Metoclopramide vs Prochlorperazine for the treatment of Nausea and Vomiting in the Emergency Care Setting: A Scoping Review

By

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DECLARATION

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Literature Review

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Abbreviations

ALS: Advanced Life Support

CTZ: Chemoreceptor trigger zone

D2: Dopamine receptor

D3: Dopamine receptor

EC: Emergency Centre

EMS: Emergency Medical Services

EPS: Extrapyramidal Symptoms

FDA: Food and Drug Administration

GI: Gastrointestinal

GIT: Gastrointestinal tract

H1: Histamine receptor

kg: Kilograms

mg: Milligrams

NK1: Neurokinin 1

M1: Muscarinic 1

RCT: Randomised Control Trials

VAS: Visual analogue scale

HPCSA: Health Professions Council of South Africa

N & V: Nausea and Vomiting

Introduction

Nausea and vomiting (N&V) are common complaints that result in patients seeking emergency medical treatment[1–3] .N&V have a variety of causes, which explains why it is such a common illness[1, 2]. N&V can be caused by medications such as opioids, cancer chemotherapeutic agents, cardiovascular agents, anticonvulsants; disorders of the gastrointestinal tract (GIT) such as bowel obstruction, cholecystitis, gastroparesis, irritable bowel syndrome; central nervous system disorders such as migraine, raised intracranial pressure and hydrocephalus[1]. Alcohol was also found to be a major contributor to N&V in a healthy population[3].

The experience of N&V is potentially distressing to the patient. As a result, drug therapy, to treat nausea and vomiting, in the emergency care setting, is often needed to improve patient care and comfort[4]. Furthermore, vomiting presents a considerable risk of airway compromise due to aspiration[2, 5]. The administering of an antiemetic has the potential to not only improve patient care and comfort, but to mitigate against complications such as: electrolyte imbalances, dehydration, and aspiration of gastric contents[6]. In a 2011 cross-sectional survey conducted by Mee et al[4], Fellows of the Australasian College for Emergency Medicine were asked to describe their most common first-, second-, and third-line antiemetic drug choice; it was found that metoclopramide was found to be the drug of first choice to treat N&V in the emergency centre (EC)[4]. Data from this study showed that the main influences on antiemetic choice was patient age, perceived effectiveness of therapy, and side effect profile of the drug[4].

Advanced life support (ALS) paramedics in South Africa (SA) only have metoclopramide available to them to use as an antiemetic[7]. Metoclopramide has been used for many years to treat N&V in the emergency care setting[4, 7], but as evidence-based medicine has evolved, healthcare practitioners need to reconsider the use of metoclopramide and phenothiazines such as prochlorperazine (or even other agents such as ondansetron which would more recently (2018) seem to be the preferred agent amongst Australian prehospital practitioners[8]) in the treatment of post analgesia nausea and vomiting.

Aims

In 2006 Sanger and Andrews[9] conducted a review on the treatment of nausea and vomiting[9] in which they reviewed the literature on the pharmacology, knowledge surrounding and the identified gaps in the treatment of nausea and vomiting[9]. They concluded that identifying a suitable anti-nausea drug is problematic and nausea is poorly treated[9], thus prompting this scoping review. This scoping review aims to review and map the available literature on the use of metoclopramide and prochlorperazine in treating nausea and vomiting in the emergency setting. The objective of this review is to provide recommendations on the selection of either metoclopramide or prochlorperazine to treat nausea and vomiting in the emergency setting

Search strategy

For the purpose of this literature review the researcher undertook a limited literature search to help build the background and rationale for the scoping review. The following online databases Pubmed, Medline, Embase Cochrane databases, CINAHL, Web of Science, TRIP and EBSCO host were searched. Identifiable MESH search terms such as “nausea”, “vomiting”, “emergency care setting”, “prehospital”, “emergency medical services”, “metoclopramide”, “prochlorperazine”, “motion-sicknesses”, “emergency department”, “paramedic”, “ambulance”, “ambulance services”, “visual analogue scale”, “assessment nausea and vomiting”, “mechanism of nausea and vomiting”, “pathophysiology nausea”, “ pathophysiology vomiting” was used to search for relevant literature. To improve search sensitivity the above search terms were entered in various combinations and truncated forms.

Articles were sourced from peer reviewed journals that are published in English, using databases such as Medline, PUBMED and Scopus. Patents, text references, animal studies, research older than 1989 were filtered out. Articles found relevant to this study were used to generate further literature. Background information was also sought from a variety of clinical and pharmacological textbooks. Inclusion criteria for selected literature was as follows:

- English print

- Peer reviewed articles
- Research conducted in the prehospital environment
- Research conducted in the emergency centre (EC)

- Case studies, Randomised control trials (RCT), systematic reviews, pharmacopeia textbooks

The search period was conducted from 1989 up to and including December 2018.

Prevalence and risk factors of nausea and vomiting

Nausea is a subjective sensation[1, 10]. It is an urge to vomit, and when severe it is associated with increased salivary secretions, sweating and vasomotor disturbances[10]. Vomiting is the forceful expulsion of gastric contents through the mouth[10]. Anxiety, gender, age, history of being sick after alcohol consumption, history of vertigo, medication usage, opioid administration are some of the risk factors associated with nausea and vomiting[10]

In a population based survey done by Rub et al[3] in 1992, the authors surveyed 596 participants, recruited from a variety of community groups, to understand the prevalence of nausea and vomiting in a healthy population[3]. Data from this survey revealed that alcohol was a major contributing factor to nausea and vomiting in a healthy population[3]. Following the study by Rub et al[3], in 2002, in Nord-Trøndelag, a county in Norway, a population based study on the prevalence of nausea was conducted by Haug et al[11]. Data from this study showed that from a population base of 94 197 inhabitants in Nord-Trøndelag at the time of the survey, 65% had gastrointestinal (GI) symptoms, and 12.5% of the population had complained of nausea in the year preceding the survey. This study also revealed that nausea for women was three times higher than that for man[11].

Ethnicity has also been identified as a risk factor for nausea and vomiting[12–14]. In a 2010 study conducted by Rodseth et al[12] in South Africa, the author aimed to test the hypothesis that the occurrence of postoperative nausea and vomiting differs between African South Africans and the non-African South African patient[12]. Data from this study showed that from a sample size of 547 patients, of which 308 were African and 239 were non-African, the incidence of post-operative nausea and vomiting was 22% in the African group and 44% in the non-African group[12]. The

effect of ethnicity on the incidence of post-operative nausea and vomiting was further investigated in two more studies. In a 2015 study conducted in a Singapore hospital, the effect of ethnicity on post-operative nausea and vomiting in elective orthopaedic cases was investigated by Leong et al[13]. From a cohort of 785 patients, post-operative nausea and vomiting occurred in 261 patients, of which 91 were Chinese, 89 were Malay, 76 were Indian, and 5 were other ethnicity[13]. In 2017 another South African study done by Alli et al[14] found that from a sample size 94 patients with 5 exclusions, non-African patients had a 25 times higher incidence of nausea than African patients[14].

Nausea and vomiting can also be caused by various motion environments[15]. Ethnicity and gender has been shown to influence motion sickness in a 2006 study by Klosterhalfen et al[16]. Data from this study showed that from a study population of 48 adults, of which 24 were Chinese and 24 were White[16]. Data from this study showed that Chinese participants reported significantly fewer symptoms than White participants[16].

Motion sickness can also occur during ambulance transport of patients, and is often associated with nausea and vomiting[17]. In 2012 Easton et al[18] conducted a prospective study, with sample size of 196 adult patients that was transported by ambulance to EC over a five month period[18]. Patients were asked whether they had experienced nausea at the scene, during ambulance transportation, or immediately upon arrival at the EC[18]. Data showed vomiting in 15 patients, nausea in 75 patients of which 57 patients reporting moderate to severe nausea[18]. From the 90 patients that reported nausea and vomiting a total of 63 patients received an antiemetic, of which 52 patients received the antiemetic in the prehospital phase[18]. Also in this study 79 patients were given an antiemetic prophylactically, of which metoclopramide was given to 76 of those 79 patients[18]. Furthermore, data from this study showed that factors most likely to influence nausea and vomiting are: female gender, age, weight, injury severity score transport time, opioid analgesic use and pain score[18].

Assessment of nausea

Nausea and vomiting is a subjective sensation, and an accurate assessment can only be given by the patient[19]. The severity of nausea and vomiting is commonly

assessed using either a discrete scale (DS), a visual analogue scale(VAS), or the analogue continuous chromatic scale(ACCS)[20–23] in which patients are asked to describe their N&V[20, 23]. With the DS, the patient is asked to rate their nausea as 0=no nausea, 1= slight nausea, 2= moderate nausea, and 3= severe nausea[20]. In the VAS, the patient is asked to move a marker along a 100mm vertical line, with “no nausea”=0 marked at the bottom and “the worst ever nausea”= 100 marked at the top[20]. Similar to the VAS, the ACCS consists of a coloured horizontal strip 100mm long and 25mm wide, and patients rate their nausea by moving a slider from the left (no nausea) to the right (worst ever nausea)[20].

In an attempt to provide validity on the existing methods of assessing nausea and how best to use these methods in clinical trials on antiemetics, a study was conducted by Del Favero et al[20] in 1990[20]. In this study, they reviewed six trials (four double blind RCT, two observational studies)[20] where they compared the discrete scale, the visual analogue scale (VAS) and the analogue continuous chromatic scale [20]. This study used Spearman’s correlation coefficient to evaluate the correlation between the three scales in assessing the dimensions of nausea[20]. There was good correlation between the DS and the VAS (r=0.68) in assessing the maximal intensity of nausea[20]. The degree of correlation between the VAS and ACCS, the two analogue scales, was even better than the degree of correlation between the DS and the VAS (r=0.74 and r=0.68 respectively)[20]. Further to this, this study found that there was no clear advantage of using any particular scale over another, and that the VAS gives a more uniform distribution of baseline maximal intensity nausea values, and a greater sensitivity in assessment of the variations of the same values in patients that are treated for nausea and vomiting[20].

The VAS, as described above, was evaluated again in another study done by Boogaerts et al[21] in 2000[21]. In this study, 128 consecutive inpatients, complaining of spontaneous post-operative nausea and vomiting were studied[21]. Comparison of VAS measurements was done by the Student paired *t*-test, and the symmetry test was used for the DS[21]. Nausea intensity in this study was assessed using the VAS and the DS[21]. and the VAS proved to be a useful scale to quantitatively assess the intensity of nausea as well as the efficacy of rescue medication in relieving the symptoms of nausea in patients[21]. Meek et al[22] conducted a prospective

observational study in 2009, assessing nausea and vomiting in the EC population[22]. Meek et al[22] assessed the association between verbal descriptors for nausea and vomiting and the VAS rating[22]. Correlation between VAS and verbal descriptors was assessed using the Spearman rank correlation coefficient[22]. It was found that there was a good correlation between the two, and VAS is a practical scale to use[22].

In 2011 a literature review was done by Wood et al[23] with the objective of providing an a comprehensive overview of the different tools used to evaluate N&V in chemotherapy patients[23]. No single assessment tool for N&V was found to be superior than any other assessment tool in this review[23]. The VAS was found to be clinically useful and easy to understand for the patient[23].

The VAS can provide the clinician with the relevant real-time information needed in assessing a patients N&V[23]. It does not place an additional burden on the already nauseated patient, by expecting the patient to answer numerous questions or go through a lengthy assessment of his/her nausea, making it useful to use in the emergency setting

Management of nausea and vomiting

The management of the patient presenting with nausea and vomiting should include a systematic approach that includes correcting any electrolyte imbalance, correcting fluid and nutritional deficiencies, and then identifying and eliminating the source of the nausea and vomiting (where possible)[24–26]. The administration of an antiemetic agent can be helpful in managing as well as limiting the risks from N&V[1, 25].

Medical treatment for N&V generally falls into two categories. There are therapies that focus on the suppression of nausea and vomiting, and therapies that focus on promoting gastric motility[1]. Commonly used antiemetic agents, as shown in Table 2, can be grouped into different classes of drugs[1, 27]

Table One. Common antiemetic agents. Adapted from Prashant Singh, Sonia S. Yoon and Braden Kuo, Nausea: a review of pathophysiology and therapeutics Ther Adv Gastroenterol 2016, Vol. 9(1) 98 –112

	Drug	Mechanism of action	Adverse effects	Indication
Antihistamine	Meclizine	Acts on central anticholinergic and antihistamine receptors (M1 and H1 receptors). Labyrinthine and vestibular stimulation is suppressed.	Drowsiness confusion blurred vision constipation urinary retention	Indicated for motion sickness, vertigo, and nausea and vomiting caused by labyrinthine disorders
	Diphenhydramine	Acts on central anticholinergic and antihistamine receptors (M1 and H1 receptors). Labyrinthine and vestibular stimulation is suppressed.	Drowsiness confusion blurred vision constipation urinary retention	Indicated for motion sickness, vertigo, and nausea and vomiting caused by labyrinthine disorders
	Cyclizine	Acts on central anticholinergic and antihistamine receptors (M1 and H1 receptors). Labyrinthine and vestibular stimulation is suppressed.	Drowsiness confusion blurred vision constipation urinary retention	Indicated for motion sickness, vertigo, and nausea and vomiting caused by labyrinthine disorders.
Phenothiazine	Prochlorperazine	Antidopaminergic agents. Act via nonselective inhibition of D2 and D3 receptors. They also act muscarinic and H1 receptors	Extrapyramidal side effects, tardive dyskinesia neuroleptic malignant syndrome prolonged QT interval, increased prolactinemia	Indicated for nausea and vomiting related to migraine, motion sickness, vertigo, as well as post-operative nausea and vomiting
	Promethazine	Antidopaminergic agents. Act via nonselective inhibition of D2 and D3 receptors. They also act muscarinic and H1 receptors	Extrapyramidal side effects, tardive dyskinesia neuroleptic malignant syndrome prolonged QT interval, increased prolactinoma	Indicated for nausea and vomiting related to migraine, motion sickness, vertigo, as well as post-operative nausea and vomiting
	Chlorpromazine	Antidopaminergic agents. Act via nonselective inhibition of D2 and D3 receptors. They also act muscarinic and H1 receptors	Extrapyramidal side effects, tardive dyskinesia neuroleptic malignant syndrome prolonged QT interval, increased prolactinemia	Indicated for nausea and vomiting related to migraine, motion sickness, vertigo, as well as post-operative nausea and vomiting
Benzamides	Metoclopramide	Dopamine D2 receptor antagonist, enhances upper GI motility and promotes gastric emptying due to its prokinetic	Sedation, anxiety, altered mood, sleep disruption, dystonic reactions,	Indicated for post-chemotherapy associated nausea and vomiting

		effect. It also works as a vagal receptor and 5-HT3 receptor antagonist and a 5-HT4 agonist	tardive dyskinesia, galactorrhoea, sexual dysfunction	
	Domperidone	Dopamine D2 receptor antagonist, enhances upper GI motility and promotes gastric emptying due to its prokinetic effect. It also works as a vagal receptor and 5-HT3 receptor antagonist and a 5-HT4 agonist Does not cross the blood brain barrier	Galactorrhoea, sexual dysfunction	Indicated for post-chemotherapy associated nausea and vomiting
5-HT3 antagonists	Ondansetron	Antagonistic effects on the 5-HT3 receptor in the CTZ	Headaches, fatigue, malaise, constipation	First line agent used for common causes of acute nausea
	Granisetron	Antagonistic effects on the 5-HT3 receptor in the CTZ	Headaches, fatigue, malaise, constipation	First line agent used for common causes of acute nausea
	Tropisetron	Antagonistic effects on the 5-HT3 receptor in the CTZ	Headaches, fatigue, malaise, constipation	
Cannabinoids	Dronabinol	Act primarily through the canniboid receptor in the medulla and the area sub postrema of the nucleus tractus solitarius	Palpitations, tachycardia, flushed face, euphoria, dizziness, visual disturbances, paranoia	Investigated in chemotherapy associated nausea and vomiting
	Nabilone	Act primarily through the canniboid receptor in the medulla and the area sub postrema of the nucleus tractus solitarius	Palpitations, tachycardia, flushed face, euphoria, dizziness, visual disturbances, paranoia	Investigated in chemotherapy associated nausea and vomiting
Benzodiazepines	Lorazepam	Acts by reducing the anticipatory component of nausea associated with chemotherapy	Cognitive dysfunction, depression, dizziness, drowsiness, irritability, impaired memory, sedative effects	Adjunctive therapy in postoperative nausea and vomiting,
	Alprazolam	Acts by reducing the anticipatory component of nausea associated with chemotherapy	Cognitive dysfunction, depression, dizziness, drowsiness, irritability, impaired memory, sedative effects	Adjunctive therapy in postoperative nausea and vomiting,
Butyrophenones	Droperidol	Acts via antidopaminergic activity in the CTZ	Prolonged QTc, orthostatic hypotension, extrapyramidal symptoms	Indicated for postoperative nausea and vomiting
NK-1 Receptor antagonists	Aprepitant	Potentiates the effects of the 5-HT3 receptor antagonist, tachykinin receptor antagonist	Fatigue, constipation, hiccups	Indicated for delayed chemotherapy induced nausea and vomiting

Corticosteroids	Dexamethasone	Mechanism of action not completely known.	Emotional disturbances, acne, hyperglycaemia, Cushing's syndrome	Indicated for postoperative nausea and vomiting
Anticholinergic	Scopolamine	Muscarinic type one receptor antagonist	Tachycardia confusion dry mouth constipation urinary retention blurred vision	Mainly used for its antispasmodic action

CTZ: chemoreceptor trigger zone; GI: gastrointestinal; mg: milligrams; kg: kilograms; NK-1: neurokinin 1 ; M1: Muscarinic 1 ; H1: Histamine receptor; D2: dopamine receptor; D3 : dopamine receptor

The focus of the remainder of this review is on the comparison of metoclopramide and prochlorperazine. Metoclopramide as well as prochlorperazine have both been long established antiemetics and have been widely used for the treatment of mild to moderate N&V[24, 28]. They have shown to be effective in postoperative as well as post-chemotherapy induced N&V[24, 28]. As well as being an antiemetic, metoclopramide is a prokinetic as well, and because of this dual action, it is particularly useful for gastric emptying before emergency surgery[28]. Unlike metoclopramide[28], prochlorperazine has been effective in treating N&V that is caused by motion sickness[24, 28]. Both these drugs are readily available in South Africa[28]. Both are easy to administer in the emergency care setting, and can be administered intravenously and intramuscularly[28]. Both these agents can be used as antiemetics in the emergency setting, but which is the better agent?

Antiemetic effectiveness

There are several well established, commonly used antiemetic drugs, but this is a rapidly evolving field. Likely fed by newer drugs and modalities used with chemotherapeutic agents, and from peri-operative use. Comparing the efficacies of drugs has been the focus of many studies, and here some are examined, with the focus on those studies including metoclopramide and prochlorperazine. The majority of studies are not from the prehospital context, and this needs to be borne in mind.

Metoclopramide was evaluated by Lambie et al[29]; Talbot-Stern et al[30]; Cham et al[31]; Bradshaw and Sen[32]; Braude et al[33]; Chae et al[34]; Barret et al[35]; Rubio et al[36] and Egerton-Warburton et al[37]. Prochlorperazine was evaluated by Ernst et al[38]; Braude et al[33] and Patka et al[39].

USE OF METOCLOPRAMIDE IN THE EC

In a pilot study conducted in 2004 in an EC with an annual patient volume of 75000 patients, by Cham et al[31] the effectiveness of metoclopramide to treat N&V using different dosing regiments was evaluated[31]. Patients received either 0.4mg/kg intermediate dose or the standard 10mg dose[31]. A total of 58 patients were enrolled in this study, where 34 patients received 10mg metoclopramide and 24 patients received 0.4mg/kg dose[31]. The mean reduction in nausea for the 10mg group was four and for the 0.4mg/kg group it was five[31]. The author found no difference in

effectiveness to treat nausea if patients received the standard dose or the intermediate dose of metoclopramide[31].

In 2006 Braude et al[33] compared metoclopramide to prochlorperazine, droperidol and a placebo in a study conducted in an urban EC with an annual patient volume of 55000[33]. . This study enlisted 97 patients of which 25 received metoclopramide, 22 received droperidol, 24 received prochlorperazine, and 26 received a placebo[33]. The primary outcome of this study was a reduction in VAS scores for nausea[33]. Data from this study showed that metoclopramide resulted in a mean change in VAS of (mean ±standard deviation) -40.2 ± 23.8mm from baseline, prochlorperazine -40.5 ± 24.1mm, and droperidol -54.5 ± 18.4mm, all taken 30 minutes after the study drug was administered[33]. Secondary outcome measures reported in the study by Braude et al[33], were nausea, anxiety and sedation[33]. The author of this study concluded that 1.25mg droperidol, when administered intravenously to patients with moderate to severe nausea, was more effective then when patients received either 10mg metoclopramide or 10mg prochlorperazine[33].

In 2011, a study conducted in an EC with an annual patient volume of 70000 patients was done by Chae et al[34], evaluating metoclopramide and tropisetron for the treatment of nausea and vomiting[34]. This study enlisted 100 patients with 50 patients in the metoclopramide group and 50 patients in the tropisetron group[34]. The primary end point in this study was the incidence of vomiting, and the secondary end points was decrease in nausea score from baseline, rescue medication requirements, adverse effects, unresolved nausea, and antiemetic requirements 48 hours post discharge from EC[34]. Data from this study showed that two patients in the tropisetron group and nine patients in the metoclopramide group had vomited at 180 minutes from the baseline[34]. Further to this, the decrease in the mean VAS nausea scores from baseline was slightly higher for metoclopramide -26.4mm than for tropisetron -25.2mm at 30 minutes[34]. In this study, data also showed that the mean akathisia scores for metoclopramide was higher than that for tropisetron[34]. Mean akathisia for metoclopramide was 1.70 and 0.57 for tropisetron at 30 minutes[34]. From the results of this study the authors concluded that tropisetron was associated with lower vomiting rates and reported akathisia than metoclopramide[34]. The authors also concluded that tropisetron had better nausea control than metoclopramide[34]

In 2011 in an urban university-affiliated adult EC with an annual patient volume of 54000 patients Barret et al[35] conducted a four arm placebo controlled study evaluating metoclopramide, promethazine and ondansetron[35]. The distribution of patients to the various treatment arms were as follows: metoclopramide 43, promethazine 45, ondansetron 42 and saline placebo 41 patients[35]. The primary outcome of this study was a change in VAS score from a baseline to 30 minutes This study found a mean reduction in VAS scores to be -30mm (95%CI= -38 to -25.5mm), -22mm (95%CI= -32mm to -15mm), -29mm (95%CI= -40mm to -21mm), -16mm (95%CI= -25mm to -3mm) for metoclopramide, ondansetron, promethazine and saline respectively[35]. Akathisia, headache, pain at intravenous site, and sedation were the reported side effects in this study[35]. Data showed that the occurrence of akathisia was highest in the metoclopramide treatment arm followed by ondansetron, 11 for metoclopramide and five for ondansetron and two for promethazine[35].The conclusion of this study, was that ondansetron is not superior to metoclopramide or promethazine in reducing nausea in the EC patients[35].

In 2014, Egerton-Warburton et al[37] conducted a prospective RCT in two EC's. The first EC being a tertiary EC receiving 70000 patients annually and the second EC being a district EC receiving 57000 patients annually[37]. A total of 258 patients were recruited of which 87 received ondansetron, 88 received metoclopramide, and 83 received a placebo[37]. The primary outcome of this study was a change in VAS 30 minutes post administration of the study drug[37]. This study found the mean decrease in VAS was 28mm (95%CI= 22-34mm) for metoclopramide, 27mm (95%CI= 22-33mm) for ondansetron, and 23mm (95%CI= 16-30mm) for placebo[37]. Furthermore, in this study it was found that nine patients reported adverse an adverse event[37]. Data showed that six of these patients were from the metoclopramide group: two patients reported akathisia, two patients reported restlessness, one patient reported muscle twitching, and one patient had sweatiness[37]. From the ondansetron group, one patient had dizziness, and one patient has stinging/burning at the injection site[37]. In the placebo group only one patient reported shaking/restlessness[37]. The authors of this study concluded that reductions in nausea severity were similar for ondansetron, metoclopramide and the placebo group[37].

Even though metoclopramide has shown it is effective in reducing nausea and vomiting[33–35, 37], it has not shown superiority to any other antiemetic.

USE OF METOCLOPRAMIDE IN THE PREHOSPITAL SETTING

In a 2011 prehospital study in America, metoclopramide, diphenhydramine and a placebo were compared to each other in the treatment of motion sickness by Rubio et al[36]. The aim of this study was to determine if metoclopramide or diphenhydramine would help relieve the symptoms of motion sickness when patients are transported in an ambulance to hospital[36]. The closest receiving hospital was 40 minutes from the ambulance station[36]. Only patients who developed signs and symptoms of motion sickness was given either metoclopramide, diphenhydramine or the placebo[36]. Twenty six patients were enrolled into this study, of which 22 patients developed motion sickness[36]. The high incidence of motion sickness in this study could possibly be attributed to the fact that the patients being transported was already sick, and this predisposed them to developing motion sickness[36]. From the 22 patients, seven patients were placed in the placebo group, seven patients in the diphenhydramine group and eight patients in the metoclopramide group[36]. Over time, all three drugs showed a significant reduction in their mean VAS from baseline, however metoclopramide showed a statistically significant decrease in VAS at 15 minutes after the initial dose of medication was given[36]. Mean VAS for nausea for the diphenhydramine group was 46.9 (95%CI = 29.2-64.6) at 15 minutes, whilst the mean VAS for the placebo group was, 51.4 (95%CI = 37.1-65.7) at 15 minutes and metoclopramide showed a mean VAS of 7.4 (95%CI = 4.1-10.7) at 15 minutes [36]. From the data in this study, the authors concluded that metoclopramide is superior in treating motion sickness when compared to diphenhydramine and a placebo[36].

USE OF METOCLOPRAMIDE PROPHYLACTICALLY WITH OPIOIDS

Metoclopramide can also be given prophylactically to a patient to prevent nausea and vomiting when an opioid analgesic is administered[29, 30, 32]. In 1999, an EC study to determine if the routine administration of metoclopramide to patients who received intravenous morphine was of benefit to the patient, was conducted by Lambie et al[29]. Patient throughput was not reported in this study. A total of 214 patients were enrolled, of which 111 patients received prophylactic metoclopramide and 103 patients received

a placebo prior to receiving morphine[29]. Data from this study showed that two patients in the placebo group reported severe nausea and no patients in the metoclopramide group reported nausea[29]. No adverse effects were reported in this study[29]. The authors of this study concluded that routine use of an antiemetic for patients receiving intravenous morphine for musculoskeletal trauma is not justifiable[29].

In 2000 a study to investigate the potential value of administering metoclopramide prophylactically to patients and the incidence of nausea and vomiting after an intravenous opioid analgesic was administered was done by Talbot-Stern and Paoloni[30]. This study was conducted in a tertiary referral EC that has approximately 45000 patients annually[30]. A total of 127 patients were enrolled into this study, where 63 patients received metoclopramide and 59 patients received a placebo immediately after receiving and opioid analgesic[30]. The results from this study showed that at 30 minutes three patients in the metoclopramide group and five patients in the placebo, and at 60 minutes four patients in the metoclopramide group and four patients in the placebo group reported nausea[30]. In addition to this, the data from this study also showed that 7.9% of the patients in the metoclopramide group reported adverse effects such as dystonic reactions, vertigo, dizziness lasting more than an hour, restlessness and drowsiness[30]. The authors of this study recommended that prophylactic metoclopramide should not be routinely used[30].

In 2006 an EC study enrolling 259 patients comparing the incidence of nausea and vomiting in patients that received either metoclopramide or a placebo prophylactically when they were given intravenous morphine for acute pain, was conducted by Bradshaw and Sen[32]. In this study 123 patients received metoclopramide and 136 patients received a placebo before receiving morphine[32]. Data from this study showed that two patients in the metoclopramide group and five patients in the placebo group had nausea[32]. No adverse events were recorded in this study. The authors concluded that the incidence of nausea and vomiting is low irrespective of whether or not the patient received metoclopramide[32].

The prophylactic use of metoclopramide when a patient receives an opioid analgesic cannot be justified[29, 30, 32]. The administration of metoclopramide unnecessarily exposes the patient to the adverse effects of metoclopramide[29, 30, 32]

USE OF PROCHLORPERAZINE IN THE EC

Prochlorperazine was evaluated in three EC studies for its use in the treatment of nausea and vomiting[33, 38, 39]. Only one study evaluated prochlorperazine and metoclopramide[33].

In 2000 prochlorperazine was compared to promethazine in the treatment of nausea and vomiting caused by gastritis or gastroenteritis by Ernst et al[38]. This study was conducted in two academic EC units but only managed to enrol 84 patients[38]. The main outcome measure was relief of nausea at 30 and 60 minutes[38]. Akathisia and drowsiness were also reported in this study[38]. Data showed that at 30 minutes prochlorperazine was much better than promethazine at relieving nausea with a median change in VAS of 4.5 vs 2.7 respectively[38], however at 60 minutes promethazine showed better VAS ratings than prochlorperazine with a median change in VAS of 2 vs 1.55 respectively[38]. Data from this study also showed that 16 pts that received prochlorperazine vs 30 pts in the promethazine group reported drowsiness and 6 pts each in both groups reported akathisia[38]. The conclusion of this study was that prochlorperazine was more effective than promethazine in treating uncomplicated nausea[38].

Following the study by Ernst et al[38], in 2011 prochlorperazine was compared to ondansetron in its effectiveness to treat vomiting in adults presenting to the EC with nausea and vomiting by Patka et al[39]. A total of 64 patients were enrolled in this study, 32 patients in the ondansetron group and 32 patients in the prochlorperazine group[39]. The primary outcome of this study was the percentage of patients with vomiting at 30, 60, and 120 minutes post administration of ondansetron or prochlorperazine[39]. Secondary outcome measures included nausea at 30, 60, and 120 minutes as well as percentage of patients experiencing sedation, headache, akathisia and dystonia[39]. Data from this study revealed that overall more patients receiving ondansetron had experienced breakthrough vomiting seven patients vs two patients. In addition to this, patients that had received prochlorperazine reported lower

mean nausea scores post receiving prochlorperazine or ondansetron[39]. Mean VAS nausea scores reported were, 47.5mm vs 50.4mm at 30 minutes, 24.9mm vs 43.7mm at 60 minutes and 16.8mm vs 34.3mm at 120 minutes for prochlorperazine vs ondansetron respectively[39]. Four cases of akathisia was reported in this study, three in the prochlorperazine group and one patient in the ondansetron group[39]. The authors of this study concluded that prochlorperazine and ondansetron are equally effective in treating nausea and vomiting[39].

Prochlorperazine has shown to be more effective than promethazine in treating nausea, but it has not shown to be more effective than metoclopramide in treating N&V[33, 38].

Rescue medication

Rescue medication, is medication administered to patients, to produce relief from the symptoms of an acute onset medical condition when these patients have a poor response to the initial drug administered[40]. This rescue medication can be administered either alone or in combination with the first drug that was administered[40].

The reporting of the use rescue medication is not consistent and not well reported in the selected studies for this review[29, 31–35, 37–39]. The choice of drug that was chosen as a rescue antiemetic was not reported in all the trials. From all the studies selected, only three studies, Bradshaw and Senl[32], Lambie et al[29], and Rubio et al[36], documented what the rescue drug was. For Bradshaw and Sen[32] and Lambie et al[29] it was cyclizine and for Rubio et al[36] it was metoclopramide. This is an important finding, because it gives an indication to the efficacy of the antiemetic used in the trial[8].

The prehospital environment

From the studies selected in this review it is only the study by Rubio et al[36] that was conducted in the prehospital setting. The other studies were all conducted in hospital emergency centres. This shows that there is very limited literature on prehospital antiemetic use.

Trauma patients are generally transported to hospital lying flat on a stretcher in the back of an ambulance[41][42].The ALS paramedic in South Africa is trained to treat patients complaining of nausea and vomiting related to gastrointestinal disorders, or nausea and vomiting that is caused by the administration of morphine[7]. The ALS paramedic needs an effective, low cost, easy to administer antiemetic in the prehospital patient presenting with nausea and vomiting. This is paramount to safe and effective patient management. Currently the only drug available to the ALS paramedic is metoclopramide. From the evidence found in this review the prophylactic use of metoclopramide when a patient is given an opioid analgesic cannot be justified[29, 30, 32]. ..

Conclusion

From the literature found for this review, it is evident that there is no clear evidence for any single antiemetic being the best option to treat nausea and vomiting in the emergency setting. There is very little literature available from studies conducted in the prehospital setting on treating nausea and vomiting, and hence much of the evidence is extrapolated from hospital emergency patients. There has been no study conducted on the use of prochlorperazine for treating nausea and vomiting in the prehospital environment. From the available literature found on metoclopramide and prochlorperazine use to treat nausea and vomiting in the emergency setting only three studies evaluated prochlorperazine. Even though both metoclopramide and prochlorperazine are effective in treating N&V, neither metoclopramide nor prochlorperazine has proven to be better at treating N&V. Further research especially in the prehospital setting is required, in order to allow an evidence-based reconsideration of the range of antiemetics available for prehospital practitioners.

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ARTICLE (In the format of an Original Article for submission to the African Journal of Emergency Medicine (AFJEM)

Metoclopramide vs Prochlorperazine for the treatment of Nausea and Vomiting in the Emergency Care Setting:

A Scoping Review

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WORD COUNT 2216

TABLES 2

FIGURES 1

Abstract

Introduction

Nausea and vomiting are a common complaint with a wide variety of aetiologies. Patients frequently present to emergency care providers seeking treatment for nausea and vomiting. Metoclopramide and prochlorperazine are well established drugs that have long been used in the treatment of nausea and vomiting. This scoping review aims to map out the available literature on metoclopramide and prochlorperazine in treating nausea and vomiting in the emergency setting, and more specifically for prehospital use.

Methods

A broad literature search was conducted using the following search terms “nausea”, “vomiting”, “emergency care setting”, “prehospital”, “motion sickness”, “emergency medical services”, “metoclopramide”, “prochlorperazine”, was done on online databases such as Pubmed, Medline, Embase Cochrane databases, CINAHL, Web of Science, TRIP and EBSCO host.

Results

A total of 11 articles were found published between 1989 and 2014. Ten studies were found from emergency centres and just one from the prehospital setting. Six studies originated in America, three in Australia, one in the United Kingdom, and one in New Zealand. The total number of patients in the 11 included studies were 1319 subjects, where 511 received metoclopramide, 448 received a placebo, and 98 patients received prochlorperazine. One study found prochlorperazine to be the better antiemetic at treating nausea and vomiting, one study found metoclopramide to be better, and three studies found that the prophylactic use of metoclopramide cannot be justified.

Conclusion

There is no consensus on the superiority of metoclopramide or prochlorperazine to treat uncomplicated nausea and vomiting in the emergency care setting. There is a paucity of research available and further studies needs to be done, particularly in the prehospital arena.

Abstract word count 267

Introduction

Nausea and vomiting (N&V) are a common and distressing complaints that results in patients seeking emergency medical treatment[4, 8]. Nausea is a subjective sensation[1] and vomiting is the forceful expulsion of gastric contents through the mouth[10]. The nauseas patient gets an urge to vomit, associated with increased salivary secretions, sweating and vasomotor disturbances[10]. It is often thought that nausea and vomiting always coexist, but this is not always the case[1]. There are situations where a nauseas does not vomit, or a patient suddenly vomits without being nauseas[1].

Anxiety, age, gender, alcohol consumption, ethnicity, opioid administration are some of the identifiable risk factors associated with nausea and vomiting[3, 10, 11]. Alcohol has been shown to be a major contributor to nausea and vomiting in a healthy population[3]. Motion sickness has been associated with patients becoming nauseas[17]. Patients travelling in the back of an ambulance can become nauseas and the administration of an antiemetic becomes necessary to safely manage these patients[18]. In the prehospital setting antiemetics are administered to relieve nausea and vomiting that potentially resulted from driving conditions, patients being placed in a claustrophobic environment, patient positioning in the ambulance, or because an opioid analgesic might have been administered[8]. Should the patient vomit in the back of an ambulance that patient is exposed to a higher risk of aspiration and airway compromise[42, 43]. The emergency care practitioner must be able to manage these conditions, to safely manage these patients

In South Africa emergency medical services (EMS) practitioners are qualified at basic, intermediate and advanced life support level. The basic life support practitioner having a very limited scope of practice focused at maintaining basic life functions through to the advanced life support (ALS) practitioner with a broader scope of practice[7].The current scope of practice only allows the use of metoclopramide to treat nausea and vomiting in the prehospital setting, administered only by ALS[7]. In Australia and America paramedics have a wider selection of antiemetics, such as ondansetron, metoclopramide, prochlorperazine, and diphenhydramine that they can administer, unlike in South Africa where the ALS paramedic only has metoclopramide available to them[44, 45].

Metoclopramide and prochlorperazine have both been long established antiemetics[24, 28]. Both these drugs are readily available in South Africa and are easy to administer in the emergency setting[28] The scoping review aims to map the available literature on metoclopramide and prochlorperazine use in the emergency setting to treat nausea and vomiting.

Methods

A scoping study, as explained by Arksey and O´Malley[46], is undertaken to view the range, depth and extent of research on a particular subject, to ascertain the value of conducting a full systematic review on a topic, to review and share the available literature on a subject, to identify research gaps in the existing literature on a topic[46]. For the purpose of this study, the scoping review definition by Daudt HML, van Mossel C and Scott SJ[47] will be used. They define a scoping review as a form of research synthesis with the objective to "*map the literature on a particular topic or research area and provide an opportunity to identify key concepts; gaps in the research; and types and sources of evidence to inform practice, policy making and research"*[47]. This review, being a stand-alone project, was guided by Arksey and O'Malley's six stage framework[46]; (1) identifying the research question, (2) searching the relevant studies, (3) selection of the relevant studies, (4) charting the data, (5) collating the results, and (6) summarising and reporting the results[46]

Search strategy

A broad literature search was done, to achieve a comprehensive scope of the literature available. The following online databases Pubmed, Medline, Embase Cochrane databases, CINAHL, Web of Science, TRIP and EBSCO host were searched. Identifiable search terms such as "nausea", "vomiting", "emergency care setting", "prehospital", "emergency medical services", "metoclopramide", "prochlorperazine", "motion-sicknesses was used to search for relevant literature.

Articles chosen for this review were subjected to the inclusion and exclusion criteria as listed in Table 1.

Table One. Inclusion and Exclusion criteria

	Inclusion	**Exclusion**
Source	Published peer reviewed journals	Not sourced from a peer reviewed journal
Publication date	Between January 1989 up to and including December 2018	Any research prior to 1989
Language	English printed articles	Any other language other than English
Study type	RCT, case studies, observational studies, cross-sectional surveys, case -control studies	Case reports, literature reviews and secondary research articles, that reviewed primary studies already included in this review.
Study intervention	Use of metoclopramide or prochlorperazine to[i] treat nausea and vomiting	Use of metoclopramide and/or prochlorperazine to treat illnesses/symptoms outside of nausea and vomiting
Study Setting	Emergency centre Prehospital research	Theatre setting, any other environment other than an emergency department or prehospital emergency setting

RCT Randomised control trial

Article Selection and Extraction

The initial search for articles identified 43 121 potential articles that was screened by title for relevance and inclusion criteria. Articles not in English print (1031) were removed. After abstract screening and reviewing 33 277 articles were removed. Patents, case reports, reference reports, secondary research articles and duplicates were also removed. Identified articles were reviewed against the inclusion and exclusion criteria in table one. The remaining articles were reviewed by a second author (IH) to verify eligibility for inclusion, with any disagreements resolved by mutual agreement, Figure 1. From the article and literature search only 11 randomised control, trials (RCT) were found that evaluated metoclopramide and/or prochlorperazine in an emergency setting and were eligible for inclusion.

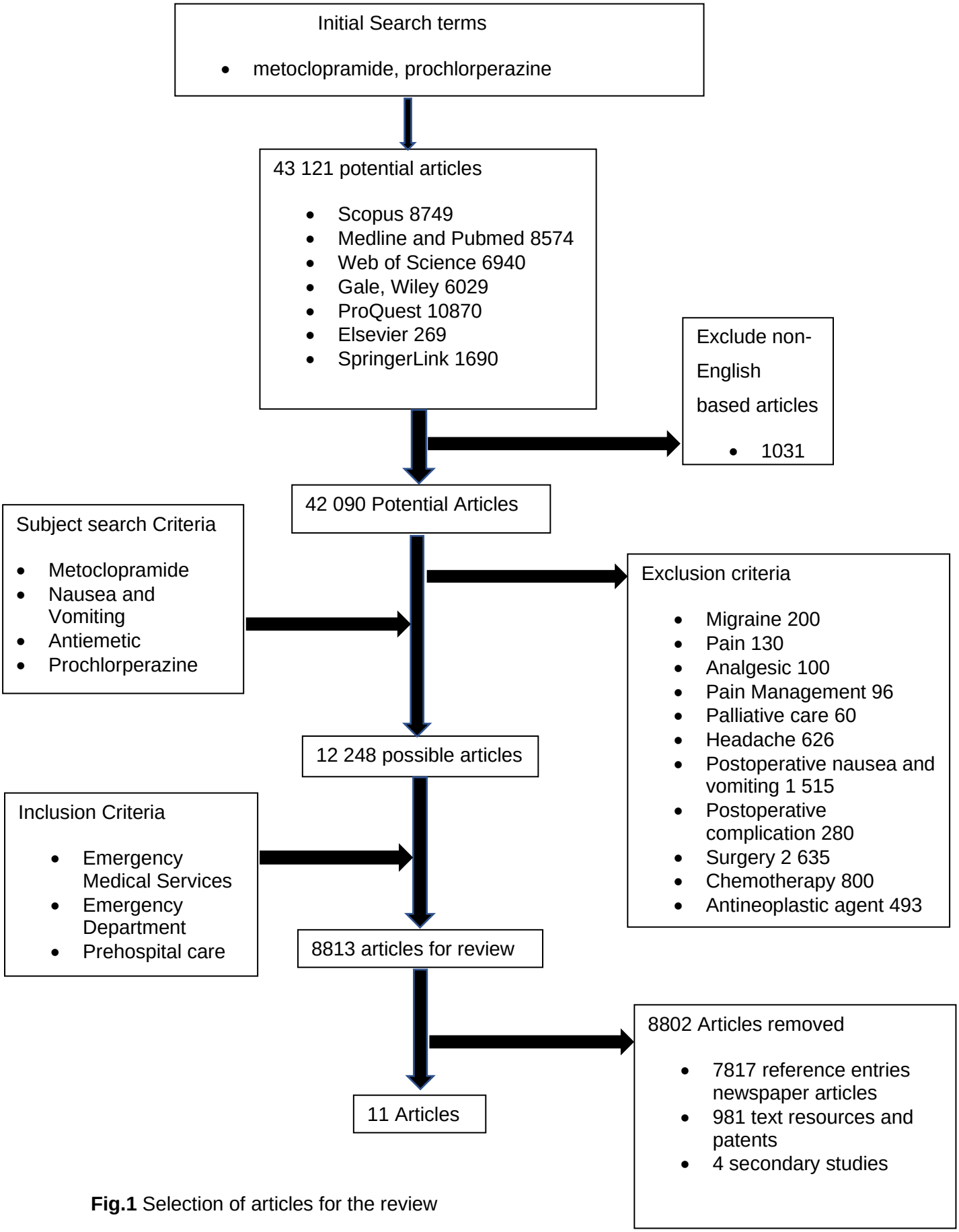

Fig.1 Selection of articles for the review

Results

Eleven studies were selected for this review[30, 31, 49, 33–39, 48] (Table 2). All 11 studies were RCTs. All of the studies were peer-reviewed journal articles. Ten of the studies were conducted in an EC[30, 31, 33–35, 37–39, 48, 49] and one in the prehospital setting[36]. Six of the studies originated from America[33–36, 38, 39], three studies originated from Australia[30, 31, 37] one from the United Kingdom[49] and one from New Zealand[48]. Nine studies evaluated metoclopramide[30, 31, 33–37, 48, 49] and three studies evaluated prochlorperazine[33, 38, 39]. All selected studies were published between 1999 to 2014.

NAUSEA ASSESSMENT

All studies reported on the presence of nausea. Eight studies reported on change in nausea post administration of an antiemetic[30, 33–39] and three studies just stated whether the patient was nauseas or not[31, 48, 49] (Table 2). Nausea can be assessed using the visual analogue scale (VAS) or discrete scale (DS) [20, 21]. Seven studies utilised VAS[33–39], Two studies utilised a DS[30, 31], one study required the patient to state whether they are nauseas or not nauseas[49].

ANTIEMETIC EVALUATION

Five studies evaluated the effectiveness of metoclopramide for the treatment of nausea and vomiting in the EC[31, 33–35, 37]. In the studies by Egerton-Warburton et al[37], Braude et al[33], and Barrett et al[35] the patient received 10mg metoclopramide. Chae et al[34] does not mention the dosage administered to the patient and in the study by Cham et al[31] one study group received 10mg metoclopramide and the second study group received 0.4mg/kg metoclopramide. One study evaluated the effectiveness of metoclopramide in the prehospital setting[36]. In the study by Rubio et al[36] patients received 20mg metoclopramide. Three studies evaluated the effectiveness of metoclopramide when administered prophylactically[30, 48, 49]. In the study by Lambie et al[48] administered 10mg metoclopramide prophylactically prior to the patient receiving morphine, Talbot-Stern et al[30] administered 10mg metoclopramide immediately after morphine or pethidine was administered, Bradshaw and Sen[49] administered 10mg metoclopramide before morphine was administered. Three studies evaluated prochlorperazine in the EC setting[33, 38, 39]. In the studies by Ernst et al[38], Braude et al[33] and Patka et al[39] patients received 10 mg prochlorperazine

ADVERSE EFFECTS

Adverse effects was reported in nine studies[30, 31, 33–39]. Akathisia was reported in four studies[34, 37–39], sedation and drowsiness reported in five studies[33–35, 38, 39], dystonic reactions and vertigo reported in one study[30]

RESCUE MEDICATION

The use of rescue medication (the administration of an additional antiemetic to treat nausea and vomiting) in all the studies found. Only three studies documented what the rescue drug was[36, 48, 49]. Seven studies mention that rescue medication was needed and administered but does report what medication was used[30, 33–35, 37–39]

STUDY CONCLUSIONS

Lambie et al[48], Talbot-Stern et al[30] and Bradshaw and Sen[49] concluded that the prophylactic administration of metoclopramide does not reduce the incidence of nausea and vomiting. Egerton-Warburton et al[37] concluded that there the reduction in the severity of nausea was the same in all study groups. Cham et al[31] concluded that the effectiveness of metoclopramide in treating N&V is the same whether the patient receives 10mg metoclopramide or 0.4mg/kg metoclopramide. Braude et al[33] found no difference between metoclopramide and prochlorperazine in treating N&V, and found droperidol to be more effective than both metoclopramide and prochlorperazine. Chae et al[34] concluded that tropisetron was associated with significantly lower vomiting rates than metoclopramide. Barret et al[35] concluded that there was no difference between metoclopramide and ondansetron in reducing nausea in the EC patients[35]. Rubio et al[36] found metoclopramide to be better at treating motion sickness than diphenhydramine. Ernst et al[38] found prochlorperazine to work significantly better than promethazine in relieving nausea and vomiting. Patka et al[39] concluded that ondansetron and prochlorperazine were the same at treating N&V in the EC.

Table 2 Overview of articles

	Author	Year	Study Type and setting Sample size	Drug studied	Scale used	Rescue Drug	Adverse effects	Study Conclusion
1	Lambie	1999	RCT EC New Zealand N=214 pts	Metoclopramide vs placebo	Pt was asked if they were nauseas or not	cyclizine	None reported	Routine administration of metoclopramide is not justified
2	Talbot-Stern	2000	RCT EC Australia N=122 pts	Metoclopramide vs placebo	Pt had to rate nausea Mild moderate Or severe		Dystonic reaction Vertigo Dizziness Drowsiness Restlessness	Metoclopramide should not be given prophylactically to patients that have received IV analgesia
3	Ernst	2000	RCT EC America N=84 pts	Prochlorperazine vs promethazine	100mm VAS		Akathisia Drowsiness	Prochlorperazine is more effective at treating uncomplicated nausea and vomiting
4	Cham	2004	Prospective RCT	Metoclopramide intermediate dosing	Verbal rating Scale		Swollen tongue Oculogyric crisis	No difference between the dosing regimens of

			EC Australia N=58 pts	vs metoclopramide standard dosing				metoclopramide in treating nausea and vomiting
5	Bradshaw	2006	RCT EC United Kingdom N=259 pts	Metoclopramide vs placebo	Pt had to say if they felt sick or not	cyclizine	None reported	Routine prophylactic administration of metoclopramide to patients that have received IV morphine is not justified
6	Braude	2006	RCT EC America N=100 pts	Droperidol vs metoclopramide vs prochlorperazine vs placebo	100mm VAS		Anxiety Sedation	No difference between metoclopramide and prochlorperazine when compared to the placebo to treat nausea. Droperidol does have a higher risk of akathisia but is more effective in treating nausea and vomiting
7	Chae	2011	RCT EC America N=100 pts	Tropisetron vs metoclopramide	100mm VAS		Akathisia Drowsiness Headache	Tropisetron proved to be more effective at treating nausea and vomiting when compared to metoclopramide

8	Barret	2011	RCT EC America N=180 pts	Ondansetron vs metoclopramide vs promethazine vs placebo	100mm VAS		Akathisia Sedation	No difference between ondansetron promethazine and metoclopramide in reducing nausea
9	Rubio	2011	RCT Prehospital America Sierra Nevada N=22 pts	Metoclopramide vs Diphenhydramine vs Placebo	100mm VAS	metoclop ramide	Dy mouth	Metoclopramide showed superiority in treating motion sickness when compared to diphenhydramine and a placebo
10	Patka	2011	Prospective RCT EC America N=64 pt	Ondansetron vs prochlorperazine	100mm VAS		Akathisia Sedation	Prochlorperazine does seem to be more effective at managing nausea
11	Egerton-Warburton	2014	RCT EC Australia N=258 pts	Ondansetron vs Metoclopramide vs Saline	100mm VAS		Akathisia Restlessness Sweatiness Muscle Twitching Dizziness	No difference in either Ondansetron or metoclopramide over saline in treating nausea and vomiting

RCT: Randomised Control Trial; EC: Emergency Centre; Pts: Patients; VAS: Visual Analogue Scale

Discussion

The use of anti-emetics to treat nausea and vomiting is common practice in the prehospital setting[8]. This scoping review evaluated the available literature on metoclopramide and prochlorperazine use in treating nausea and vomiting in the emergency care patient. Even though a broad-based literature search was done only 11 articles were found that evaluated metoclopramide and or prochlorperazine use in the emergency setting to treat nausea and vomiting[18-28]. The limited available research for this review, is surprising, considering the fact that nausea and vomiting are frequent symptoms in patients presenting to the emergency centre[25].

A systematic review done in 2011 by Simpson et al[50], was conducted on prophylactic metoclopramide in the emergency setting, and identified only three studies[50]. Simpson et al[50] concluded in their review that the prophylactic administration on metoclopramide could not be justified[50]. The authors acknowledged that their analysis would be underpowered and they would have to enrol approximately 2000 patients to be able to achieve 80% power and statistical significance[50]. Following the systematic review by Simpson et al[50], in 2014 a Cochrane review was conducted by Fury et al[25], on drugs to treat nausea and vomiting in the EC[25]. and identified only eight studies[25].

The authors of this review also found that there is limited research available on antiemetic use in the emergency setting. Consistent with the findings of this scoping review, Fury et al[25] also found no convincing evidence supporting the superiority of any particular antiemetic over another[25]. In 2018 Verma et al[8] conducted a systematic review on antiemetic safety and efficacy in the prehospital setting[8]. Seven articles were found to be eligible for the review by Verma et al[8]. This review also found reporting be variable across the selected studies[8]. The administration of any medication comes with side effects[51]. Reporting on adverse effects of the antiemetics administered varied across the studies found for this review. As noted above, not all the studies found reported on adverse drug reactions to metoclopramide and or prochlorperazine. Akathisia, drowsiness and sedation were the most commonly reported adverse effects, and it is concerning that some studies found did not report on any adverse effects[25, 48, 49]

What is apparent from this scoping review is that metoclopramide is widely used to treat nausea and vomiting in the emergency care setting. Metoclopramide was evaluated in nine studies. In South Africa and other resource constrained countries, the low cost of metoclopramide, will most certainly influence its availability and the choice of antiemetic used

to treat nausea and vomiting. Metoclopramide is cheaper than prochlorperazine and more readily available [52].

From the evidence found in this review, neither metoclopramide nor prochlorperazine showed any superiority in treating nausea and vomiting in the emergency setting. Further to that the evidence found in this review does not support the prophylactic use of metoclopramide in the prehospital setting when a patient receives an opioid analgesic. This is similar to the findings by Meltzer et al[53], whose take home message was that the only antiemetic that had a statistically significant decrease in VAS score at 30 minutes was droperidol[53]. Metoclopramide was also evaluated in a study by Henzi et al[54] who analysed data on more than 6000 adults and children in the postoperative setting. Henzi et al[54] concluded that metoclopramide does not show any clinically relevant antiemetic effect[54].

Conclusion

In conclusion there is no consensus on the superiority of any one drug to treat nausea and vomiting, yet it is important to effectively treat nausea and vomiting in the emergency care setting. The use of metoclopramide or prochlorperazine to treat nausea and vomiting in the emergency care setting does expose the patient to a significant risk of harm from the adverse effects of the drugs, and needs to be carefully considered, especially in the light of the overwhelming evidence that neither drugs are particularly effective in this role. Further research needs to be conducted on the safety and efficacy of metoclopramide and prochlorperazine to treat nausea and vomiting in the emergency setting, as well as to consider other agents which have shown promise elsewhere.

Strengths and Limitations

This is the first scoping review attempting to map out the available literature on metoclopramide and prochlorperazine use in the treatment of nausea and vomiting in the emergency setting. This review has highlighted the need for further research on antiemetic use in the South African emergency care setting.

The homogeneity of the evidence found for this review was not established; and only English-language research was included which may subject the results to language and publication bias. The paucity of research available on the topic also limited this research

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Appendix One

Breakdown of studies selected for review:

1. **A randomized, placebo-controlled trial of ondansetron metoclopramide, and promethazine in adults**[35]

Author	Barret
Study method	Randomised Control Trial (RCT) placebo controlled Double blind Control was the placebo arm
Study year	2011
Study setting	Emergency Department Vanderbilt University Medical Centre Nashville Tennessee
Study Aim	Whether Ondansetron is superior to metoclopramide, promethazine or saline placebo in reducing nausea in patients in the emergency department
Population	180 Consenting adults 18 years or older 163 completed the study Pt's presented to the emergency department complaining of nausea and vomiting, requiring intravenous antiemetics to be administered
Pt. Demographics	Median age 32 Interquartile range 23-47 68% females
Method to assess nausea	100 mm Visual analogue scale (VAS)
Drug protocol	Pts received either 10mg metoclopramide 4mg ondansetron 12.5mg promethazine 2ml saline All drugs diluted to a 2ml volume
Nausea Relief	A mean reduction 30 minutes after medication given VAS Ondansetron -22 (-32 to -15)

	Metoclopramide -30 (-38 to -25.5) Promethazine -24 (-40 to-21) Saline -16 (-25 to -3) CI 95%
Adverse effects	**Akathisia** Metoclopramide N=43 9 mild 1 moderate 1 severe Ondansetron N=36 3 mild 1 moderate 1 severe **Sedation** Metoclopramide 10 mild 8 moderate 3 severe Ondansetron 10 mild 4 moderate 2 severe
Rescue Medication	9 pts that got metoclopramide received rescue medication 23 pts in the placebo arm and 19 pts in the ondansetron arm
Outcome of this study	No difference between ondansetron promethazine and metoclopramide in reducing nausea

2. **Antiemetics in the ED: a randomised controlled trial comparing 3 common agents** [33]

Author	Braude
Study method	RCT placebo double blind controlled trial Control was the placebo arm
Study setting	Emergency Department Fresno California

Study year	2006
Study Aim	To prospectively compare the efficacy of droperidol, metoclopramide, prochlorperazine with each other and a saline placebo in patients complaining of moderate to severe nausea
Population	Adult patients presenting with nausea to the emergency department 100 patients enrolled Pt's were between 18 to 65 years complaining of nausea and vomiting with a baseline nausea rating of at least 40mm on the 100mm VAS
Pt. Demographics	Total of 97 patients 42 males 55 females
Method to assess nausea	100mm VAS
Drug protocol	2ml prefilled syringes 1.25mg droperidol, 10mg metoclopramide,10mg prochlorperazine 2ml saline
Nausea Relief	Mean ± standard deviation Droperidol -54.5 ± 18.4 Metoclopramide -40.2 ± 23.8 Prochlorperazine -40.5 ± 24.1 Saline -38.7 ± 21.1
Adverse effects	[mean ± SD] **Anxiety** Droperidol -23.8 ± 25.4 Metoclopramide -25.4 ± 24.3 Prochlorperazine -21.9 ± 38.0 Saline -31.7 ± 31.6 **Sedation** Droperidol 13.5 ± 32.2

	Metoclopramide 0.4 ± 30.1 Prochlorperazine 5.1 ± 26.5 Saline -4.8 ± 25.0 Droperidol caused more anxiety or restlessness that was self-reported by the patients
Rescue Medication	Droperidol 1 patient Metoclopramide 1 patient Prochlorperazine 6 patients Saline 4 patients
Outcome of study	Metoclopramide and prochlorperazine were not more effective than saline in treating nausea. Droperidol when administered intravenously does have a higher risk of akathisia, but was more effective than metoclopramide and prochlorperazine in treating nausea

3. Randomised Control Trial of Ondansetron vs. Prochlorperazine in Adults in the Emergency Department[39]

Author	John Patka
Study method	Prospective RCT, Double blind active controlled
Study setting	Emergency Department South Regional Hospital Riverdale
Study year	2011
Study Aim	To compare the effectiveness of ondansetron and prochlorperazine in the treatment of nausea in adult emergency department patients
Population	Adult patients admitted to the emergency department complaining of nausea and vomiting. Pt's were older than 18 years
Pt. Demographics	**Prochlorperazine group** N=32 17 females

	Ondansetron group N=32 18 females
Method to assess nausea	100mm VAS
Drug protocol	Patients received either 4mg ondansetron intravenously or 10mg prochlorperazine intravenously
Nausea Relief	Mean ± SD **0 minutes** Ondansetron 72.4 ± 25.6 Prochlorperazine 78.6 ± 28.5 **0 to 30 minutes** Ondansetron 50.4 ± 33.0 Prochlorperazine 47.5 ± 33.3 **31 to 60 minutes** Ondansetron 43.7 ± 33.5 Prochlorperazine 24.9 ± 31.8 **61 to 120 minutes** Ondansetron 34.3 ± 31.7 Prochlorperazine 16.8 ± 29.1
Adverse effects	**Increased sedation** Ondansetron 5 (16%) Prochlorperazine 7 (22%) **Akathisia** Ondansetron 1 (3%) Prochlorperazine 3 (9%)

Rescue Medication	Ondansetron 5 patients Prochlorperazine 1 patient
Outcome of study	Prochlorperazine does seem to better at managing nausea when compared to ondansetron. There is very little difference between the two drugs when used to treat vomiting

4. **Prochlorperazine Versus Promethazine for Uncomplicated Nausea and Vomiting in the Emergency Department: A Randomised Double-Blind Clinical Trial**[38]

Author	Amy A Ernst
Study method	RCT Double blind study
Study setting	Emergency Department Vanderbilt University hospital in Nashville Tennessee University of California-Davis Sacramento California
Study year	2000
Study Aim	To compare prochlorperazine and promethazine to treat uncomplicated nausea and vomiting in the emergency department. The null hypothesis was that prochlorperazine and promethazine are equally effective at relieving nausea and vomiting symptoms
Population	Pt's that were 18 years or older that came to the emergency department with uncomplicated gastritis or gastroenteritis
Pt. Demographics	**Prochlorperazine group** N=42 14 males 28 females **Promethazine group** N=42 11 males 31 females

Method to assess nausea	100mm visual analogue scale
Drug protocol	Pts received either 10mg prochlorperazine diluted in 9ml saline or 25mg promethazine diluted in 9ml saline
Nausea Relief	Median **Baseline** Prochlorperazine 6.5 Promethazine 7.3 **30 minutes** Prochlorperazine Median 2 Median change from base line 4.5 Promethazine Median 4.6 Median change from base line 2.7 **60 minutes** Prochlorperazine Median 0.45 Median change from 30 min VAS 1.55 Promethazine Median 2.6 Median change from 30 min VAS 2.0
Adverse effects	**Prochlorperazine** Drowsiness 16 pts Akathisias 6 pts **Promethazine**

	Drowsiness 30 pts Akathisias 6 pts
Rescue Medication	Prochlorperazine 4 pts Promethazine 13 pts
Outcome of study	Prochlorperazine proved to be more effective than promethazine in treating uncomplicated nausea and vomiting. The risk of akathisia is the same for both drugs, and promethazine does cause more drowsiness in the patients

5. Antiemetic Use for Nausea and Vomiting in Adult Emergency Department Patients: Randomised Controlled Trial Comparing Ondansetron, Metoclopramide, and Placebo[37]

Author	Diana Egerton-Warburton
Study method	Prospective double-blind RCT Placebo controlled
Study setting	Emergency Department Monash Medical Centre and Dandenong Hospital Australia
Study year	2014
Study Aim	The study compared the efficacy of ondansetron and metoclopramide with a placebo in treating uncomplicated nausea and vomiting
Population	Pts were 18 years or older and presented to the emergency department complaining of nausea and vomiting.
Pt. Demographics	**Ondansetron** N=87 Median age 42 Females 56 **Metoclopramide**

	N=88 Median age 42 Females 58 **Saline placebo** N=83 Median age 42 Females 55
Method to assess nausea	100mm VAS
Drug protocol	Metoclopramide 10mg/2ml drawn up in 2ml syringe. 2*2ml syringes filled with 2ml metoclopramide were sealed in a pack. Total dosage 20mg Ondansetron 4mg/2ml drawn up in a 2ml syringe. 1*2ml syringe filled with 0.9%saline and another 2ml syringe with ondansetron were sealed in another pack Placebo 2*2ml syringes filled with 0.9% saline sealed in a third pack
Nausea Relief	Median **Initial rating** Ondansetron 52mm Metoclopramide 50mm Placebo 52mm **Post treatment** Ondansetron 19mm Metoclopramide 18mm Placebo 27mm **Change in VAS** Ondansetron 27mm (95% CI 22 to 33mm) Metoclopramide 28mm (95% CI 22 to 34mm) Placebo 23mm (95% CI 16 to 30mm)
Adverse effects	**Metoclopramide**

	Akathisia 2 Restlessness 2 Sweatiness 1 Muscle twitching 1 **Ondansetron** Dizziness 1 Stinging at injection site 1 **Placebo** Shaking/restlessness 1
Rescue Medication	Ondansetron 29 pts (34.5%) (95% CI 25% to 45%) Metoclopramide 15 pts (17.9%) (95% CI 10.8% to 27.2%) Placebo 29 pts (36.3%) (95% CI 26.3% to 47.2%)
Outcome of study	Reduction in nausea and vomiting were similar in all three drugs. The use of antiemetic drugs did not show a significant benefit over the placebo in treating nausea and vomiting

6. Intermediate dose metoclopramide is not more effective than standard dose metoclopramide for patients who present to the emergency department with nausea and vomiting: A pilot study [31]

Author	Swee Cham Mary Basire
Study method	Prospective RCT Single blind study
Study setting	Emergency Department Western Hospital in Footscray and Northern Hospital in Epping Victoria Australia
Study year	2004
Study Aim	To ascertain if intermediate dosing of metoclopramide is better than standard dosing for the patient that comes to the emergency department complaining of nausea and vomiting
Population	Patients were 18 years and/or older and required treatment for nausea and vomiting

Pt. Demographics	**10mg metoclopramide** N=34 Age median 34 Males = 9 **0.4mg/kg metoclopramide** N =24 Age median 42 Males = 8
Method to assess nausea	A verbal rating scale 0 to 10
Drug protocol	Patients either received 10mg metoclopramide 0.4mg/kg metoclopramide maximum dose -weight 80kg (32mg)
Nausea Relief	Median Nausea reduction 4 pts in the 10mg group (95% CI 3 – 5) 5 pts in the 0.4mg/kg group (95% CI 4 – 6)
Adverse effects	2 pts in the 0.4mg/kg group 1 oculogyric crisis 1 Swollen tongue
Rescue Medication	10mg group 5 pts 0.4mg/kg 3 pts
Outcome of study	There is no difference between standard dose 10mg metoclopramide and 0.4mg/kg in treating nausea and vomiting in the emergency department patient.

7. Prophylactic Metoclopramide is Unnecessary With Intravenous Analgesia in the ED[30]

Author	Janet Talbot-Stern Richard Paoloni
Study method	RCT double blinded placebo-controlled trial
Study setting	Emergency department

	Royal Prince Alfred Hospital Sydney Australia
Study year	2000
Study Aim	To assess the effect of metoclopramide on the incidence of nausea and vomiting after the patient received morphine or pethidine analgesia
Population	Pts that presented to the emergency department in acute pain requiring intravenous morphine and pethidine. Pts were 16 years or older
Pt. Demographics	**Metoclopramide** N=63 Males= 48 (75%) Mean age= 41 Age range 17-83 **Placebo** N=59 Males= 41 (68%) Mean age= 38 Age range 16-86
Method to assess nausea	Patients had to rate their nausea as mild, moderate, or severe. Author does not mention if the VAS was utilised
Drug protocol	An equal number of ampoules each containing a volume of 2ml of either normal saline or metoclopramide (10mg/2ml)
Nausea Relief	**Metoclopramide** N=63 30 minutes= 3.2% 60 minutes= 4.8% **Placebo** N=59 30 minutes= 6.8% 60 minutes= 3.4%
Adverse effects	7.9% of the pts that received metoclopramide reported adverse effect not related to nausea and vomiting. The reported side effects were, dystonic reaction, vertigo and dizziness, drowsiness and restlessness
Rescue Medication	No patient required rescue medication

Outcome of study	Metoclopramide should not be given prophylactically routinely to patients that have received IV analgesia. The severity and the frequency of side effects cannot be ignored

8. Use of a prophylactic antiemetic with morphine in acute pain: randomised control trial[32]

Author	M Bradshaw A Sen
Study method	Prospective RCT double blind placebo-controlled study
Study setting	Emergency Department Wrexham Maelor Hospital United Kingdom
Study year	2006
Study Aim	To compare the occurrence of nausea and vomiting in patients treated with morphine for acute pain that have received either prophylactic metoclopramide or placebo saline IVI
Population	Patients over the age of 12 years that came to the emergency department with any acute painful condition that required IV morphine to be administered
Pt. Demographics	**Metoclopramide** N=123 Median age 53 Males= 54 **Placebo** N= 136 Median age= 52.5 Males= 65
Method to assess nausea	Patients were asked if they were feeling sick, or if they vomited. The answers had to be either Yes/No.
Drug protocol	Syringes were prefilled with either 2ml normal saline or 2ml 10mg/2ml metoclopramide. Syringes were numbered and selected at random to be administered to the patient

Nausea Relief	**Metoclopramide** 2 patients vomited **Saline** 5 patients vomited
Adverse effects	Not reported on in the study
Rescue Medication	If any patient got nauseas and/or vomited they were given 50mg cyclizine
Outcome of study	Routine use of metoclopramide prophylactically to treat nausea in patients that were to receive IV morphine was not justifiable

9. The role of prophylactic anti-emetic therapy in emergency department patients receiving intravenous morphine for musculoskeletal trauma[48]

Author	Bruce Lambie
Study method	Double blind placebo-controlled RCT
Study setting	Emergency Department Dunedin Hospital New Zealand
Study year	1999
Study Aim	To determine if the routine administration of IV metoclopramide will be beneficial to the patient that has received IV morphine for musculoskeletal trauma
Population	Any patient older than 16 years that presented to the emergency department requiring IV morphine for musculoskeletal trauma
Pt. Demographics	**Metoclopramide** N=111 Mean age=46.5 Males=55 **Placebo** N=103 Mean age=48 Males=53

Method to assess nausea	Patients were asked if they were nauseas and/or vomited either by personal interview or by telephonic interview if the patient was discharged from the emergency department
Drug protocol	Syringes were independently prepared in batches of twenty and coded by number. Syringes either contained 2ml normal saline or 2ml 10mg metoclopramide
Nausea Relief	**Metoclopramide** No patients experienced severe nausea **Placebo** 2 patients experienced severe nausea
Adverse effects	not reported on in this study
Rescue Medication	2 patients in the metoclopramide group and one patient in the placebo received cyclizine
Outcome of study	Routine administration of metoclopramide to reduce vomiting when a patient is to receive IV morphine is not justified

10. Motion Sickness: Comparison of Metoclopramide and Diphenhydramine to Placebo[36]

Author	Stephanie Rubio
Study method	Prospective double-blind placebo-controlled RCT
Study setting	Prehospital environment Sierra Nevada, Fresno Country
Study year	2011
Study Aim	To evaluate the efficacy of metoclopramide or diphenhydramine to relieve symptoms of motion sickness in patients being transported by an ambulance in a mountainous setting
Population	Any patient adult patient between 18 and 65 years old that required ambulance transportation in the mountainous areas of Fresno County

Pt. Demographics	**Metoclopramide** N=8 Mean age=34.5 Males= 5 Females=3 **Diphenhydramine** N=7 Mean age 44.6 Males= 5 Females=2 **Placebo** N=7 Mean age=43.7 Males= 3 Females=4
Method to assess nausea	100mm Visual analogue scale
Drug protocol	The night paramedic coming off night shift would draw up the medication and label the medication with a randomly assigned number
Nausea Relief	**Metoclopramide** 5 min 19.1 (95%CI =7.9-30.3) 10 min 11.0 (95%CI= 4.7-10.7) **Placebo** 5 min 53.1 (95%CI= 37.1-69.1) 10 min 54.1 (95%CI= 40.1-68.1) **Diphenhydramine** 5 min 54.9 (95%CI= 40.4-69.4) 10 min 53.9 (95%CI= 39.4-68.4)
Adverse effects	One patient in the placebo group reported a dry mouth. No dystonic reactions reported.
Rescue Medication	12 patients requested a rescue dose of metoclopramide at 15 minutes. 6 pts were in the placebo group, 5 in the diphenhydramine group and 1 in the metoclopramide group
Outcome of study	Use of metoclopramide to reduce motion sickness during ambulance transportation is superior to diphenhydramine and a placebo

11. Tropisetron versus metoclopramide for the treatment of nausea and vomiting in the emergency department: A randomised, double-blinded, clinical trial[34]

Author	John Chae
Study method	Double blind placebo-controlled RCT
Study setting	Emergency department Austin Hospital Melbourne Australia
Study year	2011
Study Aim	To compare the efficacy of tropisetron and metoclopramide in treating undifferentiated nausea and vomiting in emergency department patients
Population	Any patient older than 18 years that presented to the emergency department with nausea and vomiting that required drug treatment
Pt. Demographics	**Metoclopramide** N=50 Mean age=56.7 Males= 21 **Tropisetron** N=50 Mean age=53.3 Males=21
Method to assess nausea	100mm VAS
Drug protocol	Patients were given either 5mg tropisetron or 10mg metoclopramide depending on their allocation
Nausea Relief	**Metoclopramide** The decrease in nausea from baseline was 37mm **Tropisetron** The decrease in nausea from baseline was 47.9mm
Adverse effects	Akathisia was reported on. Tropisetron showed lower mean akathisia scores and one patient in the metoclopramide arm required benztropine There was no difference in mean drowsiness

	Headaches were reported by 11 pts in the tropisetron group and 5 in the metoclopramide group
Rescue Medication	13 patients in the metoclopramide group and 5 patients in the tropisetron group required a rescue anti-emetic
Outcome of study	Tropisetron was associated with a lower vomiting rate and shows promise as an alternative antiemetic

Appendix Two

INTRODUCTION The African Journal of Emergency Medicine (AfJEM, ISSN: 2211-419X) is the official journal of the African Federation for Emergency Medicine. It is an international, peer-reviewed journal aimed in particular at supporting emergency care across Africa. AfJEM publishes original research, reviews, brief reports of scientific investigations, case reports as well as commentary and correspondence related to topics of scientific, ethical, social and economic importance to emergency care in Africa. Articles will be of direct importance to African emergency care but may have originated from elsewhere in the world.

TYPES OF ARTICLES

Original Article:

Original studies of basic or clinical investigations in areas relevant to emergency medicine. Reference to the relevance of the research in a resource poor setting is essential and should be alluded to in the discussion section. References and a structured abstract (see Preparation below) are required. Maximum length: 3,000 words, 5 tables and/or figures, plus the abstract (300 words) and references (max 50).

The checklists found on the following websites should be used to structure your manuscript (a copy of the checklist indicating which elements of the reporting format you adhered to, a signed conflict of interest form and Author statement form - see below- should be submitted with your manuscript):

a. For randomised control trials: http://www.consort-statement.org
b. For cohort, case-control, and cross-sectional studies: http://www.strobe-statement.org/
c. All other studies: http://www.equator-network.org/

2. Review Articles:

Extensive reviews of the literature on a narrow clinical topic. References must include, but need not be limited to, the past 3 years of the literature. A structured abstract is required (see Preparation below). Maximum length: 3,000 words, plus the abstract (max 300 words) and references (max 50). Please contact the editor in chief before you submit a review.

The following reporting checklists should be used to structure your manuscript (a copy of the checklist indicating which elements of the reporting format you adhered to, a signed conflict of interest form and Author statement form - see below- should be submitted with your manuscript):

a. A Resourced-tiered review checklist is the standard reporting format for publication in AfJEM: http://www.afjem.com/resource-tiered-checklist.html
b. If your topic does not lean itself towards a resourced tiered review consider alternative reporting checklists for systematic reviews and meta-analyses such as Prisma checklist (http://www.prisma-statement.org) or similar.

Please check with the editor-in-chief before using a checklist other that the resources-tiered checklist.

3. Case Reports:

Brief descriptions of a previously undocumented disease process, a unique unreported manifestation or treatment of a known disease process, or unique unreported complications of treatment regimens. Case reports should be structured as follow: Introduction, Case report and Discussion. It should not contain an exhaustive review of the literature. Consider consent for patient identifiable information (download from website). A structured abstract (see Preparation below) is required. Maximum length: 1,000 words, plus abstract (max 150 words) and references (max 10), and 1 table or figure a copy of the checklist indicating which elements of the reporting format you adhered to, a signed conflict of interest form and Author statement form - see below should be submitted with your manuscript). Case reports listed for publication after 2015 are published online only and compiled within a virtual issue once a year.

4. Practical Pearl (upload as Technical note):

Descriptions of novel approaches to provision of emergency care; and practical "tricks of the trade" describing aspects of emergency medicine management. An abstract is not required (enter: Not required, practical pearl when prompted). Maximum length: 800 words, 5 tables and/or figures and references (max 5). A manuscript template is available at http://www.afjem.com/#author and can be used for submission (a signed conflict of interest form- see below- should be submitted with your manuscript). Note that author details should be included in the manuscript.

5. Abbreviated paper (previously Brief Research Reports):

Reports of preliminary data and findings or studies with small numbers demonstrating the need for further investigation. References and a structured abstract (see Preparation below) are required. Maximum length: 1,500 words, plus the abstract (max 300 words) and references (max 10) and 3 tables and/or figures. Checklists described for original research above should be used to structure your manuscript (a copy of the checklist indicating which

elements of the reporting format you adhered to, a signed conflict of interest form and Author statement form - see below- should be submitted with your manuscript)

6. Commentary: Descriptions of clinical and nonclinical problems and solutions; descriptions of novel approaches to planning, management, or provision of emergency services; and practical " how-to" articles describing aspects of emergency medicine management (includes African country acute care profiles). A narrative abstract (see Preparation below) is required. Maximum length: 3,000 words, plus the abstract (max 300 words) and references (max 50). A signed conflict of interest form- see below- should be submitted with your manuscript.

7. Editorials (commissioned and including op-ed): Authoritative comments or opinions on major current problems of emergency physicians or on controversial matters with significant implications for emergency medicine; or, qualified, thorough analysis and criticism of articles appearing in AfJEM. Maximum length: 1,500 words plus references (max 5). An abstract is not required. A signed conflict of interest form- see below- should be submitted with your manuscript.

8. Correspondence: Discussion, observations, opinions, corrections, and comments on topics appearing in AfJEM; very brief reports or other items of interest. Maximum length: 500 words, plus references (max 5). An abstract is not required. Please enter: Not applicable, Correspondence when prompted to enter an abstract. Letters discussing an AfJEM article should be received within 6 weeks of the article's publication. The article must be included in the references. Authors of articles about which letters are received will be given the opportunity to reply, which will not be shared with the letter writer prior to publication. Letters of political or other topics unrelated to the science of medicine, as well as those containing personal criticisms, will not be published. A signed conflict of interest form see below- should be submitted with your manuscript

9. Erratum: Corrections on topics appearing in AfJEM. Maximum length: 300 words, plus references (max 5). An abstract is not required. Please enter: Not applicable, Erratum when prompted to enter an abstract. Letters discussing an AfJEM article should be received within 6 weeks of the article's publication. The article must be included in the references. Authors of articles about which letters are received will be given the opportunity to reply, which will not be shared with the letter writer prior to publication. Letters of political or other topics unrelated to the science of medicine, as well as those containing personal criticisms, will not be published elsewhere including electronically in the same form, in English or in any other language, without the written consent of the copyright-holder. A signed conflict of interest form- see below- should be submitted with your manuscript.

Submission Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail. Please submit your article via https://www.evise.com/profile/api/navigate/AFJEM

Submission Checklist

You can use this list to carry out a final check of your submission before you send it to the journal for review. Please check the relevant section in this Guide for Authors for more details.

Ensure that the following items are present:

One author has been designated as the corresponding author with contact details:
• E-mail address
• Full postal address
All necessary files have been uploaded:
Title page
Cover letter
Manuscript:
• Include keywords
• All figures (include relevant captions)
• All tables (including titles, description, footnotes)
• Ensure all figure and table citations in the text match the files provided
• Indicate clearly if color should be used for any figures in print Graphical Abstracts / Highlights files (where applicable)
Conflict of Interest Form
Supplemental files (where applicable): Author Statement document and relevant reporting checklist
Further considerations • Manuscript has been 'spell checked' and 'grammar checked'
• All references mentioned in the Reference List are cited in the text, and vice versa
• Permission has been obtained for use of copyrighted material from other sources (including the Internet)
• A competing interest's statement is provided, even if the authors have no competing interests to declare
• Journal policies detailed in this guide have been reviewed
• Referee suggestions and contact details provided, based on journal requirements

Appendix Three - Ethics Approval

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E52-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

14 May 2018

HREC REF: 306/2018

Dr P Hodkinson
Emergency Medicine
F51, OMB

Dear Dr Hodkinson

PROJECT TITLE: METOCLOPRAMIDE vs. PROCHLORPERAZINE FOR THE TREATMENT OF NAUSEA AND VOMITING IN THE EMERGENCY CARE SETTING: A SCOPING REVIEW-(MPhil-candidate- Mr S Areff)

Thank you for submitting your request to the Faculty of Health Sciences Human Research Ethics Committee.

The HREC note that this is a scoping review of published, freely accessible literature.

HREC approval is not required.

This is in accordance with Section 1.1.8 of the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015), which states: "*Research that relies exclusively on publicly available information or accessible through legislation or regulation usually need not undergo formal ethics review. This does not mean that ethical considerations are irrelevant to the research.*"

The HREC recommend that researchers refer to the PRISMA website, for the PRISMA statement and checklist, to facilitate the reporting of systematic reviews and meta-analyses. For more information, please refer to http://www.prisma-statement.org/.

Further, fundamental ethical principles for health-related research should be considered in the objectives and methods of the systematic review. See, for example, the Declaration of Helsinki (Fortaleza, Brazil, 2013) and the Department of Health's Ethics in Health Research: Principles, Processes and Structures (South African Department of Health, 2015)

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE

Title of study

Metoclopramide vs Prochlorperazine for the treatment of Nausea and Vomiting in the Emergency Care Setting: A scoping review

STUDENT: Shamiel Areff

M.Phil. Emergency Medicine Clinical Emergency Care

ARFSHA003

SUPERVISOR(s): 1

Ian Howard

B EMC, Mphil. Emer. Med

2

Peter Hodkinson

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Declaration

This study is in partial fulfilment of the MPhil (Clinical Emergency Care) Emergency Medicine degree

Declaration:

I, Shamiel Areff, hereby declare that the work contained in this assignment is my original work and that I have not previously submitted it, in its entirety or in part, at any university for a degree.

Signature:  Date: 2017

List of Abbreviations and terms

ALS: Advanced Life Support

CINAHL: Cumulative Index to Nursing and Allied Health Literature

CTZ: Chemoreceptor trigger zone

EMS: Emergency Medical Services

EPS: extrapyramidal symptoms

FDA: Food and Drug Administration

GI: Gastro Intestinal

HPCSA: Health Professions Council South Africa

NMS: Neuroleptic Malignant Syndrome

Researcher and supervisors

SA: Shamiel Areff

IH: Ian Howard

PH: Peter Hodkinson

Title

Metoclopramide vs Prochlorperazine for the treatment of nausea and vomiting in the emergency care setting: A scoping review

Introduction to the study

The South African EMS system is a 3 tiered system. EMS training is provided at a basic, intermediate and advanced level. Qualified practitioners have to be registered with the Health Professions Council to be able to practice. The current scope of practice only allows metoclopramide to treat nausea and vomiting in the prehospital setting, administered only by ALS providers. Treatment of nausea and vomiting is desirable to improve patient comfort during transport and help mitigate the complication risks such as dehydration, electrolyte abnormalities and aspiration.

Background (Literature Review)

Metoclopramide is a benzamide agent, gastroesophageal reflux disease, and post- operative nausea and vomiting used for the treatment of chemotherapy induced nausea and vomiting. It has the following side effect profile; EPS in more than 10% of patients receiving metoclopramide. Some other side effects are fatigue, restlessness, sedation, headache, dizziness, and somnolence. NMS, diarrhoea, impotence, nausea, menstrual disorders have also been reported, although the frequency of occurrence has not been established[55].

Prochlorperazine is a phenothiazine derivative agent[56]. Patients receiving prochlorperazine have reported experiencing the following side effects; insomnia, restlessness, dizziness, anxiety, euphoria, agitation, depression weakness and headache, constipation, dry mouth, blurred vision[56].

There are few studies published that evaluates the medications used to treat nausea and vomiting in the prehospital environment and the emergency department. In a systematic review study done by Simpson Bendall and Middleton in 2011, where metoclopramide was compared to a placebo in the emergency care setting (either prehospital or in the emergency department), it was found that as many as 23% of patients receive metoclopramide for the

treatment of nausea and vomiting after they have received an opioid analgesic[57]. This study failed to provide rigorous evidence showing benefit to the patient after they have received metoclopramide[57]. They found no significant difference in vomiting when patients received either metoclopramide or a placebo. They concluded that the routine administration of metoclopramide to treat nausea might expose the patient to an unjustifiable risk of harm[57].

In a prospective double blind randomised study done by Janet Talbot-Stern and Richard Paoloni in 1999; where prophylactic metoclopramide was administered to patients in the emergency department, it was found that 7.9% of the patients receiving metoclopramide experienced side effects not relating to nausea and vomiting[30]. The overall incidence of side effects in patients that have received metoclopramide is 11%[30]. The specific side effects reported by patients in the Talbot-Stern Paoloni study was restlessness, limb jerking, drowsiness, dizziness and vertigo[30].

The current ALS guidelines have been published in September 2006[58]. The only drug listed for the treatment nausea and vomiting is Metoclopramide[58]. The HPCSA have recently compiled new clinical guidelines for prehospital practitioners', but these are not yet approved for practice[59]. There information presented in the 2006 guidelines may be outdated. It recommends that the patient be given a bolus dosage of 10mg IVI to treat nausea and vomiting, yet studies have shown that if that same dosage is given as an infusion over 15 minutes it has a 78% relative risk reduction in causing akathisia[60]

Rationale

Data from a private SA emergency medical service provider, from April 2012 up until January 2017, shows their ALS paramedics had administered metoclopramide to 3.6% of their patients[61]. From a total of 48 023 patients that their ALS paramedics had treated, 1776 patients received metoclopramide before admission to the emergency department[61].

Vomiting exposes the patient to a higher risk of airway compromise and aspiration, because these patients are often lying supine in the back of the ambulance. The aspiration risk is exacerbated when these patients have been given a sedative in conjunction with the opioid analgesic (70% (1247) of the patients that received metoclopramide at ER24 had received an opioid analgesic). In order to appropriately manage these patients' the ALS practitioner needs

to be able to treat this condition and prevent the patient from vomiting. It is noted that the above figure only represent data from one private emergency medical service in South Africa. This data is readily available from the above service provider.

Metoclopramide has a blackbox warning because of the risk of tardive dyskinesia[55], yet it is the only drug made available to the ALS paramedics in South Africa to treat nausea and vomiting[58]. To effectively treat nausea and vomiting should employ a multinodal approach[56] and possibly the use of a safer more effective drug.

Research Question

What does the current scientific literature show comparing metoclopramide with prochlorperazine for the treatment of nausea and vomiting in the emergency care setting?

Specific Aims

To review the scientific literature comparing metoclopramide with prochlorperazine for the treatment of nausea and vomiting in the emergency care setting.

Methods:

Study design

The scoping review methodology as described by Arksey and O' Malley will be used to review and describe the literature [46]. A literature search will be done using Pubmed, Medline, Embase, Cochrane, Web of Science, and CINAHL online databases. Additionally, a web search through TRIP databases will be done to identify any grey literature. Lastly, a reference search of all included articles will be conducted to identify any literature not identified in the database search. A combination of MESH terms identified but not limited to nausea, vomiting, anti-emetic, emergency department, out-of-hospital, prehospital, emergency medical services, ambulance, ambulance service, metoclopramide, and prochlorperazine.

The results of the electronic database search will involve an initial title and abstract scan for the identification of relevant articles. This initial scan will be done by SA. The chosen articles will then undergo an independent review by IH to ensure rigor in the process. Identified articles will be subjected to the inclusion and exclusion criteria to ensure that only relevant articles and studies have been chosen. PH will review the selection process and articles chosen to ensure that the process is transparent and reproducible.

Study population and sampling

All relevant studies that meet the inclusion criteria listed will be use where either Metoclopramide or Prochlorperazine was used for the treatment of nausea and vomiting in the prehospital or emergency department setting, will be considered for the review.

The inclusion criteria for the studies is the date range January 1990 up to and including December 2016:

1. Patient population of all ages (adult and paediatric)
2. Research conducted in the prehospital setting
3. Research conducted in the emergency department setting
4. Studies where metoclopramide was compared to prochlorperazine in the prehospital environment or emergency care setting

The exclusion criteria will be:

1. Use of the study medication for illness/symptoms outside of nausea and vomiting
2. Use of either metoclopramide or prochlorperazine outside of the emergency care setting
3. Non-English language research

Measurements and Results to be reported on

A database will be created and the following data from included studies that will be collected and analysed:

1. Study methodology; such as RCT, case-study, systematic review, prospective study
2. Author of the study
3. Years of study publication
4. Study aim
5. Study setting
6. Study population
7. Patient clinical data if provided
8. Methods to assess nausea and/or vomiting pre/post intervention
9. Drug administration protocol
10. Time to relief of nausea/vomiting
11. Adverse events reported by patients in the studies

12. Administration of rescue medication for the relief of nausea and vomiting

Data management

All data from the study will be entered into a Microsoft Excel 2013 database. This database will be password secured and protected. The data will saved in a shared folder between SA and IH. A further backup of the data will be saved onto a removable storage hard drive that SA will keep under lock and key. Access to the data on that drive will also be password secured and encrypted.

Ethical considerations

There is minimal ethical considerations because:

1. There are no human or animal patients and /or participation in the study.
2. No patient or participant information or data will be utilised in the study.
3. All data recorded will be entered into a password protected worksheet that is only accessible to SA IH and PH
4. Data will be backed up to a shared folder on Dropbox only accessible to SA IH and PH. Access will be protected by a password
5. A secondary back up will be made onto an external hard drive that is password protected and encrypted that will only be accessible to SA and kept under lock and key

Strengths and limitations

SA acknowledges that this study will be subjected to the following biases[62]:

1. Selection bias
2. Publication
3. Language bias

This reason this study will be subjected to the above three biases is because of the time frame limitation attached to this review. A balance between the need to do further searching for articles and the additional costs incurred will have to be done[62]. As a result of these biases and the time limitation attached to this review, not all studies conducted with metoclopramide or prochlorperazine will be included. SA also acknowledges that the available pool of evidence will biased as a result of publication and language bias

The strengths of this research project is:

1. The project will be low cost
2. This project can be used by the Professional Board of Emergency Care of the HPCSA and provide the ALS with an alternative drug to treat nausea and vomiting in the prehospital setting
3. It will provide us with an understanding on the available research on the treatment of nausea and vomiting in the emergency care setting

Project timeline

2017	Aug	Sep	Oct	Nov	Dec	Jan 2018	Feb 2018					
Sx-DRC	x	x										
Ethics	X	X										
Gathering of studies		X	X									
Transcribing of Data			X	X	X	X						
Data Analysis				X	X	X						
Compilation of Final Report					X	X						
Submission							X					

Resources and budget

Budget				
February – December 2013				
Item	**Description**	**Unit cost**	**Nº of Units**	**Total cost**
Consumables				
1. materials and supplies	Printer paper			R500
2. materials and supplies				
3. specialized services				
4. office supplies, printing & reproduction for data collection				R600
5. office supplies, printing & reproduction for reports				
Research travel				
1. travel to sites				
2. other, specify	INTERNET			700
Minor research equipment				
1.				
2.				
3.				
Personnel				
1. Statistician				
2. Research Assistant(s)				
Sub-Total				

Total				

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Appendices

Data extraction table

Study year	Author	Methodology	Study Aim	Study Setting	Study Population

- Methodology is the type of study is selected; if the study is a randomised control trial, a case-study, a systematic review or a prospective study
- Study Aim is what the end points of the study was
- Study setting is whether the study was conducted in the prehospital environment or in the emergency department
- Study population describe if the study subjects were adults or paediatrics
- Drug administered describes if metoclopramide or prochlorperazine or a placebo was administered
- Dosage is the first dosage administered and the route of administration
- Time to effect describes the length of time needed before the patient experienced relief from nausea and vomiting
- Methods to assess nausea describes how nausea was assessed in the patient. If the researcher used a visual analog scale or patient feedback