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RESEARCH ARTICLE

Evaluation of the need of prophylactic antiemetic with injection Morphine in treating acute musculoskeletal pain in the Indian population.

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Abstract

Objective: The objective of our study was to determine whether injection morphine cause nausea or vomiting in patients attending an Indian Emergency Department with acute musculoskeletal pain.

Method: A prospective double-blinded trial was done on 236 patients with musculoskeletal trauma receiving intravenous morphine for analgesia. Children ≤ 18 years, patients who had been vomiting, raised ICP, or had already received prehospital analgesia or antiemetic, and those unable to give consent were excluded from this study. Along with injection morphine – group one received Ramosetron, group two received Metoclopramide, group three received Promethazine and group four received placebo. Any vomiting or nausea within 4 hours of receiving intravenous morphine was recorded.

Result: The four groups were evenly matched for age groups, gender, comorbidities, trauma sites, morphine dose and antiemetic drug volumes. Overall, 12.4% of the patients experienced nausea (9.4% in the group receiving Ramosetron, 18.5% in the group receiving Metoclopramide, 14.3% in the group receiving Promethazine and 6.5% in the group receiving placebo) and 9.9% vomited (7.5% in the group receiving Ramosetron, 14.8% in the group receiving Metoclopramide, 10.2% in the group receiving Promethazine and 6.5% in the group receiving placebo). This difference was however not statistically significant in both the groups (P = 0.27 and P = 0.50 respectively).

Conclusion: The incidence of nausea and vomiting in musculoskeletal trauma patients receiving intravenous morphine is low and the routine use of an antiemetic in these patients not needed. Intravenous antiemetic in these patients does not reduce the incidence of nausea & vomiting.

Introduction

Pain is a common presenting complaint in all Emergency Departments and the duty of the physician is to address pain immediately **[1], [2].** Acute pain relief is considered as one of the major performance and quality indicators for Emergency Departments all around the world. It is a common practice to use injectable opioids like morphine for pain relief in the Emergency Department. The incidence of nausea and vomiting in patients treated with opioids for pain ranges from 10% to 50% **[3], [4], [5], [6].**

Though, there is very little evidence on the incidence of nausea or vomiting with intravenous morphine use, several western trials (Talbot et al, Paoloni et al, Bradshaw et al **[7], [8]**) strongly advocates against the prophylactic administration of antiemetic. However, an antiemetic is always given prophylactically to patients who receive opioid for acute pain. The primary aim of our study was to evaluate the incidence of nausea and vomiting in Indian patients

treated for acute pain with intravenous morphine. Our study also compared the efficacy of the commonly used antiemetics in preventing nausea and vomiting with morphine use.

Materials and Methods:

We did a randomized, double blinded, placebo controlled trial in the Emergency Department of a tertiary care hospital in Kolkata, India from April 2012 to January, 2014. Total numbers of cases screened for inclusion into the study were 236. Children ≤ 18 years, patients who had been vomiting, raised ICP, or had already received prehospital analgesia or antiemetic, and those unable to give consent were excluded from this study. 'Ethical Committee' approval was obtained for the study.

One of the triage nurses was assigned responsibility for screening the study subjects (according to the inclusion and exclusion criteria) in order to establish eligibility for participation in the study. Patients who were designated as eligible were explained in details about the study in a language in which he/she was comfortable, and written consent was obtained from the patients or the next of kin in case the patient was incapacitated in any way due to injury or ongoing pain.

There was factorial randomization of the cases as per the need of the study design. Three antiemetic(s) namely Ramosetron, Metoclopramide and Promethazine and a placebo (normal saline) were prefilled in 2 ml sterile syringes and were marked as drug A, B, C, D respectively. All the syringes had equal amounts of the study drugs and looked exactly alike. Syringes were prepared and replenished by the pharmacist who was blinded to the study. Once the randomization and selection process was done – the participants were given morphine 5 mg intra –venous along with an injection from any of the four prefilled syringes. Once the injections were given, patients were observed in the Emergency Department for next 4 hours for any obvious nausea or vomiting.

The primary outcome measure of this study was the incidence of nausea and vomiting during the first 4 hours after morphine injection. Injection Ondansetron 4 mg was given intravenously as a rescue medication for all the patients who needed further anti-emetic management. The nausea and vomiting caused by injection morphine were evaluated using the following variables: incidence of nausea & vomiting, need of rescue antiemetic.

Nausea was assessed by patient subjective reports only. Vomiting was defined as the forceful expulsion of gastric contents through the mouth. For the purpose of data collection, retching (the same as vomiting but without expulsion of gastric contents) was also considered vomiting. If events of vomiting were separated by more than 60 seconds, they were considered to be separate episodes.

Sample size was predetermined using a power analysis to achieve an 80% chance ($\beta = 0.2$) of detecting a 40% reduction in morphine induced nausea and vomiting from a basal incidence of P= 80% (from 42 % to 70%) with an assumed significance level of $\alpha = 0.05$. A calculated minimum sample size was 50 patients in each group. A larger number of patients were planned to include allowing for possible incomplete data collection or patient dropout. Statistical analysis was performed using SPSS of Windows. Categorical variables were analysed using the Pearson Chi-Square test. Likelihood ratio and linear-by-linear association were also measured where necessary. A P – value of 0.05 was considered statistically significant. Data were presented as mean (SD), numbers, or percentages.

Results:

A total of 236 patients of different age groups participated in the study of which 66 were females and rest 170 were males (fig 1). Out of 236 participants, 34 were excluded for reasons like morphine allergy, nausea and/or vomiting before morphine injection and refusal of morphine after consenting for the study. The remaining 202 patients, who were included for the study, the number of patients in each drug group (Ramosetron, metoclopramide and Promethazine) were 54 and 53 received placebo (saline group) (fig 2). The groups were evenly matched for the types of painful condition, age, sex, co morbidities and dose of IV morphine (table 1).

All the patients were observed in the department for at least 4 hours, before they were either discharged or admitted. Out of 202 patients 25(12.4%) experienced significant nausea and 20(9.9%) had vomiting within the 4 hours of observation. The following table depicts the incidence of nausea and vomiting in the different groups:

	Nausea	**Vomiting**
Drug A (Ramosetron)	5(9.4%)	4(7.5%)
Drug B (Metoclopramide)	10(18.5%)	8(14.8%)
Drug C (Promethazine)	7(14.3%)	5(10.2%)
Drug D (Placebo)	3(6.5%)	3(6.5%)
Total	25(12.4%)	20(9.9%)
P value	0.27	0.50

The Pearson Chi square test showed that in this study the P values for incidence of nausea and vomiting were P=0.27 and P=0.50 respectively, but this difference was not statistically significant. All the 32 patients who

experienced nausea and vomiting responded well to a single dose of IV ondansetron (4 mg) and no other adverse events were recorded.

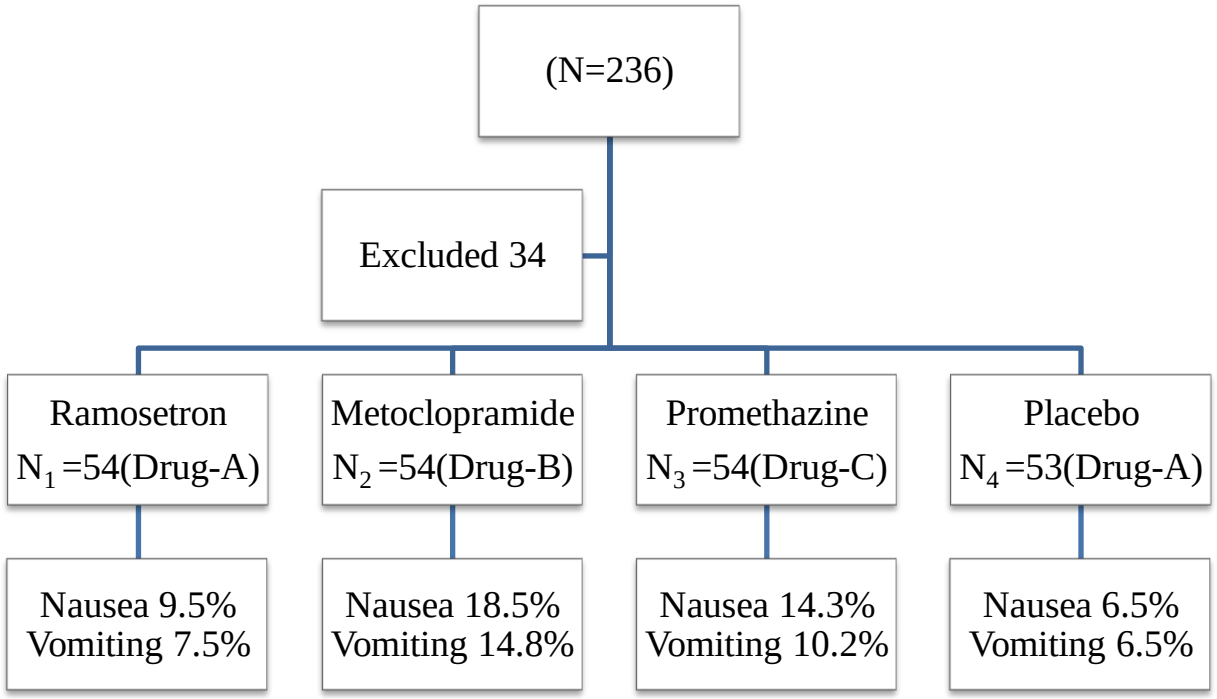

Figure-1:- Flow chart showing the process of the study

Characteristics	**Drug-A**	**Drug-B**	**Drug-C**	**Drug-D**
Age: 18-20 yrs	5.6 %	1.9 %	14.8 %	3.8 %
21-40yrs	29.6 %	20.4 %	11.1 %	28.3 %
41-60yrs	33.3 %	40.7 %	51.9 %	37.7 %
61-80yrs	31.5 %	37 %	22.2 %	30.2 %
Gender: Male (155)	37(23.9%)	39(25.16%)	40(25.8%)	39(25.16%)
Female (60)	18(30%)	15(25%)	13(21.7%)	14(23.33%)
Co morbidities:				
HTN (%)	6(11.1%)	4(7.4%)	9(16.7%)	10(18.9%)
DM (%)	5(9.3%)	9(16.7%)	4(7.4%)	4(7.4%)

COPD (%)	1(1.9%)	4(7.4%)	1(1.9%)	1(1.9%)
IHD (%)	4(7.4%)	3(5.6%)	2(3.7%)	5(9.4%)
GERD (%) Hyperacidity	23(42.6%)	26(48.1%)	21(38.9%)	27(50.9%)
Ac pancreatitis (%)	1(1.9%)	0	0	1(1.9%)
Trauma Sites: **(Extremity)**	51(94.4%)	50(92.6%)	49(90.7%)	50(94.3%)
Injection Morphine Dose	5 mg	5 mg	5 mg	5 mg
Volume of antiemetic drug	2 ml	2 ml	2 ml	2 ml

Table -1:- Basic characteristics of the cases

Discussion:

Morphine is well recognized for side effects such as nausea and vomiting by stimulation of the central chemoreceptor trigger zone and dopamine receptors in the brain, peripheral stimulation of labyrinthine receptors and reduced gastric emptying **[9]**. Traditionally prophylactic anti-emetics have always been used with morphine to reduce these side effects. Two articles published from Australia found that respectively 22.6% and 33% of patients had been given anti-emetics prophylactically, **[7] [10]**. Another chart review of 65 consecutive patients presenting to a U.K. Emergency Department showed that 72% of patients given morphine received anti-emetics along with. In our hospital ED prophylactic anti-emetics are regularly used along with morphine.

Our study, which is the first study of its kind done on the Indian population, aimed to find the incidence of nausea and vomiting with morphine and an appropriate antiemetic at the same time. Our findings are discussed below under the following sub – headings:

Prophylactic antiemetic with morphine for acute pain in ED:

Most current data on opiate-induced nausea and vomiting comes from anaesthetic literature, and suggests post-operative rates varying from 8-92% **[11]** though few studies on pre-operative patients noted a low incidence of nausea (4-11%) and vomiting (1-6%) **[12], [13]**. Previous studies done on the incidence of nausea and vomiting in adult Emergency patients receiving intravenous morphine for acute pain is however low, between 2-12% in most studies **[7], [8], [14], [15], [16]**. Thus, the higher rates seen amongst post-operative patients compared to Emergency patients is possibly attributable to other factors like anaesthetic agents and a surgical procedure.

In our study, the overall percentage of nausea and vomiting in patients receiving morphine for acute pain was 12.4% was 9.9 % respectively which matches with the previous literature. This rate is statistically and clinically insignificant to justify the routine use of antiemetic prophylaxis with morphine for acute pain. Moreover, there is no previous literature showing reduction of nausea and vomiting with prophylactic use of antiemetics **[17], [18]**. Also, The incidence of side-effects from antiemetics are high, with metoclopramide having the highest of approximately 11% as shown from large surveys **[7]**. So, we recommend that antiemetic should not be prophylactically used with morphine to reduce nausea and vomiting in patients presenting to Emergency Department with acute pain.

Superior antiemetic in case of vomiting:

No previous studies have been done to compare the relative efficacy of different anti-emetics used for prophylaxis or treatment of opiate-induced nausea and vomiting in the Emergency Department. Our study found 5-HT3 receptor antagonists (Ramosetron and ondansetron) to be superior when compared to Metoclopramide and Promethazine in treating morphine induced nausea and vomiting **(TABLE I)**. All the patients were observed in the department for at least 4 hours and those who complained of nausea and/or vomiting responded well to a single IV dose of 4 mg Ondansetron. Our finding has been supported by a large multicentre study done by Sussman et al **[18]** who also found Ondansetron to have superior therapeutic performance.

Though our sample size was small with regards to comparing the efficacy of different antiemetics and may not be immediately generalisable - we still recommend the use of 5-HT3 receptor antagonists (Ramosetron or Ondansetron) therapeutically in patients who experience nausea and vomiting after morphine injection in the Emergency department setting. Our views being supported by available literature on the above subject. Further studies on larger population groups are required to support the above.

Nausea and vomiting in ED pain patients - probably multi factorial:

In our study, we found that the incidence of nausea and vomiting in the (opiate + placebo) arm (6.5%) was less than the incidence of side-effects noted with the other arms (opiate + antiemetics). A previous study done by Talbot-Stern et al (2000) **[7]**. also had very similar findings. This reinforces the fact that the etiology of nausea and vomiting to be most likely multifactorial. It is interesting to note that a number of factors such as pain, vagal stimulation, and the underlying disease may be responsible for nausea and vomiting. Previous studies done by Paoloni et al (2002) **[15]** and Greenwald et al (2005) **[19]** have found that reduction of nausea is directly proportional to reduction of pain in adult ED patients presenting with complaints of acute pain. In our study, we found that placebo worked as good as an antiemetic when administered. It is therefore possible that the nausea and vomiting in patients presenting to the ED with pain are multi factorial in origin. It would thus be inappropriate to attribute the occurrence of these symptoms to the use of morphine alone. Though it is early to make a general statement – further research in bigger population is needed to demonstrate the presence of other factors causing nausea and vomiting, which may be related to both the underlying physical condition as well as contribution by psychological factors.

Conclusion:

According to the findings of our study, the incidence of nausea and vomiting with injection morphine is low and we could not justify the use antiemetics prophylactically with morphine for acute pain in Emergency setting. It is worth mentioning that the causes of nausea and vomiting probably are multifactorial as the incidence with placebo was observed to be less than all the other antiemetics used in this study.

In conclusion, we suggest to reserve the use of antiemetics for patients who actually vomit, and then to select a 5-HT3 receptor antagonists (Ramosetron or Ondansetron), which has not only been found to be superior compared to the other antiemetics, but also have a safer side effect profile.

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