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Prophylactic Intravenous Metoclopramide Use in Patients Given Intravenous Tramadol: A Retrospective Cross-Sectional Study [TRAMAX STUDY]

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Abstract: **The routine use of Intravenous prophylactic antiemetics with Intravenous opioid analgesics is common practice in the Emergency & Trauma Department (ETD) of Hospital Tuanku Ampuan Najihah (HTAN) to prevent opioid-induced nausea and vomiting. However, this practice has dubious clinical benefits, generates additional costs, and might expose patients to potentially adverse effects. Approximately 6000 ampules of IV Metoclopramide are used by ETD HTAN annually. The sum seems ignorable, but in 10 years, this may total over RM1,000,000. The study aimed to evaluate the benefit of intravenous metoclopramide prophylaxis in patients receiving intravenous tramadol for acute pain relief. A retrospective cross-sectional study was conducted at the ETD of HTAN using convenient sampling. Patient details were extracted from the medical record via standardized data collection form and analysed with the Statistical Package for Social Sciences version 25. A total of 272 patients were included, half of whom were given intravenous Metoclopramide prophylactically. The overall incidence of nausea in the study population was 12.1%, with most cases rated mild. Only two patients (0.7%) in the metoclopramide group vomited within 2 hours of intravenous tramadol administration, which did not demonstrate a statistically significant association between metoclopramide prophylaxis and reduced emesis episode (P= 0.498, Fisher's exact test). The low incidence of nausea and vomiting does not warrant the prophylactic use of intravenous Metoclopramide in tramadol-treated patients, suggesting a need to educate ETD medical officers on the findings to implement change in the routine prescribing practice in HTAN and subsequent cluster hospitals.**

Keywords: **metoclopramide, tramadol, nausea, vomiting, emesis, prophylaxis.**

I. INTRODUCTION

Tramadol is a weak opioid commonly used for moderate to severe pain management and is available in oral and intravenous formulations [1]. However, a common side effect of Tramadol use is nausea and vomiting due to the complex mechanisms involved in nausea, including activating mu-opioid receptors in the chemoreceptor trigger zone and the vestibular apparatus [2].

The FDA has approved Metoclopramide to treat nausea and vomiting, which antagonizes dopamine-two receptors in the medullary chemoreceptor trigger zone [3]. Metoclopramide can be administered intramuscularly or intravenously for faster onset of action, but it is known to have side effects such as torticollis, akathisia, dystonia, and tardive dyskinesia [3].

In a randomized double-blind study carried out in the Emergency and Trauma Department of Sarawak General Hospital, routine intravenous Metoclopramide prophylaxis was administered to patients prescribed with intravenous Tramadol. The study showed that Metoclopramide significantly reduced nausea severity compared to the placebo group (p=0.029, Fisher's exact test), with no reported adverse reactions in either group. The study concluded that using Metoclopramide in this way may benefit patients [4].

The routine use of intravenous prophylactic antiemetics with intravenous opioid analgesics is common practice in the Emergency & Trauma Department (ETD) of Hospital Tuanku Ampuan Najihah (HTAN) to prevent opioid-induced nausea and vomiting. However, this practice has dubious clinical benefits, generates additional costs, and might expose patients to potentially adverse effects. Approximately 6000 ampules of IV Metoclopramide are used by ETD HTAN annually, which may total over RM1,000,000 in 10 years.

II. MATERIALS AND METHODS

A. Study design

In this retrospective, cross-sectional study, a convenient sampling method was used to select the study population from the Yellow and Red zones of the Emergency Department at HTAN. The medical records of 956 patients were screened (Jan 2022-Oct 2022), and after applying the selection criteria, 246 patients were included in the final analysis. A data collection form was used to extract all patients' personal and clinical information. The 272 patients were divided into two arms: Arm 1 (n=136) received only Intravenous Tramadol, while Arm 2 (n=136) received Intravenous Tramadol with Intravenous Metoclopramide.

B. Inclusion and exclusion criteria

This study included all Malaysian individuals aged 18 years and above who were admitted to the Emergency and Trauma Department (ETD) and prescribed Intravenous Tramadol. Patients who were psychiatric, brain trauma patients, spent less than 2 hours in ETD, were pregnant, unconscious, and had a history of allergies to Tramadol and Metoclopramide were excluded from the study.

C. Tools and confidentiality

Data collection form is used as the medium to extract data from patient medical records. All characteristics of the study and related protocols were reviewed and authorized by the National Medical Research Register. The privacy of patients' personal information will be treated with complete confidentiality, where only the principal investigator can access the study data.

D. Data analysis

The collected data were analyzed with the Statistical Package for Social Science (SPSS) software Version 26.0. Skewness and kurtosis were used to validate the normality of the data. Fisher exact test was used to analyze the relationship between the test groups and vomiting. Paired T-test was used to analyze the efficacy of Intravenous Tramadol in reducing pain and the ability of Intravenous Metoclopramide to reduce nausea.

III. RESULTS

TABLE I: SOCIODEMOGRAPHIC DISTRIBUTION

Gender	Male	172
	Female	100
Race	Malay	199
	Chinese	30
	Indian	27
	Others	16
Age	≥65	82
	<65	190
Department	Surgical	100
	ETD discharge	63
	Orthopedic	49
	Medical	54
	Others	6

Table I shows the general distribution population involved in this study. The population is mostly skewed due to the Kuala Pilah district being populated mainly by Malays, and the surgical department as the primary team prescribed most Intravenous Tramadol.

TABLE II: SYMPTOMS DISTRIBUTION

Nausea	No symptoms	239
	Mild Nausea	20
	Moderate Nausea	13
	Severe Nausea	0
Pain score	Pain score on arrival (Mean)	3.79
	Post 2 hours (Mean)	1.80
Indicated for opioid		`50%

Table II displays the distribution of nausea and pain scores among the participants included in this study. Additionally, it presents the average pain score before and after administering Intravenous Tramadol. Based on the data collected, it was found that only 136 individuals had a pain score higher than 4, which meets the criteria for opioid analgesic administration as per the pain ladder recommended by the Ministry of Malaysia.

TABLE III: COMPARISON BETWEEN ARMS

Arm 1	0 hour vomiting episode	8
	Post 2 hours Vomiting episode	0
Arm2	0 hour vomiting episode	9
	Post 2 hours Vomiting episode	2

According to Table III, although 8 patients from arm 1 experienced vomiting upon arrival at ETD, none of them experienced any episode's post-administration of Intravenous Tramadol. Similarly, among the 9 patients from arm 2 who had vomiting episodes upon arrival to ETD, only 2 patients experienced such episodes after the administration of Intravenous Tramadol along with Intravenous Metoclopramide.

TABLE IV: PAIN REDUCTION PRE AND POST-IV TRAMADOL

Variable	Pre-intervention	Post-intervention	Z statistics	$p - value^b$
Pain	3.797	1.808	-9.865	0.001

a. Wilcoxon Signed Ranks Test
b. P<0.05 is significant

Table IV displays that the administration of Intravenous Tramadol resulted in an average reduction of 2 pain scores. This reduction was found to be statistically significant, as determined by the Wilcoxon signed-rank test.

TABLE V: NAUSEA REDUCTION PRE AND POST-IV METOCLOPRAMIDE

Variable	Pre-intervention	Post-intervention	Z statistics	$p - value^b$
Nausea	1.213	1.102	-2.297	0.022

a. Wilcoxon Signed Ranks Test
b. P<0.05 is significant

According to Table V, the administration of Intravenous Metoclopramide in arm 2 resulted in a significant reduction in nausea symptoms. This reduction was found to be statistically significant.

TABLE VI: ASSOCIATION BETWEEN ARMS AND VOMITING

Variable	**ARM 1**	**ARM 2**	$p - value^b$
Vomiting	0	2	0.498

a. Fisher exact test
b. P<0.05 is significant

Table VI shows that there is no significant association between the use of intravenous Metoclopramide prophylaxis and a decrease in vomiting. The findings indicate that administering routine Metoclopramide prophylaxis is not effective in preventing Tramadol-induced vomiting.

IV. DISCUSSION

This study examined the efficacy of routine administering intravenous Metoclopramide as a prophylactic measure in patients receiving Intravenous Tramadol. The study included a total of 272 subjects, with 63.2% being male and 36.8% female. Of the subjects, 30.2% were aged 65 and above, while 69.8% were below 65 years old. Additionally, 73.2% of the subjects were Malay, with the remaining being non-Malay. Among the different disciplines, patients in the surgical discipline received the highest prescription of intravenous Tramadol compared to other disciplines.

Upon arrival, the subject reported a mean pain score of 3.79. After being administered intravenous Tramadol for two hours, the pain score was reduced by 1.81 points, which is a nearly 2-point reduction. This indicates a significant 52.24% reduction in pain score, with a statistical significance of $p<0.001$. Tramadol is a potent opioid analgesic, but the study found that medical practitioners did not adhere to the Ministry of Health Malaysia's recommended pain ladder. Out of 272 individuals, only 137 required intravenous opioid analgesics, with one out of every two patients receiving inappropriate opioid prescriptions. However, it's worth noting that Tramadol may have adverse effects, such as constipation and delirium, according to Drugs.com [5]. A study published in the journal "Pain Medicine" in 2018 evaluated the effectiveness of Tramadol in managing acute pain in the emergency department. The study concluded that Tramadol provided effective pain relief in patients with various acute pain conditions, such as fractures, renal colic, and abdominal pain [6].

Opioid-induced nausea and vomiting are one of the common side effects. It has been presumed that routine administration of prophylactic antiemetic is beneficial in patients receiving opioids in order to prevent opioid-induced nausea and vomiting [7]. According to one Australian study, 23% of ED patients were given prophylactic Metoclopramide after opioid administration. However, the efficacy of prophylactic Metoclopramide was poorly established, causing further doubt in routine prophylactic Metoclopramide [8]. Some literature reviews mentioned that prophylactic antiemetics generally are not necessary before administration of opioid [9].

In arm 1, only 8 subjects had experienced vomiting before receiving Intravenous Tramadol, but none of the patients vomited during the 2-hour observation period in the Emergency Department (ETD) HTAN after receiving the medication. In contrast, in arm 2, where patients received both Intravenous Tramadol and Intravenous Metoclopramide prophylaxis, 9 patients had vomited upon arrival, and even after administering the prophylaxis, 2 patients still had vomiting episodes. However, our analysis using the Fisher exact test revealed no significant relationship between intravenous Metoclopramide prophylaxis and a reduction in vomiting ($P=0.498$).

Although routine prophylaxis with intravenous Metoclopramide did not demonstrate any superiority in patients receiving intravenous Tramadol, there was a statistically significant but mild reduction in the severity of nausea ($P<0.05$).

V. CONCLUSION

The low incidence of nausea and vomiting does not warrant the prophylactic use of intravenous Metoclopramide in Tramadol-treated patients, suggesting a need to educate ETD medical officers on the findings to implement change in the routine prescribing practice in HTAN and subsequent cluster hospitals.

A consensus was reached between the Pharmacy department and ETD HTAN that the prophylactic use of intravenous Metoclopramide in Tramadol-treated patients does not provide any clinical benefit and increases costs for HTAN. As a result, routine use of Intravenous Metoclopramide as prophylaxis is not recommended. It should only be used in cases where patients experience emesis on arrival, increased severity of nausea post-Tramadol administration, or emesis post Tramadol administration. This consensus has significantly reduced the use of intravenous Metoclopramide, although some individuals continue to implement routine prophylaxis. To address this, routine education and audit will be conducted in collaboration with ETD and Pharmacy HTAN. Additionally, awareness campaigns will be conducted in cluster hospitals as a next step.

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