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The Effects of Calcium Carbonate/Magnesium Carbonate Combination Chewable Tablets in Comparison to Calcium Carbonate Tablets on Visual Analogue Scale Pruritus Scoring System in Hemodialysis Patients

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Abstract—
Objectives: *Pruritus is an intractable and a common symptom in chronic hemodialysis patients that can be minimized by using phosphate binders. Both calcium carbonate/magnesium carbonate (CaCO3/MgCO3) combination chewable tablets and calcium carbonate (CaCO3) tablets can be used as phosphate binders.* ***The aim of this study is*** *to evaluate the differences between the two phosphate binders on hemodialysis patients in terms of Visual analogue scale (VAS) scoring for pruritus Assessment (0-10) value.*
Methods: *The randomized, controlled, open study will be conducted at renal /hemodialysis unit of King Hussein Medical Center for six weeks. Patients who will met the inclusion and will not met the exclusion criteria will enroll and randomly allocate into either interventional groups (Group I or II) or control groups (Group III or IV).Group I & III will include hemodialysis patients who are taking proton pump inhibitors, while Group II & IV will include hemodialysis patients who are taking H_2_Blockers. The collected data at the end of 6 weeks will be analyzed using Kruskal-Wallis Test followed by Mann-Whitney U-Test with Bonferroni correction (with p-value <0.05 as a level of significance) to determine whether there were significant differences between the four studied groups.*
Results: *Calcium Carbonate/Magnesium Carbonate ($CaCO_3$/$MgCO_3$) combination chewable tablets had at least the same activity as $CaCO_3$ tablets in reducing the VAS scoring for pruritus assessment value.*

Key words— *Hemodialysis, Phosphate binders, Pruritus, Acid suppressive.*

I. INTRODUCTION

Healthy kidneys are very necessary for cells functioning by maintaining the extracellular environment. This is achieved by specifically adjusting the urinary excretion of water and electrolytes to match net intake and excretion of waste products of metabolism, such as creatinine, urea, and uric acid. In addition, the kidneys produce hormones that participate in red blood cell production, the regulation of blood pressure and bone- and mineral metabolism (Rock, *et al*., 1987).

The most common type is hemodialysis (HD), in which waste products are removed from the body by diffusion mechanism across a non-biological semipermeable membrane in an artificial kidney. HD is usually performed at a dialysis center from two to three times per week for three to four hours (National Kidney Foundation: K/DOQI, 2003).

The kidneys regulate the calcium and phosphorus homeostasis together with the gastro-intestinal tract and bone tissue. Calcium and phosphorus are minerals that are of great importance for regulation of several processes in the body and they are a primary composition of bones. When kidney function deteriorates, regulation of calcium and phosphorus concentrations will be significantly affected (Drueke and Foley, 2006).

Chronicrenal failure is associated with an increased incidence, severity, and frequency of acid-related gastrointestinal disorders. Those disorders may be of significant concern, because the symptoms with which they are associated can result in altered dietary intake and decrease quality of life. Higher acid production can occur secondary to hypergastrinemias a consequence of decreased clearance of gastrin in CKD patients (Gold, *et al*., 1980) and may also be due in part to increased density of G cells that secrete gastrin secondary to a hyperparathyroid state (Crivelli, *et al*., 1979 and Carlei, *et al*., 1984).

Uremic pruritus is an intractable and a common symptom in chronic hemodialysis patients (Pisoni, *et al.,* 2006 andMathur, *et al.,* 2010). It negatively affects the quality of life by causing serious discomfort and skin damage, and may be associated with sleep disturbance and higher mortality (Hiroshige, *et al*., 1995 and Duque, *et al*., 2006). The pathophysiology of uremic pruritus is complex and remained poorly characterized. Previous studies have shown that divalent ions, calcium-phosphate product, C-reactive protein, immune derangement, opioid system alternation, and hyperparathyroidism may be associated with uremic pruritus (Morton, *et al*., 1996).

Aim of the study:

The aim of this study is to evaluate the differences between HD participants who are taking PPIs+$CaCO_3$/$MgCO_3$combination chewable tablets (Rennie®) with or without $CaCO_3$ tablets (Group I), HD participants who are taking H_2-Blockers+

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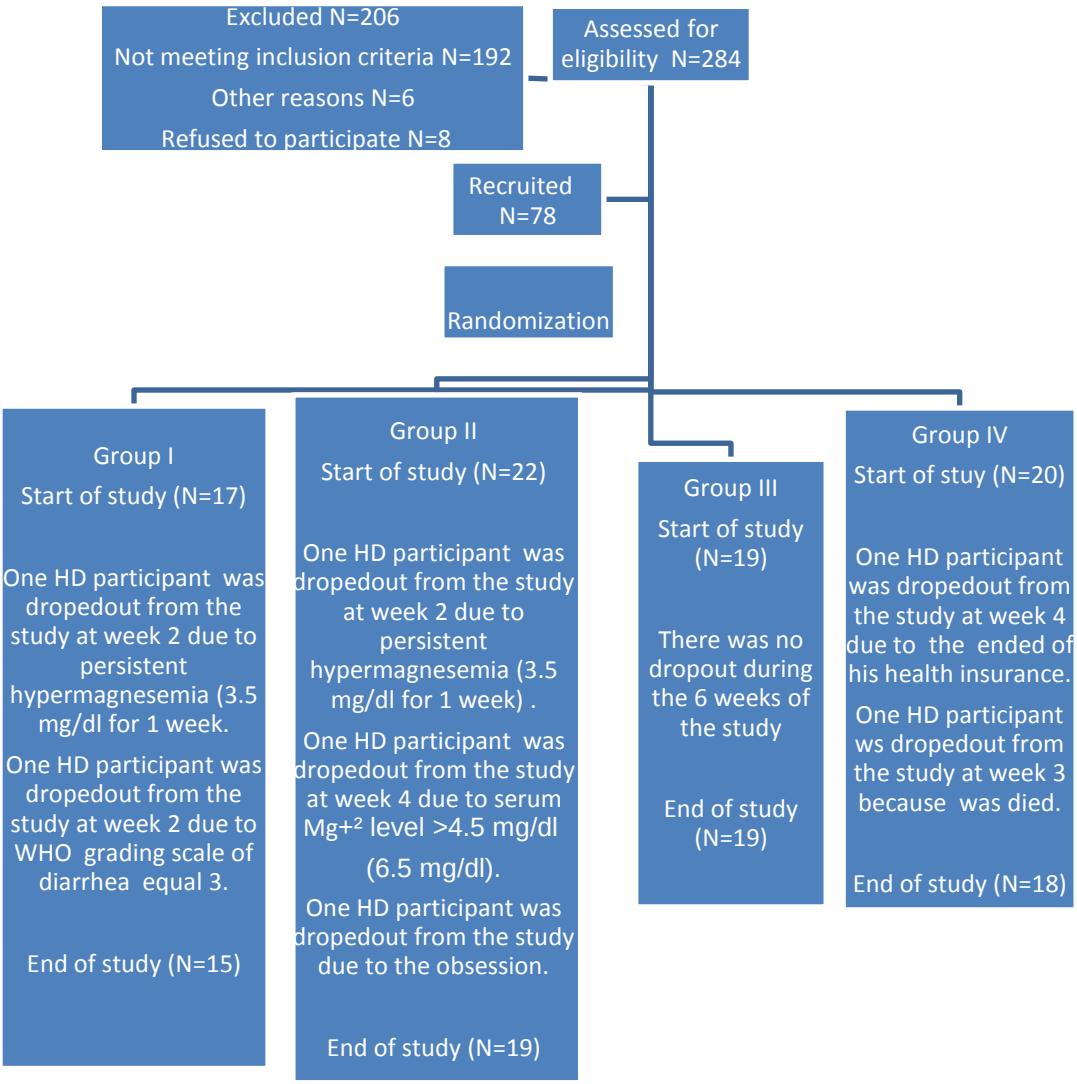
$CaCO_3/MgCO_3$ combination chewable tablets (Rennie®) with or without $CaCO_3$ tablets (Group II), HD participants who are taking PPIs + only $CaCO_3$ tablets (Group III) and HD participants who are taking H_2-Blockers+ only $CaCO_3$ tablet (Group IV) in term of VAS scoring for pruritus Assessment (0-10) value

We assessed the severity of itching by using VAS scoring for pruritus assessment (0-10) in which no pruritus takes score 0, mild pruritus takes score from 1 to 3, moderate pruritus takes score from 4 to 6, severe pruritus takes score from 7 to 8 and very severe pruritus takes score from 9 to 10.



Recruitment, randomization, and dropout processes scheme.

Demographics:

All demographic characteristics of 71 HD participants in the four studied groups are summarized in Tables (3-4).

Demographic characteristics of the four studied groups.

Characteristics			Group I N=15 Mean±SEM	Group II N=19 Mean±SEM	Group III N=19 Mean±SEM	Group IV N=18 Mean±SEM	Total N=71 Mean±SEM	*P*-Value	significance
Age (years)		KHMC	41.86±2.41	39.47±2.47	38.68±2.32	43.21±2.01	40.81±2.31	0.349	NS
		JUH	39.86±2.86	35.47±2.44	30.68±2.97	33.33±1.98	34.84±2.55		
sex	Male (%)	KHMC	5 males (62.5%)	4 males (57.1%)	8 males (66.6%)	4 males (40.0%)	21 males (56.7%)	0.438	NS
		JUH	3 males (37.5%)	3 males (42.8%)	4 males (33.3%)	6 males (60.0%)	16 males (43.2%)		
	Female (%)	KHMC	4 females (57.1 %)	9 females (75 %)	5 females (71.4 %)	8 females (100 %)	26 females (76.5 %)		
		JUH	3 females (42.8 %)	3 females (25 %)	2 females (28.6 %)	0 females (0 %)	8 females (23.5 %)		
BMI (kg/m²)		KHMC	25.2±0.057	22.21±0.043	25.26±0.040	26.51±0.039	24.79±0.043	0.897	NS
		JUH	23.2±0.097	24.21±0.047	21.20±0.041	20.50±0.034	22.27±0.053		

Data are presented as Mean difference ±SEM or as percentage by using One-Way ANOVA test (at *p*-value< 0.05)

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S*: Significant -NS: Non significant-BMI: Body mass index -KHMC: King Hussein Medical Center -JUH: Jordan University Hospital

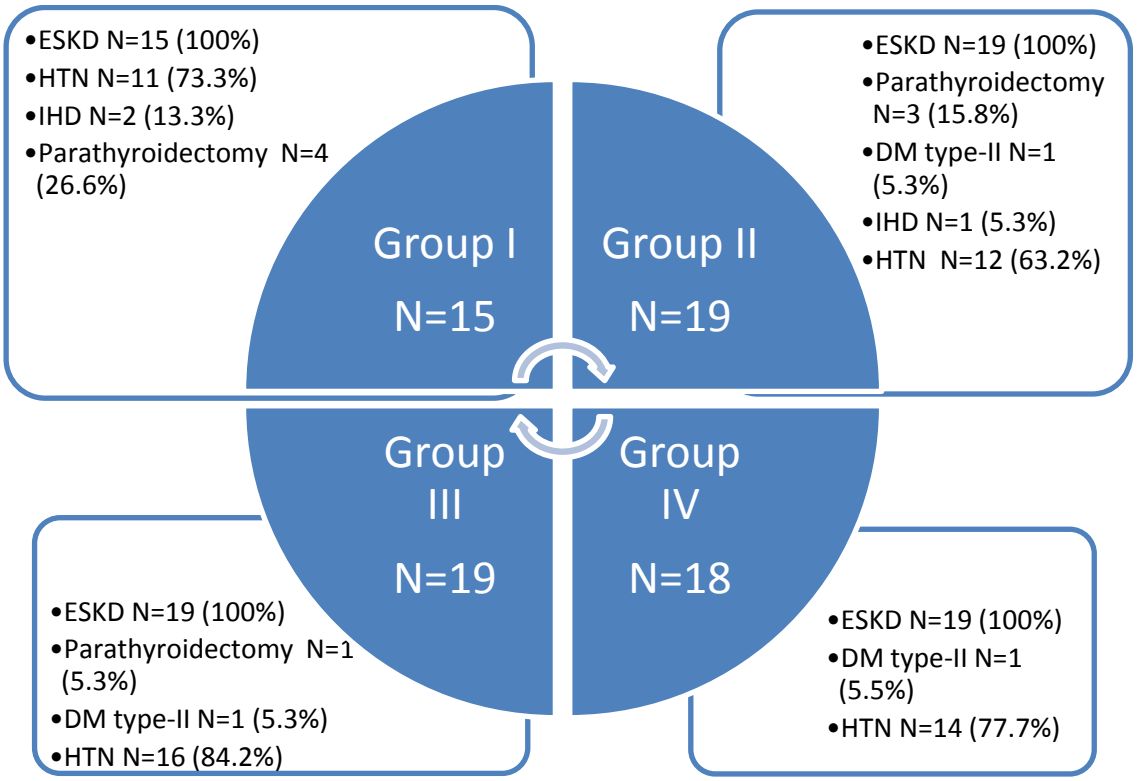
Other demographic characteristics of the four studied groups.

Characteristics		Group I N=15 Mean± SEM	Group II N=19 Mean± SEM	Group III N=19 Mean± SEM	Group IV N=18 Mean± SEM	Total N=71 Mean± SEM	*P*-Value	Significance
Duration of dialysis (months)		127.33± 22.787	97.68± 15.338	64.63± 6.642	93.44± 11.628	94.03± 7.496	0.036	S*
Duration of using $CaCO_3$ tab as phosphate binder (months)		127.33± 22.787	97.68± 15.338	64.63± 6.642	93.44± 11.628	94.03± 7.496	0.036	S*
Duration of using either PPIs or H2-Blockers (months)		99.33± 24.484	75.47± 11.136	64.63± 6.642	90.33± 11.998	81.38± 6.945	0.315	NS
HD duration per session (hours)		4.27± 0.137	4.18± 0.109	3.97± 0.060	4.08± 0.061	4.12± 0.047	0.158	NS
HD frequency per week (%)	**1*per week**	0 patient (0)	1 patient (5.3%)	0patient (0%)	0 patient (0%)	1 patient (1.4%)	0.313	NS
	2*per week	7patients (46.7%)	5 patients (26.3%)	2patients (10.5%)	5 patients (27.8%)	19 patients (26.8%)		
	3*per week	7patients (46.7%)	13patients (68.4%)	17patiens (89.5%)	13patients (72.2%)	50 patients (70.4%)		
	4* per week	1 patient (6.7%)	0 patient (0%)	0 patient (0%)	0 patient (0%)	1 patient (1.4%)		

Data are presented as Mean difference ±SEM or as percentage by using One-Way ANOVA test (at *p*-value< 0.05)
- S*: Significant -NS: Non significant

Patients medical history:

The HD patient's medical history in each group of the four studied groups are summarized in Figure (2).



Patient's medical history of the HD participant patients presented as (percentage).

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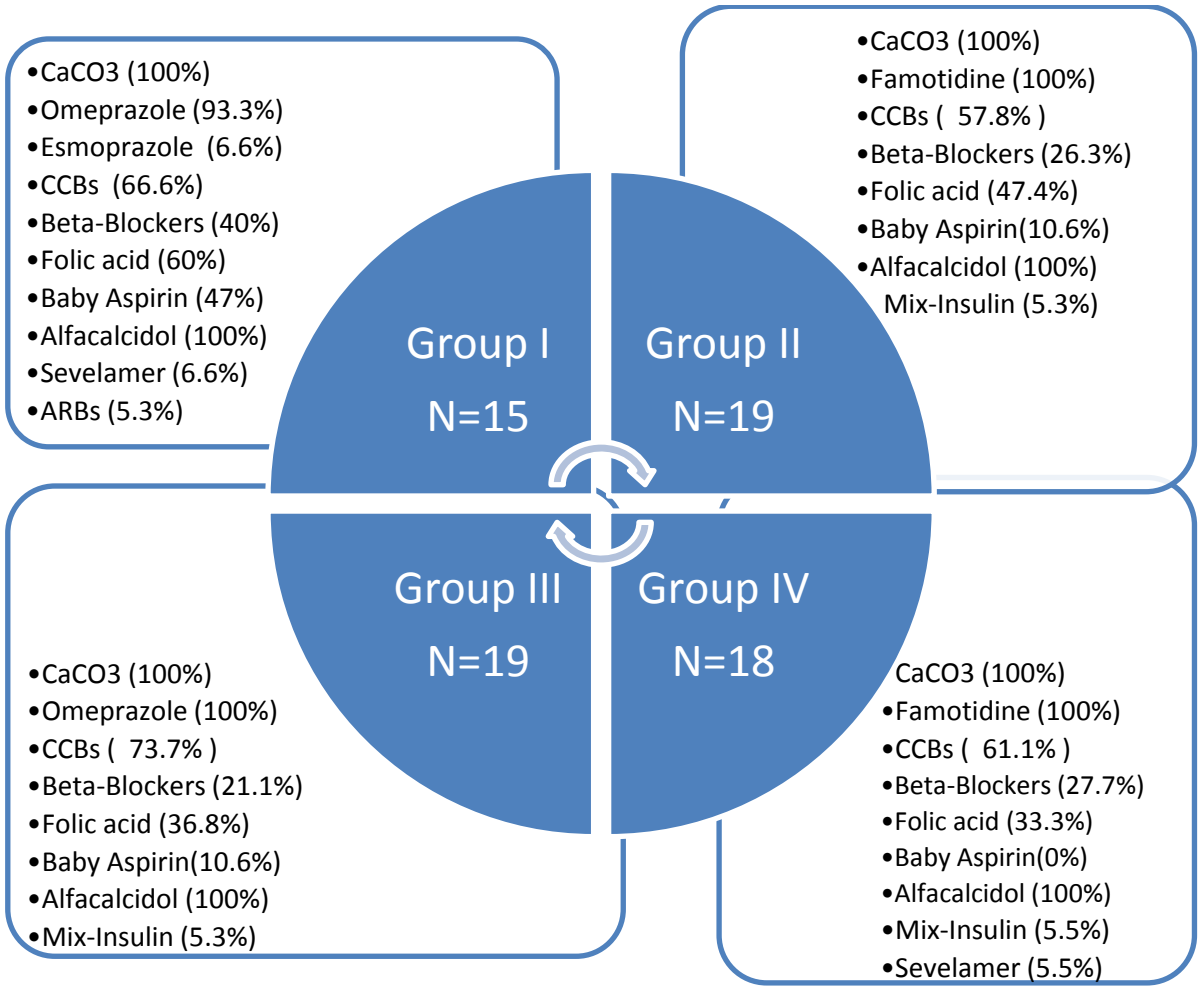

Current patient's medications history of the HD participant patients presented as (percentage).

Between and within groups comparisons of VAS scoring for pruritus Assessment (0 -10)values.

Results of VAS scoring for pruritus Assessment (0 -10)values analysis between and within four studied groups are summarized in Table (3).

Between and within groups comparisons results ofVAS scoring for pruritus Assessment (0 -10) values.

Interval	Group I N=15 Mean±SD	Group II N=19 Mean±SD	Group III N=19 Mean±SD	Group IV N=18 Mean±SD
Before	4.40±3.460	2.68±2.083	2.79±2.070	2.78±1.927
After	3.07±2.631	2.16±1.500	2.42±1.774	2.33±1.680
Median before (Range)	4 (9)	2 (9)	2 (8)	2 (8)
Median after (Range)	2 (8)	2 (6)	2 (7)	2 (7)
Median Differences (Range)	-1 (5)	0 (4)	0 (1)	0 (1)
Z	-2.553	-1.563	-2.646	-2.828
***p*-value**	0.011	0.118	0.08	0.05
significance	S*	NS	NS	NS
Between groups comparisons *p*-value (significance)	0.213 (NS)			

Data are presented as Median (Range) and are analyzed by using Wilcoxon Signed Ranks Test. Also, the between groups data are analyzed by using Kruscal-WallisTest.

- S*: Significant -N: Number of HD participants -NS: Non significant
–VAS: visual Analogue Scale

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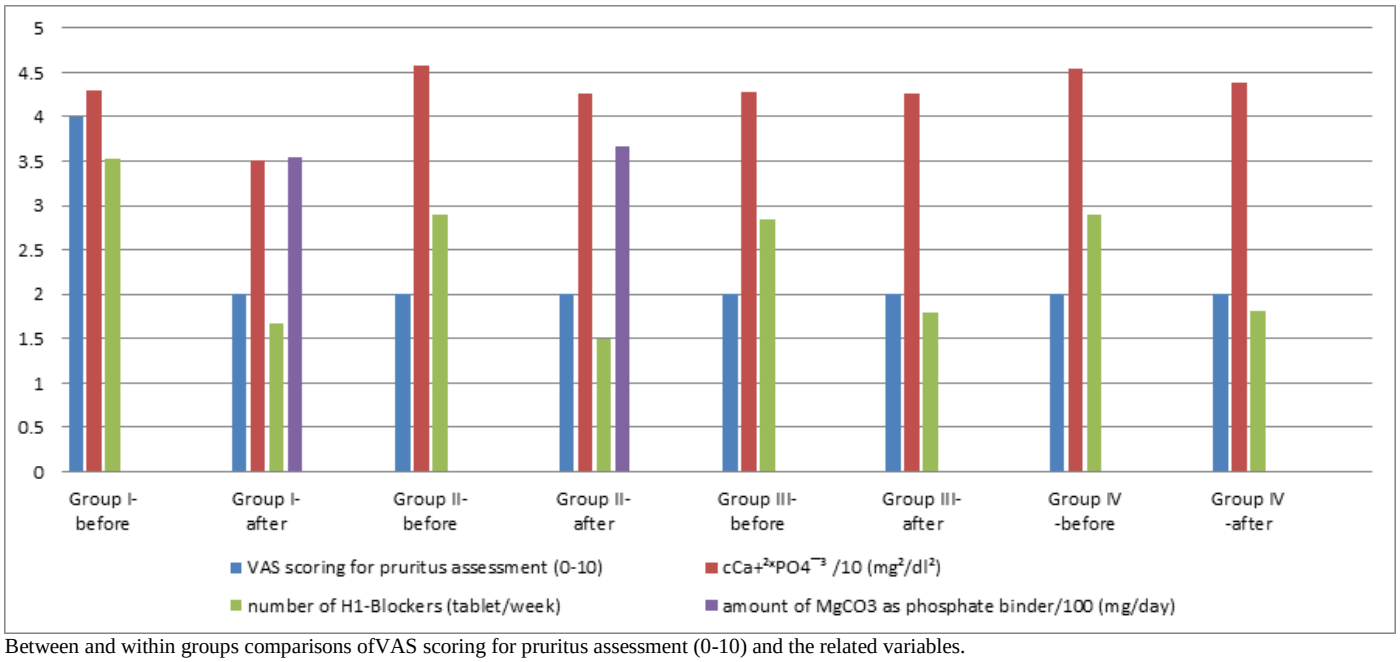

Between and within groups comparisons ofVAS scoring for pruritus assessment (0-10) and the related variables.

The VAS scoring for pruritus assessment (0-10) and the related variables values differences within the comparative groups.

Comparative Groups / Affective Variables	Group 1 after Versus Group I before	Group II after Versus Group II before	Group III after Versus Group III before	Group IV after Versus Group IV before
VAS scoring for pruritus assessment (0-10) Median difference (Range) (Sig)	-1 (5) (S*)	0 (4) (NS)	0 (1) (NS)	0 (1) (NS)
$cCa^{+2}\times PO4^{-3}$ mg^2/dl^2 Mean difference ±SD (Sig)	-7.93±4.86 (S*)	-3.19±8.09 (NS)	-0.22±3.95 (NS)	-1.52±3.33 (NS)
$MgCO_3$ (mg/day) Mean difference ±SD(Sig)	+354.45 ±89.55 (S*)	+367.368 ±82.879 (S*)	0	0
Number of H_1-Blockers (tablet/week) Mean difference ±SD (Sig)	-1.86± 1.53 (S*)	-1.41± 1.65 (S*)	-1.04± 1.13 (S*)	-1.06± 1.07 (S*)

Data are presented as Mean difference ±SD or as median difference (Range) and are analyzed by using Paired T-Test or Wilcoxon Signed Ranks Test (at p-value<0.05).
- S*: Significant -NS: Non significant - $MgCO_3$ (mg/day): Amount of $MgCO_3$ in mg per day from $CaCO_3/MgCO_3$ combination chewable tablets.

The VAS scoring for pruritus assessment (0-10) and the related variables values differences between the comparative groups.

Comparative Groups / Affective Variables	Group 1 Versus Group II	Group I Versus Group III	Group I Versus Group IV	Group II Versus Group III	Group II Versus Group IV	Group III Versus Group IV
VAS scoring for pruritus assessment (0-10) Median difference (Range) (Sig)	(NS)	(NS)	(NS)	(NS)	(NS)	(NS)
$cCa^{+2}\times PO4^{-3}$ mg^2/dl^2 Mean difference ±SEM(Sig)	-4.746 ± 1.878 (NS)	-7.718 ± 1.878 (S*)	-6.409 ± 1.902 (S*)	-2.972 ± 1.765 (NS)	-1.663 ± 1.789 (NS)	+1.309± 1.789 (NS)
$MgCO_3$ (mg/day) Mean difference ±SEM(Sig)	-12.92 ± 20.49 (NS)	+354.45 ± 20.49 (S*)	+354.45 ± 20.75 (S*)	+367.37 ± 19.25 (S*)	+367.37± 19.52 (S*)	0.00 ± 19.52 (NS)
Number of H_1-Blockers (tablet/week) Mean difference ±SEM(Sig)	(NS)	(NS)	(NS)	(NS)	(NS)	(NS)

Data are presented as Mean difference ±SEM or as median difference (Range) and are analyzed by using Tukey Kramer post-hoc multiple comparison analysis (at p-value< 0.05) or post-hoc multiple comparison analysis using Mann-Whitney U-test and bonferroni correction (at p-value <0.01).

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- S*: Significant -NS: Non significant
- $MgCO_3$ (mg/day): Amount of $MgCO_3$ in mg per day from $CaCO_3/MgCO_3$ combination chewable tablets.

II. Discussion

In case of both VAS scoring for pruritus assessment (0-10), the study revealed insignificant reduction in the interventional groups in comparison to the control groups. The only significant reduction was in Group I (after versus before interval) which can be explained by the greatest reduction in $cCa^{+2}xPO4^{-3}$ product in Group I after the $CaCO_3$ tablets were replaced either totally or partially by $CaCO_3/MgCO_3$combination chewable tablets in comparing with the other groups

Limitations of the Study

The following limitations were present in this study:
-There was no washout period in this study.
-The sample size was small and should be increased.
-The $CaCO_3$ tablets were not replaced totally in all cases by the $CaCO_3/MgCO_3$combination chewable tablets to assess the differences between the two study drugs more accurately.
-The number of either PPIs or H_2-Blockers weren't constant during the study to assess their effects on either $CaCO_3$ tablets or$CaCO_3/MgCO_3$ combination chewable tablets more accurately.
-The number of$CaCO_3/MgCO_3$combination chewable tablets and $CaCO_3$ tabletsweren't constant during the studyto assess the differences between the two study drugs more accurately.
-The interventional study on the HD participants wasn't started at the same time due to the different HD days, HD shift and HD center between our study HD participants.

III. Conclusions

Calcium Carbonate/Magnesium Carbonate ($CaCO_3/MgCO_3$) combination chewable tablets had at least the same activity as $CaCO_3$ tablets in reducing the VAS scoring for pruritus assessment value

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