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Research Article

A COMPARATIVE STUDY OF DOXYLAMINE SUCCINATE WITH PYRIDOXINE HYDROCHLORIDE AND ONDANSETRON IN TREATING UREMIA-INDUCED NAUSEA AND VOMITING IN CHRONIC RENAL FAILURE PATIENTS

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ABSTRACT

Objective: Advanced-stage chronic kidney disease (CKD) patients often complain of uremic dyspeptic syndrome specifically nausea and vomiting. This is a distressing phenomenon that compromises the patients' quality of life. There is no guideline available for a complete cure for nausea and vomiting in CKD. The objective of this study was to evaluate and compare the effect of doxylamine succinate with pyridoxine hydrochloride and routinely used ondansetron in improving the symptoms of non-dialyzed conservative CKD patients.

Methods: A randomized, open-label, comparative study was done with 70 patients in the doxylamine succinate-pyridoxine group and 65 in the ondansetron group, a total of 135 patients completed the study. The study duration was 7 days. A catboost regression on the response of area under curve matric was carried out to compare the visual analog scale (VAS) score differences. Analysis of covariance and Wilcoxon signed-rank test was used to compare biochemical parameters and quality of life (SF-36) scores of both groups.

Results: It was observed that there was a stark difference in the VAS score (nausea scale) for the non-dialysis patients in doxylamine succinate-pyridoxine hydrochloride in comparison to the ondansetron. Among the different measures of quality of life, physical function, physical role, and social function were found to be significantly improved by doxylamine succinate-pyridoxine hydrochloride as compared to ondansetron.

Conclusion: Doxylamine succinate-pyridoxine hydrochloride is frequently prescribed for pregnancy-induced nausea and vomiting but is also effective in reducing uremia-induced nausea and vomiting symptoms in conservative CKD patients.

Keywords: Doxylamine succinate, pyridoxine hydrochloride, Ondansetron, Uremia, Nausea, Vomiting, Chronic kidney disease.

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INTRODUCTION

Chronic kidney disease (CKD) patients typically develop uremic dyspeptic syndrome, which includes early satiety, anorexia, abdominal distension, nausea, and vomiting [1]. The well-known gastrointestinal consequence of nausea and vomiting is frequently a direct result of uremia in chronic renal failure [2-4]. Except for peptic ulcer, hiatus hernia, gastroparesis, and gastrointestinal cancers, the actual cause of these dyspeptic symptoms is unclear in a significant portion of patients. Although there are numerous receptors for different neurotransmitters and neuropeptides such as muscarinic, serotonin, dopamine, glutamine, and norepinephrine [5,6], it is still unknown which specific neurotransmitter is released in the chemoreceptor trigger zone (CTZ) in the area postrema (AP) of the medulla oblongata, in the floor of the fourth ventricle to induce the effect of nausea and vomiting in presence of uremic toxins [5]. This problem can be brought on by a variety of various etiologies related to the impact of CKD and its treatment on the digestive system, dietary patterns, pharmacotherapy, and acquired impairments. Hypotension and anxiety in CKD patients may also be contributory factors [7].

Vomiting and nausea are not only uncomfortable for the patients, but they are also disturbing, and they are seen as a significant obstacle to their quality of life as well as post-treatment convalescence [7,8]. Dopamine antagonists, antihistamines such as serotonin (5HT3) antagonists, and other medications (anticholinergics, neurokinin 1-antagonists, etc.) are among the groups of antiemetics that are readily available [9]. None of these medications have demonstrated an effective reduction in the nausea and vomiting symptoms associated with CKD [10]. The identical symptoms seen in CKD have not yet been successfully treated by medication.

Although they are unrelated, pyridoxine hydrochloride and doxylamine succinate are thought to work together synergistically to reduce pregnancy-related nausea and vomiting [11]. In cases of pregnancy, it is the first line of defense [12]. Unless there are pre-existing diseases that interfere, this medication, which is classified as a category pregnancy drug, has very few side effects. Doxylamine succinate, an antihistamine blocks the H1 receptor, which indirectly affects the vestibular system and lessens the stimulation of the vomiting center. Although its antiemetic impact is unclear, pyridoxine, a water-soluble Vitamin B6, is a crucial coenzyme that assures the metabolism of amino acids, lipids, and carbohydrates. Deficiency of this vitamin also encourages nausea and vomiting [12].

To the best of our knowledge, there is a dearth of literature on the action of antiemetics to treat nausea and vomiting in CKD patients. Therefore, the current study aimed to conduct a prospective, randomized, open-label study to compare the effectiveness of doxylamine succinate with pyridoxine hydrochloride versus the commonly prescribed antiemetics such as ondansetron, in treating nausea and vomiting symptoms in CKD patients, receiving conservative treatment.

METHODS

Patient population

This research study incorporated eligible patients from the Outpatient Nephrology Department of ILS Hospital, Kolkata, West Bengal, India. The subjects (patients) were suffering from CKD and were on conservative (non-hemodialysis) treatment management. Subjects were further randomized and incorporated into two treatment groups (drug group 1: Doxylamine succinate [10 mg] with pyridoxine hydrochloride [10 mg]; and drug group 2: Ondansetron [4 mg]. Institutional ethics committee approval [no. IORG0010440 dated April 24, 2019] and informed consent from the subjects were taken before the study.

Sample size calculation

The minimum sample size required for the study was calculated (n=64 for each treatment arm) using G* Power 3.1.9 software [13], which enabled us to detect a 2-point difference in visual analog scale (VAS) improvement between doxylamine succinate-pyridoxine hydrochloride and any other treatment arm at 80% power with 95% significance level and $p<0.05$ considered significant. Considering 10% dropout the final sample size in each group considered a minimum of 64; thus, a total of 170 was targeted.

Population randomization

A patient will be considered randomized as soon as the patient is allocated to any of the two study arms, assigned by the random number table system. In group I a total of 70 subjects were enrolled. In group II a total of 65 subjects were enrolled (Fig. 1). The inclusion and exclusion criteria for the study are as follows:

Inclusion criteria

1. Male or female of age >18 or <80 years.
2. Ability to understand and provide informed consent for participation in the study.
3. Chronic renal failure subjects with CKD III to CKD V (not on dialysis) on conservative treatment receiving standard of care based on the discretion of the investigator.
4. The subject should exhibit symptoms of nausea and vomiting with a baseline score ≥2 was included in the study.

Exclusion criteria

1. ESRD patients with hemodialysis or transplantation.
2. Subjects exhibiting gastrointestinal disorders (GERD, gastric or duodenal ulcer, gastritis, pancreatitis, CLD, IBD, IBS, cholecystitis. or cholelithiasis).
3. Subjects with gastrointestinal dysfunction requiring parental nutrition.
4. Subjects with ongoing acute inflammation.
5. Subjects with a history of drug abuse.
6. Other serious diseases (e.g., Cirrhosis, stage IV NYHA cardiac failure, stroke, etc.) within the last 3 months.
7. Subjects exhibiting psychiatric disorder, cerebrovascular accident.
8. Ongoing treatment for chronic infections such as tuberculosis, hepatitis B or hepatitis C, and HIV.

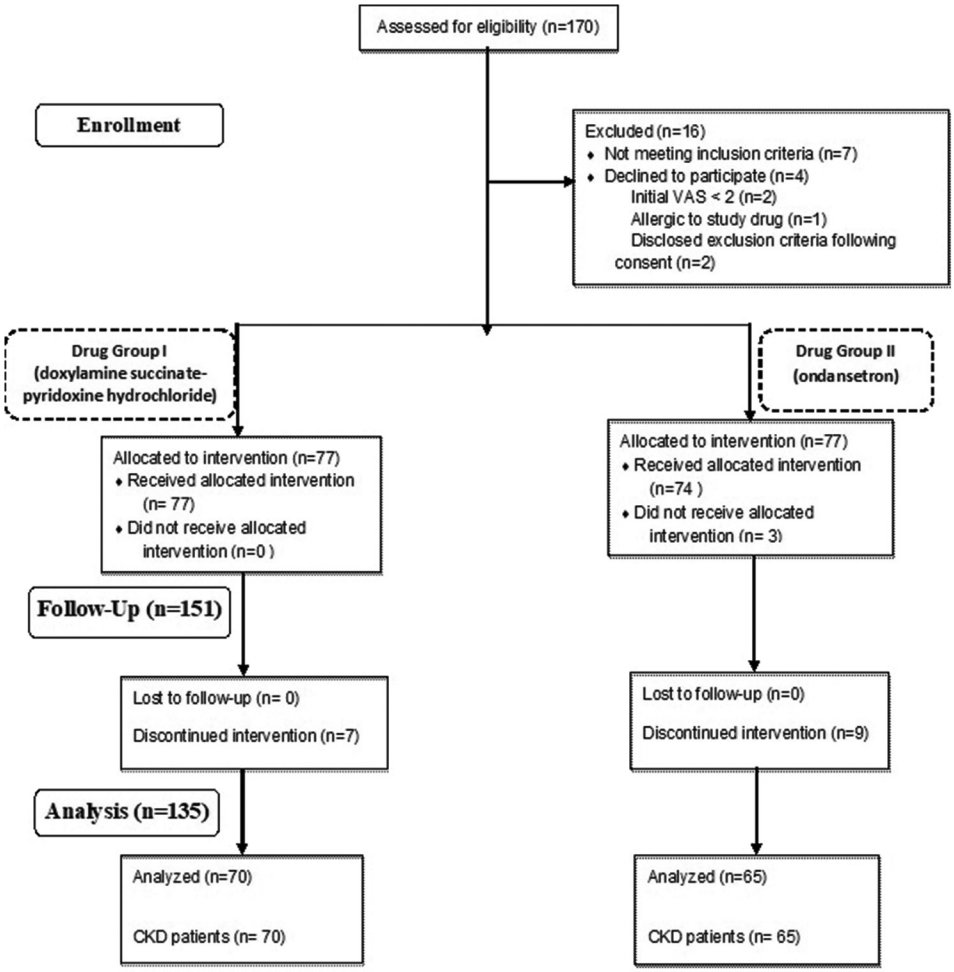

Fig. 1: Flow diagram of patients for the study of antiemetics trial (drug group 1: Doxylamine succinate with pyridoxine hydrochloride; drug group 2: Other antiemetics-ondansetron)

9. Subjects should be non-alcoholic.
10. Subjects diagnosed with malignancy or ongoing treatment for malignancy 6 months before study inclusion.
11. Pregnant women or nursing females
12. Any other systemic disease or any other abnormal laboratory values that as per the investigator will interfere with the patient's participation in the study

Study design

This was a prospective, randomized, open-label study to compare the effect of doxylamine succinate-pyridoxine hydrochloride (study arm 1: Drug group 1) with the routinely used antiemetic ondansetron (study arm 2: drug group 2) for the treatment of nausea and vomiting among subjects with CKD and on conservative management (non-hemodialysis). During the 7 days of treatment and follow-up period, subjects were evaluated every day in the course of the study. Eligible subjects were randomized, by exploiting a random number table system in the two treatment arms in a 1:1 ratio. Each subject was assigned to any one of the two study arms: (i) Doxylamine succinate-pyridoxine hydrochloride and (ii) other antiemetics (ondansetron). The medications had been administered orally. The study did not restrict any subject from continuing their usual standard of life.

The questionnaire used for the study consisted of two parts. The first part inquired about the demographic details of the subject, which included the age, gender, subject type, blood parameter, and etiology of CKD. A detailed concomitant drug history of the subject was also taken. The second part involved rating the nausea and vomiting tendency of the subject on a VAS for nausea and vomiting. The total marking in the analog scale was from 0 to 10 where 0 indicated no nausea and 10 specified extreme nausea and vomiting.

Therapeutic intervention

The medicines were administered twice daily. Concomitant medications were recorded throughout the study beginning with 15 days before the start of the first dose of the study intervention till end-of-study. Many of these drugs being taken are capable of increasing or decreasing nausea and hence were categorized into two new variables, namely "nauseapro" and "nauseadem" that take values 0, 1. "Nauseapro" equals 1 if the patient takes medicines that promote nausea and 0 if he/she does not. A similar protocol was followed for "nauseadem." All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements, non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, and exercise regimens) different from the study intervention were recorded in the case record form.

Treatment compliance

Treatment compliance was verified for every subject at each follow-up visit. Study intervention discontinuation was defined as a minimum of 2 days without intervention intake. Subjects were not considered in the study if the dosage mentioned was not taken in a day.

Measurements

Participants independently rated their nausea on a scale at the baseline. The VAS had the words none on the extreme left (score 0) and severe on the extreme right (score 10). The participants were asked to score that corresponded to the severity of the symptoms of nausea and vomiting. The unknown unintentional effects of the intervention drug and comparative drug were recorded, which might be akathisia, headache, and sedation. Quality of life was assessed using standard SF-36 questionnaires at baseline and day 7 for CKD subjects.

Statistical analysis

The results obtained were presented as mean ± standard deviation. To test the variations in the explanatory variables on day 1 and day 7 were performed for each drug group using R programming language.

To ascertain the confounding between the other variables, the analysis of the covariance model with the test for the significance of the individual interactions was performed separately when considering only the drug groups in the model.

The differences in the drug effects in conservative CKD populations were calculated separately using the AUC or "area under curve" metric that explained the area enclosed by the VAS and X-axis. A catboost regression on the response AUC was carried out initially, ignoring the effect of the responsive variable (i.e., drug group variable) using the package gbm in R programming language [14]. The same catboost regression model was applied again using logistic regression on the drug groups (categorical data), considering the remaining explanatory variables. Finally, ordinary least squares (OLS) regression was performed between the drug groups and all the variables to identify the differences between the drug effects in the studied population. Wilcoxon signed-rank test was conducted to compare the quality of life (SF36) among 1st day and 7th day of treatment for each drug, followed by a proportion test to check whether the differences in SF 36 in 7 days are the same for both groups.

RESULTS

The subjects of both treatment groups had a common complaint of nausea and vomiting. The mean age of the subjects considered was 55.97±10.74 years for drug group 1 and 58.49±9.87 years for drug group 2. Detailed demographic data are presented in Table 1. The leading cause of the renal impairment was due to diabetic nephropathy, followed by hypertensive nephropathy (Fig. 2) as observed from the etiological records of the subjects. There was no significant difference in the baseline value of hemoglobin, urea, creatinine, albumin, alanine transferase, and aspartate aminotransferase in both groups (Table 2). Test of significance in the ANCOVA model showed that the categorical variables did not contribute to the responses significantly in the presence of drug groups (Table 3).

Reduction in the mean VAS score in the 7 days is presented in Fig. 3 for conservative subjects. The mean data in the VAS score exhibit significant ($p<0.01$) differences among the two drug groups from the 4th day onward. The mean difference in the VAS score was found to be significantly high for subjects treated with doxylamine succinate-pyridoxine hydrochloride in comparison to ondansetron (Fig. 3b), indicating that doxylamine succinate-pyridoxine hydrochloride was more effective in subjects on conservative treatment.

A similar trend was noticed when AUC responses after catboost analysis for VAS score were analyzed, comparing both the drugs in the non-dialysis population. Calcium, potassium, sodium, systolic pressure, aspartate aminotransferase (serum glutamic-oxaloacetic transaminase [SGOT]), alanine aminotransferase (serum glutamic pyruvic transaminase [SGPT]), creatinine, and phosphate were the explaining variables during catboosting in non-HD patients. Further OLS analysis revealed significant differences among the two drug groups and doxylamine succinate-pyridoxine hydrochloride was

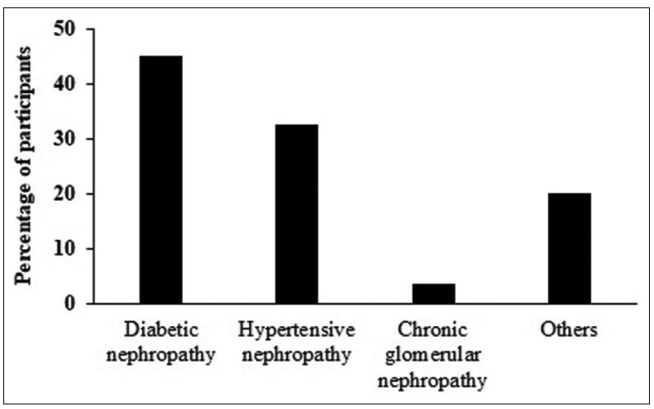

Fig. 2: Etiology of the patients

Table 1: Descriptive demographic details of the participants

Characteristics	Drug groups		
	Drugs group-1 (doxylamine succinate-pyridoxine hydrochloride), n (%)	Drug group-2 other antiemetics (ondansetron), n (%)	p
Total	70 (51.85)	65 (48.14)	
Age (mean±SD)	55.97±10.74	58.49±9.87	0.158
Age distribution			
<50	19 (14.07)	10 (7.41)	
50–59	23 (17.03)	28 (20.74)	
60–69	23 (17.03)	24 (17.78)	
>70	5 (3.70)	8 (5.93)	
Sex			
Male	44 (29.76)	37 (29.30)	
Female	26 (22.79)	28 (17.67)	
Weight (kg), mean±SD	61.91±11.35	62.57±12.53	0.697
Systolic blood pressure, mean±SD	138.45±18.99	140.15±17.45	0.575
Diastolic blood pressure, mean±SD	78.60±9.84	79.76±9.45	0.973
Hypertension	67 (49.63)	59 (43.70)	
Diabetic	56 (41.48)	47 (34.81)	
Food habit			
Veg	17 (12.59)	12 (8.88)	
Nonveg	53 (39.25)	53 (39.25)	
Etiology of CKD			
Diabetic nephropathy	33 (24.44)	28 (20.74)	
Hypertensive nephropathy	22 (16.29)	20 (14.81)	
cGN	2 (1.48)	3 (2.22)	
Others	13 (9.63)	14 (10.37)	

SD: Standard deviation, CKD: Chronic kidney disease

Table 2: Baseline blood biochemistry details of the subjects

Biochemical variables	Drug group I	Drug group II	p-value
Serum Hb (g dL^{-1})	9.35±1.96	9.60±2.09	0.930
Serum urea (mg dL^{-1})	102.20±59.43	85.82±53.85	0.116
Creatinine (mg dL^{-1})	5.51±3.36	5.28±3.25	0.784
Serum albumin (g dL^{-1})	3.55±0.49	3.56±0.79	0.930
SGOT (U L^{-1})	16.45±10.80	16.19±7.82	0.880
SGPT (U L^{-1})	17.59±6.35	17.85±6.93	0.812

SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase

Table 3: Analysis of covariance of categorical variables in the presence of drug groups

Variables considered	r^2	p (KS)	p (eliminated the effect of drugs)
Drug group	0.019	$<2\times10-^{16}$	0.032
Drug group and T2DM	0.025	$<2\times10-^{16}$	0.253
Drug group and HTN	0.021	$<2\times10-^{16}$	0.759
Drug group and nauseapro	0.021	$<2\times10-^{16}$	0.611
Drug group and nauseadem	0.020	$<2\times10-^{16}$	0.766

T2DM: Type II diabetes mellitus, HTN: Hypertension, Nauseapro: Concomitant medicines that promote nausea, Nauseadem: Concomitant medicines that don't promote nausea

found to give better relief in comparison to ondansetron in non-HD patients (F=2.525; Intercept for doxylamine succinate-pyridoxine hydrochloride= −32.4637, p=5.44649e^{-27}).

To determine whether the medications given to the individuals for the aim of the study had any effect on their quality of life, the subjects' quality of life assessment scores (SF-36) were taken. Based on the eight domains of SF-36, it was observed that drug group 1, that is, doxylamine succinate-pyridoxine hydrochloride had significant improvement in physical function (p<0.01), physical role (p<0.001), and social function (p<0.05) (Table 4). There were no serious adverse events observed among the study participants. Table 5

Table 4: Quality of life defined by the SF-36 scores for each drug group (mean±SD)

SF-36 domain	Drug group	n	Mean±SD	p-value
Physical function	Drug group-1	70	6.46±5.45	<0.01
	Drug group-2	65	4.25±3.86	
Role physical	Drug group-1	70	2.73±1.75	<0.001
	Drug group-2	65	1.90±1.66	
Bodily pain	Drug group-1	70	1.63±1.54	0.702
	Drug group-2	65	1.55±1.48	
General health	Drug group-1	70	1.88±0.961	0.704
	Drug group-2	65	1.82±1.38	
Vitality	Drug group-1	70	2.36±1.97	0.180
	Drug group-2	65	2.73±1.87	
Social function	Drug group-1	70	1.88±1.01	<0.05
	Drug group-2	65	1.52±1.20	
Role emotional	Drug group-1	70	2.43±1.80	0.342
	Drug group-2	65	2.24±1.13	
Mental health	Drug group-1	70	3.60±2.44	0.657
	Drug group-2	65	3.47±1.79	

n: Number of samples, p: Level of significance. SD: Standard deviation

Table 5: Concomitant medications

Drug category	Drug group-I (n=70), n (%)	Drug group-III (n=65), n (%)
PPI drugs (nauseapro)	48 (35.55)	40 (29.62)
Prokinetics (nauseadem)	2 (1.48)	2 (1.09)
Oral iron supplements (nauseapro)	17 (12.59)	10 (7.40)
Oral multivitamins (nauseadem)	16 (11.85)	7 (5.19)
Acetylcystein (nauseapro)	33 (24.44)	26 (19.26)
Calcium acetate (nauseapro)	27 (20)	16 (11.85)
Oral sodium bicarbonate (nauseadem)	25 (18.52)	14 (10.37)
Antidepressants drugs (nauseapro)	2 (1.48)	1 (0.74)
Antibiotics (nauseapro)	35 (25.93)	29 (21.48)
Opioids (nauseapro)	9 (6.66)	6 (4.44)

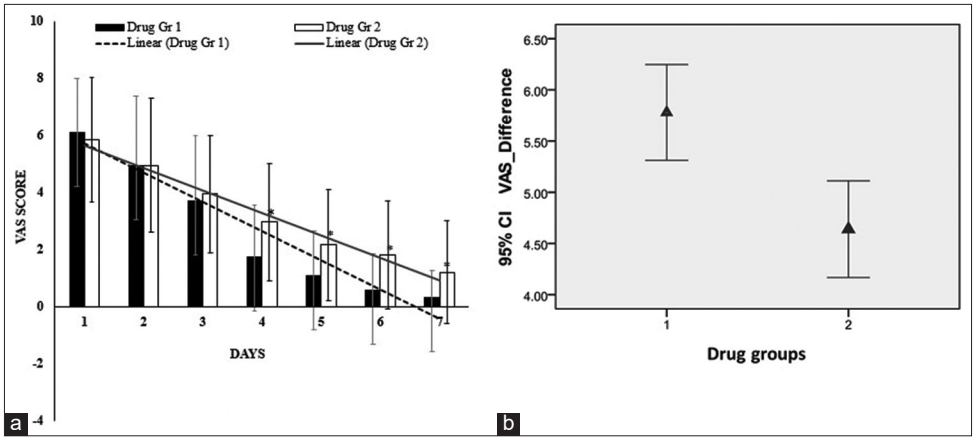

Fig. 3: (a and b) VAS score and mean difference of VAS score observed in the two arms of the study for non-dialysis patients.*Indicates the significant difference (p<0.05) among the two drug groups (drug Gr 1 and drug Gr 2). VAS: Visual analog scale

shows different concomitant medications with % of patients(n) who have taken these medications along with Doxylamine succinate with pyridoxine hydrochloride and Ondansetron.

DISCUSSION

In the present study, patients who received doxylamine succinate with pyridoxine hydrochloride and who were essentially not on dialysis showed a significant improvement in nausea and vomiting scores across all severity levels (mild, moderate, and severe), while the patients who received the other antiemetic drug group, ondansetron, showed a slow or non-existent improvement. The brain's medulla oblongata contains the vomiting trigger zone. The AP (Area Postrema) , also known as CTZ (Chemoreceptor Trigger Zone) has numerous receptors that can detect vomiting-inducing stimuli and transmit that information to the vomiting center, which then triggers the vomiting reflex [15]. Opioid μ, κ, dopamine-type 2 (D2), neurokinin-1 (NK-1), and serotonin-type 3 (5-HT3) receptors have been identified as CTZ receptors that cause emesis [16]. Enkephalin histamine 1 and 2 receptors have also been shown to affect the emetic reflex in AP [17]. The chosen medications ondansetron and doxylamine succinate-pyridoxine hydrochloride act on the serotonin and histamine receptors, respectively.

Numerous alterations in the gastrointestinal system and brain contribute to nausea in CKD patients. Higher urea inside the brain itself can induce metabolic changes in the brain [18]. Accumulation of urea stimulates the stimulus region of the CTZ, which then routes it to the vomiting center in the brain stem in the medulla [19,20]. In CKD patients, increased urea level in the digestive system has been linked to nausea by causing intestinal mucosal inflammation [21]. If not treated immediately, nausea can escalate to vomiting, which can irritate the stomach. Patients may have a lower quality of life if their chronic nausea and vomiting last for an extended period.

Ondansetron, the 5-HT3 receptor antagonist also blocks the serotonin in the vagal nerve terminals of the gastrointestinal tract as well as in the AP of the brain [22]. The active constituents of doxylamine succinate-pyridoxine hydrochloride are both doxylamine and pyridoxine, which together have a synergistic effect on the symptoms of nausea and vomiting [12]. Doxylamine is an antihistamine that inhibits the activity of histamine at the H1 receptors directly, lowering the stimulation of the vomiting center. It also indirectly affects the vestibular system. Because the medication has anticholinergic qualities that support its antihistamine antiemetic effect, it is anticipated that it will also demonstrate muscarinic receptor inhibition [12].

The main rationale behind giving the category of pregnancy drugs as first-line therapy to patients with renal impairment was that, even though the pathogenesis of nausea and vomiting during pregnancy is multifactorial, gastrointestinal factors and CNS chemoreceptors are primarily involved, which is comparable to the mechanism of uremia-induced nausea in patients with CKD [23]. Ondansetron may cause seizures [24] and other adverse events, including diarrhea, headache, fever, akathisia, acute dystonic reactions, etc. [25]. Based on our understanding nausea and vomiting due to uremia in CKD are stimulated by the stimulus received from the brain, vestibular system, and GI tract. The stimulus is triggered to the CTZ through histamine receptors. Doxylamine succinate-pyridoxine hydrochloride prevents stimulation of the CTZ and vomiting center by blocking histamine receptors and indirectly suppressing the vestibular pathway.

The combination of pyridoxine and doxylamine was widely prescribed to women with nausea and vomiting in pregnancy since 1958 and was associated with a 70% reduction in nausea and vomiting [15]. In contrast to our result, Capp *et al*. [26] reported the efficacy of ondansetron over the combination of pyridoxine and doxylamine in the management of nausea during the first trimester of pregnancy; however, the effect of the same on vomiting was found to be insignificant. Similar observations were stated by Oliveira *et al*., 2014 [11] in a double-blind, randomized, controlled trial and reported a significant reduction in nausea and vomiting on the VAS. However, an increased risk for cleft palates and congenital heart defects was reported among women treated with ondansetron for nausea and vomiting in the first trimester.

Yahia *et al*. 2020 [27] found that: Women on ondansetron reported better alleviation of nausea compared to those receiving pyridoxine and doxylamine [96.2% vs. 52.6%, p<0.001, respectively]. The most frequently reported side effects were headache, dry mouth, gastrointestinal [GI] disturbances, and abdominal pain were noted.

Another study done by Ljutić *et al*., in 2002, [28] found that ondansetron was more effective in controlling nausea and vomiting than metoclopramide, either objectively (2.80±0.422 vs. 1.40±0.699, p<0.005) or subjectively (4.10±0.738 vs. 2.10±0.994, p<0.005). They concluded that at the dosage level studied ondansetron is about twice as effective as metoclopramide in the symptomatic relief of uremia-induced nausea and vomiting.

A comparative study of ondansetron, prochlorperazine, and metoclopramide in acute kidney injury patients done by Gray *et al*., in 2022, [29] stated that ondansetron was associated with a 5.48% decrease (CI −6.17−−4.79) in death within 90 days of ICU-admission, which was independent of acute kidney injury (AKI) status; an effect not seen with other antiemetics. Antiemetic usage was not associated with a change in the time to the first AKI. Antiemetic usage did not alter AKI risk. Ondansetron was associated with a significant decrease in 90-day mortality that was not seen by other antiemetics.

In our study, we found that the patients' quality of life was significantly enhanced by doxylamine succinate-pyridoxine hydrochloride as compared to ondansetron (Table 4).

CONCLUSION

There were no previous studies available to show the effect of doxylamine succinate with pyridoxine hydrochloride on uremia-induced nausea vomiting. Although, based on the results we found that doxylamine succinate-pyridoxine hydrochloride can be the better option to decrease the incidence of nausea in conservative (non-hemodialysis) CKD with minimal side effects. Our study had several limitations, including a very small sample size and the use of the VAS scale to grade patients with CKD because there was no established and registered nausea and vomiting scale. To establish doxylamine succinate-pyridoxine hydrochloride as the safest and most affordable antiemetic option that can be used, the study should be conducted with a larger sample size and for a longer duration.

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AUTHOR CONTRIBUTIONS

Each author contributed important intellectual content during manuscript drafting and accepts accountability for the overall work by ensuring that questions of the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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