiting and pruritis) without affecting pain scores[8-12], and hence naloxone administration may also decrease the incidence of PONV following general anesthesia including fentanyl supplementation. Metoclopramide has been used for the treatment of PONV in the PACU[13-14], and for breakthrough PONV after prophylaxis[15].

The purpose of this study is to compare the antiemetic effectiveness of bolus intravenous naloxone 0.5mcg/Kg versus metoclopramide 10mg for the treatment of PONV in the PACU, in patients undergoing general anesthesia including fentanyl supplementation.

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Methods

After obtaining Institutional review board approval and informed consent for this randomized controlled prospective study; ASA I and II patients aged 18-70 years, scheduled for elective surgery under general anesthesia including fentanyl supplementation were recruited. Exclusion criteria included patient's refusal, renal or liver diseases, pregnant or lactating mothers and patients who were on antiemetic drugs preoperatively. Using standardized monitoring techniques of EKG, pulse oximetry, and blood pressure, induction of general anesthesia was done using propofol 2mg/Kg, lidocaine 1.5 mg/Kg and fentanyl 2mcg/Kg. Muscle relaxation was achieved with rocuronium 0.6mg/Kg. For maintenance of anesthesia, nitrous oxide/ oxygen mixture with sevoflurane was used. Additional doses of fentanyl and muscle relaxants were administered as needed. At the end of the surgical procedure reversal of the neuromuscular blockade was achieved with neostigmine 0.05mg/Kg and glycopyrrolate 0.01mg/Kg. The total dose of fentanyl used, as well as, the duration of the operation were recorded. Upon arrival to the PACU, assessment of nausea was done according to a four points verbal descriptive scale (VDS)[16] (0 = no nausea, 1 = mild, 2 = moderate, 3 = severe). The assessment was done by one PACU nurse involved in the study. Vomiting was recorded as either present of absent.

Treatment for PONV was given if nausea was moderate to severe and lasted for 10 minutes, more than one episode of vomiting occurred, or at any time the patient requested treatment. A total of 44 patients experienced PONV in the PACU and warranted treatment. Patients were randomly selected to receive either metoclopramide 10mg or naloxone 0.5mcg/kg, both drugs diluted to 10ml.

The person administering the medications was unaware of the treatment drugs. Assessment of the patients was done at 2, 5, 10 minutes following the study medication. Response was documented as complete(i.e no nausea and vomiting and no antiemetics given) or partial (i.e improvement in the nausea score). After 10minutes, if the patient continued to complain of nausea or vomiting, or had a partial response to either naloxone or metoclopramide and requested treatment, ondansetron 4mg intravenously was given.

Assessment of pain was also recorded according to the 10 point verbal analogue scale (zero being = no pain, and 10 being = the worst pain ever). As regards to safety, we reported all possible drug-related side effects and observed vital signs before and 10 minutes after treatment.

Continuous variables were analyzed using Student t-test, and quantitative variables were analyzed using Fisher's Exact Test. All tests performed were two-sided with significance level set at $P < 0.05$.

Results

Twenty two patients were treated with Naloxone and 22 with Metoclopramide. Both groups were comparable in terms of age, sex, operative duration, total intraoperative fentanyl used, and number of PONV risk factors (Table 1).

Table 1
Demographic and Clinical characteristics of Patient Population (N = 44)

	Naloxone (N = 22)	Metoclopramide (N = 22)
Age (years)	46 ± 14	46 ± 17
M:F	7:15	7:15
Weight (Kg)	78 ± 19	78 ± 22
Operative duration (hours)	2.5 ± 1.6	2.2 ± 1
Total fentanyl (µg)	236 ± 137	322 ± 194
Risk Factor Score (median)	1.5	1

Total response (ie the total number of patients who responded partially or completely) to naloxone was comparable to the effect of metoclopramide at five minutes14 patients (64%) versus 16 patients (73%) respectively. Also, at 10 minutes14 patients (64%) naloxone versus 18 patients (82%) metoclopramide ($P = 0.255$) as shown (Table 2). However, the number of patients who were free of nausea and vomiting (complete response) in the naloxone group at 5 minutes (27%, n = 6) was statistically higher than in the metoclopramide group (5%, n = 1), ($P = 0.046$). Complete response at 10 minutes was 7 patients (32%)

in the naloxone group versus 3patients (14%) in the metoclopramide group. The antiemetic effect was not related to the total amount of fentanyl used, operative time, age, weight, or initial pain score (Tables 3, 4). Pain did not increase after treatment with naloxone, and the mean pain score was 4.1/10 at 2, 5 and 10 minutes. In the metoclopramide group, mean pain score did not change significantly (Table 5).

Table 2
Response at 2,5 and 10 minutes

		Naloxone Group	Metoclopramide Group
	Partial Response	7 (32%)	9 (41%)
2 Minutes	Complete Response	4 (18%)	1 (5%)
	Total Response	11 (50%)	10 (45%)
	Partial Response	8 (36%)	15 (68%)
5 Minutes	Complete Response	6 (27%)*	1 (5%)*
	Total Response	14 (64%)	16 (73%)
	Partial Response	7 (32%)	15 (68%)
10 Minutes	Complete Response	7 (32%)	3 (14%)
	Total Response	14 (64%)	18 (82%)

* The difference is statically significant
Complete response: no nausea and vomiting and no antiemetics given.
Partial response: improvement in the nausea score.
Total response: partial and complete response

Table 3
Clinical characteristics of patients who responded to naloxone compared to those who did not respond

Did not respond (N = 8)	Responded (N = 14)	
56 ± 12	41 ± 14	Age
65 ± 15	80 ± 20	Weight
171 ± 70	176 ± 74	Total amount of fentanyl
2.5 ± 1.6	2.1 ± 1.1	Operative Duration
4.3 ± 1.1	4.0 ± 1.5	Pain score

Table 4
Clinical characteristics of patients who responded to metoclopramide compared to those who did not respond

Did not respond (N = 8)	Responded (N = 14)	
51 ± 20	45 ± 17	Age
67 ± 12	81 ± 23	Weight
275 ± 210	332 ± 196	Total amount of fentanyl
1.9 ± 0.9	2.3 ± 1.1	Operative duration
2.8 ± 3.5	3.4 ± 2.3	Pain score

Table 5
Pain score

	Initial	2 Minutes	5 Minutes	10 Minutes
Naloxone	4.1 ± 1.4	4.1 ± 1.4	4.1 ± 1.4	4.1 ± 1.3
Metoclopramide	3.3 ± 2.4	3.2 ± 2.3	3.2 ± 2.3	3.0 ± 2.2

With regards to the vital signs, no variations of blood pressure or heart rate, compared to pretreatment values, were recorded in any group during the study period, with no reported side effects. Also, 4 patients in the naloxone group, as well as, 4 patients in the metoclopramide group received rescue antiemetic therapy by ondansetron 4mg intravenously. Patients who received ondansetron were nausea free and did not request further treatment.

Discussion

Despite the increasing use of prediction models and guidelines for PONV prophylaxis, PONV remains a "10-20% problem" in the postoperative period. There is evidence that patients at a considerable high risk of developing PONV can benefit from prophylactic antiemetic treatment. However, applying the same approach for patients at a low or moderate risk is not unequivocally supported and fails to improve patient satisfaction compared to symptomatic treatment in the PACU[17].

The rescue treatment of PONV has not been well studied, because of the difficulty in performing therapeutic trials, as compared to preventive studies. Only about 10%-20% of patients can be expected to experience PONV in the first 2 hours in the PACU. Drugs given prophylactically cannot be used to treat

PONV in the PACU which means that a different class of drugs has to be used[1,5].

Postoperative nausea and vomiting seem to have many causes, and it is perhaps naive to think that an anti-emetic, working at one specific receptor, should be universally effective[18]. Nausea and vomiting can be mediated via peripheral and/or central nervous pathways. Within the peripheral nervous system, vagal afferents are of importance. While the chemoreceptor trigger zone, an important center for the control of emesis, is located outside the blood-brain barrier, other centers which modulate emesis are located within the brain, e.g. the nucleus tractus solitaries (NTS). Ligands of the mu-opiate receptor (MOR) are known to influence many functions that involve vagal afferent input to the nucleus tractus solitarius (NTS), including cardiopulmonary responses, gastrointestinal activity, and cortical arousal. MOR ligands modulate either the presynaptic release from or the postsynaptic responses to largely separate populations of vagal afferents in the intermediate NTS[19]. Hence the direct effect of opioids and opioid antagonists which can cross the blood-brain barrier.

Low dose naloxone infusion, has been shown to decrease epidural and PCA opioid related side effects (nausea, vomiting and pruritis) without increasing pain score[8-12]. However, the efficacy of naloxone as a treatment for PONV following general anesthesia with fentanyl supplementation has not been reported. Efficacy data of several antiemetics, particularly metoclopramide has been previously published. Metoclopramide was found to be significantly better than propofol for the treatment of PONV in the PACU[13], and was comparable to ondansetron[20].

Anesthesiologists have used metoclopramide for the treatment of PONV in the PACU[13,14,20]. 11% of anesthesiologists in the USA use metoclopramide for the treatment of PONV when no prophylaxis is given[14], or for breakthrough PONV despite prophylaxis[15].

Our study is the first to show, in patients receiving general anesthesia including fentanyl, that naloxone in a dose of 0.5 μg/Kg can be used to treat PONV in the PACU without increasing pain scores. Naloxone is found to be comparable to metoclopramide. However at 5 minutes, complete response was significantly better with naloxone than with metoclopramide. It is known that the initial distribution half-life phase of naloxone is 4 minutes. Whereas, its half life in serum following distribution is 64 minutes. Based on animal studies, the rapid onset of the narcotic antagonist action of naloxone can be related to its rapid entry into the brain, whereas its potency stems in part from its high lipid solubility which allows a high brain concentration to be achieved[23].

Defining the success of the treatment as partial or complete is only arbitrary. What matters most is the patient's request of further treatment for PONV. Only 4 patients in each group needed rescue ondansetron treatment, the clinical effectiveness of naloxone and metoclopramide would be comparable and is >80% in this small group of patients. This constitutes higher numbers than would be expected by placebo. It has been reported that the chance of recurrence of PONV after a first episode, treated with placebo, is 65% during the early period of 0-2 hours[22]. Polati et al reported a 66.7% early effectiveness of metoclopramide in PONV treatment compared to 35% in the placebo group[21].

Why would a small-dose naloxone infusion prevent opioid-induced side effects and, in some studies, even paradoxically enhance analgesia? Opioid receptors are linked to G proteins[23,24]. Opioids have traditionally been thought to produce their analgesic effects via agonist binding to $G_{i/o}$ receptor-coupled complexes[23]. Crain and Shen[25,26] have proposed that opioids also bind at remarkably small doses to G_s-coupled receptors. Opioid binding to G_s protein-coupled receptors may be responsible for the hyperalgesia occasionally reported with opioid administration and with some opioid-induced side effects, such as pruritus and nausea and vomiting. Crain and Shen also hypothesized that small doses of opioid antagonists may decrease opioid-induced side effects and improve pain control by inhibiting only the excitatory G protein receptor complexes and leaving the inhibitory complexed receptors available for pain control[25,26]. Thus, this theory would predict that, in patients receiving opioids for pain, a small-dose infusion of an opioid antagonist would prevent side effects and produce a paradoxical enhancement of analgesia. Indeed, Gan et al.[11] observed these results in adult patients being treated with Intravenous morphine and naloxone. Similarly, Maxwell et al. saw a dramatic

diminution of opioid-induced side effects with small-dose naloxone therapy in children and adolescents[27].

Conclusion

Single low dose naloxone (0.5mcg/kg) was found to be effective in relieving PONV in the PACU, in patients receiving general anesthesia including fentanyl supplementation, without increasing pain scores. The total response was comparable to metoclopramide. However, the complete response at 5 minutes was even better with naloxone.

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