Comparison of the Effects of Ca-Mg Carbonate Chewable Tablets with Calcium Carbonate Tablets on Phosphate Binding in Patients on Hemodialysis Taking H2-R Blockers

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ABSTRACT

Objectives: Calcium carbonate/magnesium carbonate (CaCO3/MgCO3) combination chewable tablets may be an attractive alternative phosphate binder to calcium carbonate (CaCO3) tablets with potential advantages of synergistic phosphate binding effect. The aim of this study is to evaluate the differences between the two phosphate binders on 42 hemodialysis patients who are taking H2-Blockers in terms of serum $PO4^{-3}$ and Mg^{+2}levels.

Methods: Randomized, controlled, open label study was conducted at the renal /hemodialysis unit of King Hussein Medical Center for six weeks (On May 2018). After the study was approved, patients who met the inclusion criteria were enrolled and were randomly allocated into an interventional group (Group I) and a control group (Group II). Follow-up continued for 6 weeks. The collected data were statistically analyzed using the independent t-test.

Results: A total of 37 hemodialysis patients were finally included in this study. The mean age was 40.81±2.31 years, 17 subjects (45.95%) were males, and 20 subjects (54.05%) were females. Despite serum $PO4^{-3}$ level decreased significantly in group I by -0.39±0.99 mg/dl after replacing CaCO3 tablets by CaCO3/MgCO3 in equivalent dose, the differences between two groups were statistically insignificant (-0.094±0.213). But when taking into consideration the incremental cost-effectiveness, the CaCO3/MgCO3 tablets are more cost effective by magnitude of 27.766 JD per week for every 1 mg/dl. Serum magnesium level increased significantly within group I and between the two groups by +0.55±0.36 mg/dl and +0.430±0.089 mg/dl respectively. Neither serum cCa^{+2} nor cCa^{+2} ×$PO4^{-3}$ products were changed significantly either among or between the two groups.

Conclusion: No significant difference was detected between Ca-Mg carbonate chewable tablets and the less expensive Ca carbonate tablets in reducing serum phosphate levels in hemodialysis patients on H2-R blockers.

Key words: Calcium carbonate, Hemodialysis, Magnesium carbonate, Phosphate binders.
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Introduction

Calcium and phosphate homeostasis is regulated by the kidneys, GIT and bones. As kidney function deteriorates, phosphate retention increased and activation of Cholecalciferol to 1-OH-cholecalciferol are decreased [1,2]. Patients with chronic kidney disease (CKD) experience hypergastrinemia due to decrease clearance of gastrin and increase density of G cells that secret gastrin, hence the prescription of histamine 2 blockers (H2-Blockers) or proton pump inhibitors (PPIs) is usually recommended to CKD patients [3] [4] .CaCO3 is routinely used as a phosphate binder in CKD patient, however there are multiple pharmacological therapies as phosphate binder; Rennie®[5] which is calcium carbonate/magnesium carbonate ($CaCO_3$/$MgCO_3$)combination chewable tablet contains 80 mg of magnesium carbonate ($MgCO_3$) and 680 mg of calcium carbonate ($CaCO_3$) per tablet.CaCO3 tablets are cheaper than Ca-Mg carbonate chewable tablets.

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However, the dissolution of calcium carbonate tablets is pH dependent and is decreased when stomach pH is increased by co-administration of H2R-blockers while the dissolution of Ca-Mg chewable tablets is less affected by alteration of stomach pH [6]. Using Mg carbonate alone no better at lowering serum phosphate levels, and was associated with more dose-limiting side effects[7] $MgCO_3$ is an effective and inexpensive agent to control serum phosphate levels in hemodialysis patients. Gastrointestinal disorders due to its use were minor, while its administration in combination with a low dialysate magnesium concentration reduces the risk of severe hypermagnesemia. Patients treated with $MgCO_3$ had, an optimum regulation of $cCa^{+2} \times PO4^{-3}$ product, relatively low serum calcium and no episodes of hypercalcemia,[8] chronic mild hypermagnesemia may decrease PTH synthesis and/or secretion, and could be a very useful adjunctive therapy in alleviating complications of CKD-MBD. In this way it can offer viable alternatives to the combination of calcium as a phosphate binder and vitamin D therapy; a strategy that may lead to frequent hypercalcemia episodes, calcium accumulation and potentially harmful cardiovascular consequences.[9]

Methods

This randomized, controlled, open label study was conducted at renal /hemodialysis unit of King Hussein Medical Hospital (KHMC) for six weeks. After the approving from the IRB committees at the Jordanian Royal Medical Services, patients in the renal /hemodialysis unit of KHMC who met the inclusion and didn't meet the exclusion criteria as described in (Figure1). patients enrolled in this study after they accepted to participate in this randomized, controlled, open label study, they were randomly allocated into interventional group (Group I) and control group (Group II). Blood samples were drawn from the HD participants before HD session and heparin infusions were started. The tests of serum $PO4^{-3}$, Serum Ca^{+2}, serum Mg^{+2}, serum K^{+}, blood glucose, SCr, and BUN levels were performed within 1-2 hours after the unheparizined blood was immediately separated by centrifugation in the KHMC chemistry laboratories. Serum cCa^{+2}, $cCa^{+2} \times PO4^{-3}$ product and $PO4^{-3} \times Mg^{+2} / cCa^{+2}$ ratios were calculated manually. All previous tests were measured on weekly basis for the first 2 weeks and then every other week. This study used a dialysate concentration of Mg^{+2} 0.73 mg/dl (0.6 meq/l) for the $MgCO_3$ group and 1.16 mg/dl (0.96 meq/l) for the $CaCO_3$ group, whereas dialysate Ca^{+2} concentration was 6 mg/dl (3 meq/l) for both groups.

The inclusion criteria for HD participants in this study included: Age greater than 18 years, age lower than 60 years, on hemodialysis for at least three months, the HD participants used $CaCO_3$ tablets as a phosphate binder and used either PPIs or H_2-Blockers for at least 3 months before participating in this study.

The exclusion criteria for HD patients in this study included: Serum cCa^{+2} level above 10.2 mg/dl , $cCa^{+2} \times PO4^{-3}$ above 55 mg^2/dl^2, serum Mg^{+2} baseline level above 3.5 mg/dl,if there was a positive history of psychiatric or other disorders leading to compliance issues, and there was a positive history of dysphagia or swallowing disorders or bowel obstruction.

Fig 1.Inclusion and exclusion criteria for hemodialysis patients.

All possible retrospective data for Group I and Group II were collected before the study period was started. The retrospective data that we collected (data of three months ago), included the last three values of serum $PO4^{-3}$ levels, serum Ca^{+2} levels, serum albumin levels, serum Mg^{+2} levels, and number of $CaCO_3$ tablets that were used as phosphate binder per day (n_1). After retrospective data were completed, the two studied groups were followed for 6 weeks in which the following outcomes were measured and assessed in the following basis:

- Serum $PO4^{-3}$ level, serum Ca^{+2} level , serum albumin level, serum cCa^{+2} level, $cCa^{+2} \times PO4^{-3}$ product, and serum Mg^{+2} level were measured on weekly basis for the first 2 weeks and then every other week
- n_1, number of $CaCO_3/MgCO_3$ combination chewable tablets (Rennie®) per day that were used as phosphate binder (n_2), and the $\sum$ phosphate binder cost per week were assessed on weekly basis.

In the interventional prospective follow-up, the $CaCO_3$ tablets in Group I were replaced totally by $CaCO_3/MgCO_3$ combination chewable tablets (Rennie®) without a washout period (maximum 6 tablets per day), in which each 1 tablet of $CaCO_3$ 1250 mg was replaced by 2 tablets of $CaCO_3/MgCO_3$ combination 680 mg/80 mg (Rennie®), while keeping all other medications without any change. During the follow-up phase, the $CaCO_3$ tablets replacement by $CaCO_3/MgCO_3$ combination chewable tablets (Rennie®) in interventional group was assessed on weekly basis and If serum Mg^{+2} level was ≥3.5 mg/dl and persisted for 1 week or serum Mg^{+2} level was ≥4.5 mg/dl we dropped-out the HD participant from our study. The $CaCO_3$ tablets in Group II were kept without any change in the prospective follow-up phase.

Blood samples were drawn from the HD participants before HD session and heparin infusions were started. The tests of serum $PO4^{-3}$, Serum Ca^{+2}, serum albumin, and serum Mg^{+2} were performed within 1-2 hours after the unheparizined blood was immediately separated by centrifugation in the KHMH chemistry laboratories. Serum cCa^{+2} and $cCa^{+2} \times PO4^{-3}$ products were calculated manually. The values of number of $PO4^{-3}$ binder(s) tablet(s)/ day were obtained directly from HD participants. The Σ cost per week was calculated manually.

After follow-up part of this open label randomized controlled trial was finished at the end of 6 weeks. The collected data of each outcome in the different two studied groups were analyzed using independent t-test.

Results

The recruitment, randomization, and dropout processes of all 142 eligible HD participantsand the medical and medication history of the study candidates in each group of the two studied groups are summarized in (Figures 2-3).All demographic characteristics of 37 HD participants in the two studied groups are summarized in (Tables I-II).

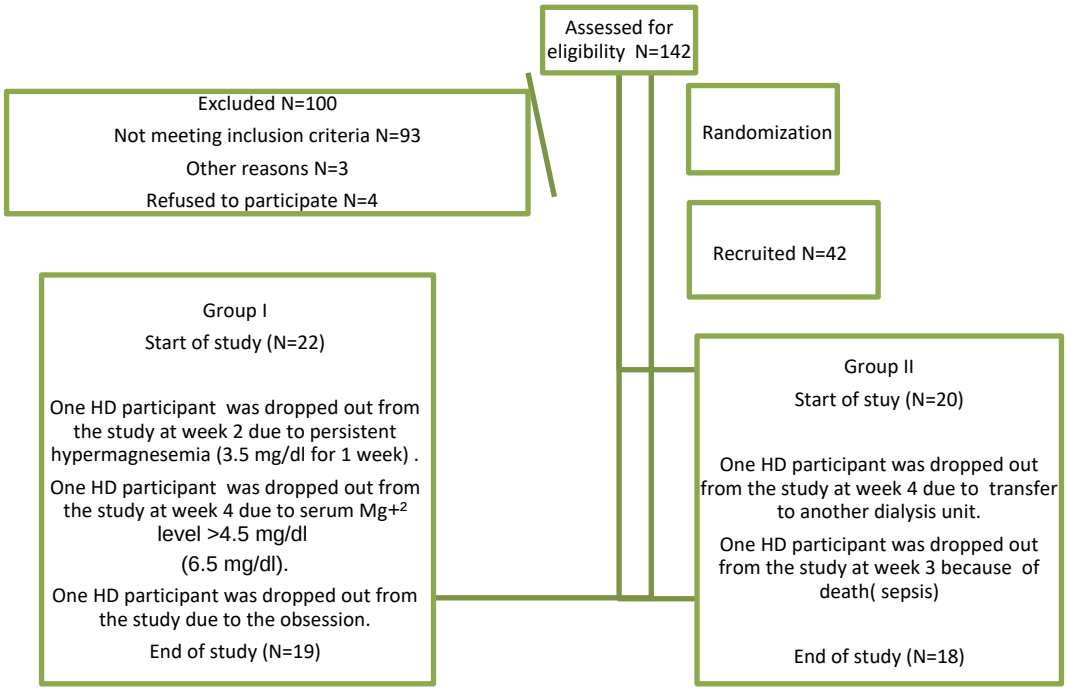

Fig 2: Recruitment, randomization, and dropout processes scheme

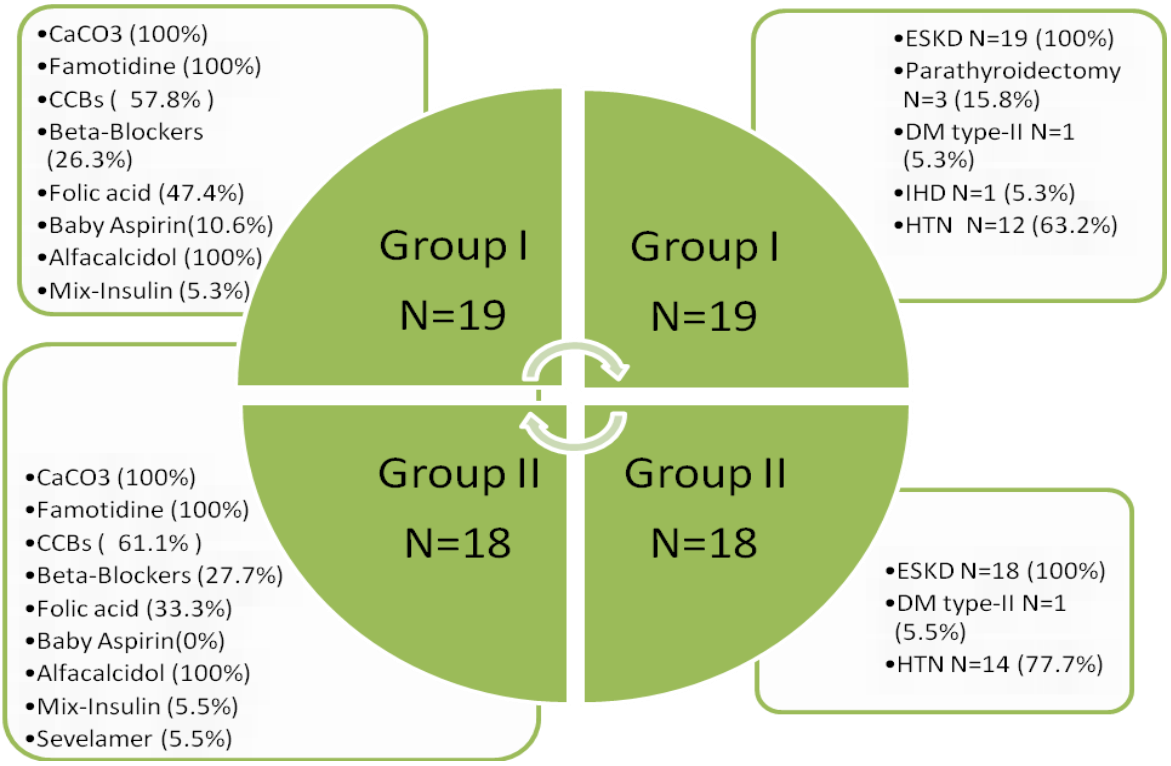

Fig 3: Patient's medical and medications history of the HD participant patients presented as (percentage).

Table I: Demographic characteristics of the two groups.

	Group I N=19 Mean±SD	Group II N=18 Mean±SD	Total N=37 Mean±SD	*P*- Value	Sig
Age (years)	39.47±2.47	43.21±2.01	40.81±2.31	0.349	NS
Male (%)	7 males (41.18%)	10 males (58.82%)	17 males (45.9%)		
Sex				0.438	NS
Female (%)	12 females (60 %)	8 females (40 %)	20 females (54.1 %)		
BMI (kg/m²)	22.21±0.043	26.51±0.039	24.79±0.043	0.897	NS

Data are presented as Mean±SDor as percentage by using Independent t-test (at *p*-value< 0.05)
S*: Significant -NS: Non significant-BMI: Body mass index -KHMH: King Hussein Medical Hospital

Table II: Other demographic characteristics of the two studied groups.

Characteristics		Group I N=19 Mean± SD	Group II N=18 Mean± SD	Total N=37 Mean± SD	*P*-Value	Sig
Duration of dialysis (months)		97.68±15.338	93.44±11.628	94.03±7.496	0.036	S*
Duration of using $CaCO_3$ tab as phosphate binder (months)		97.68±15.338	93.44±11.628	94.03±7.496	0.036	S*
Duration of using H2-Blockers (months)		75.47±11.136	90.33±11.998	81.38±6.945	0.315	NS
HD duration per session (hours)		4.18±0.109	4.08±0.061	4.12±0.047	0.158	NS
HD frequency Per week (%)	**1*per week**	1 patient (5.3%)	0 patient (0%)	1 patient (2.7%)	0.313	NS
	2*per week	5 patients (26.3%)	5 patients (27.8%)	10 patients (27%)		
	3*per week	13 patients (68.4%)	13 patients (72.2%)	26 patients (70.3%)		
	4* per week	0 patient (0%)	0 patients (0%)	0 patient (0%)		

A dependent T-test was conducted to determine whether there were significant differences within the two studied groups and independent t-test in parameters that are summarized in (Table III).

Table III: Serum $PO4^{-3}$ levels and the related variables values differences between the comparative groups.

Comparative Groups / Affective Variables	Group I after Versus Group I before	Group II after Versus Group II before	Group I Versus Group II
Serum $PO4^{-3}$ level (mg/dl) Mean difference±SD (Sig)	-0.39±0.99 (S*)	-0.29±0.35 (S*)	-0.094±0.213 (NS)
Serum cCa^{+2} level (mg/dl) Mean difference±SD (Sig)	+0.08±0.48 (NS)	+0.23±0.39 (S*)	(NS)
$cCa^{+2} \times PO4^{-3}$ (mg^2/dl^2) Mean difference±SD (Sig)	-3.19±8.09 (NS)	-1.52±3.33 (NS)	-1.663±1.789 (NS)
Serum Mg^{+2} level Mean difference±SD (Sig)	+0.55±0.36 (S*)	+0.12±0.17 (S*)	+0.430±0.089 (S*)
n_1 (tablet/day) Mean difference±SD (Sig)	-2.433±0.667 (S*)	-0.083±0.354 (NS)	-2.35±0.15 (S*)
n_2 (tablet/day) Mean difference±SD (Sig)	+4.592±1.036 (S*)	0	+4.59±0.24 (S*)
$CaCO_3$ (mg/day) Mean difference±SD (Sig)	+81.84±608.84 (NS)	0.000±0.000 (NS)	(NS)

Σ Cost per week Mean difference±SD (Sig)	-2.37±0.75 (S*)	+0.24±2.54 (NS)	-2.610±0.532 (S*)
$MgCO_3$ (mg/day) Mean difference±SD (Sig)	+367.368±82.879 (S*)	0	+367.37±19.52 (S*)

Data are presented as Mean difference ±SD (at p-value< 0.05)
- S*: Significant -NS: Non significant
- n_1 (tablet/day): Number of $CaCO_3$ tablets per day that were used as phosphate binder.
-n_2 (tablet/day): Number of $CaCO_3$/$MgCO_3$combination chewable tablets per day.
-n_4 (tablet/week): Number of H_2-Blocker tablets per week.
-$CaCO_3$ (mg/day): Amount of $CaCO_3$ in mg per day from either CaCO3 tablets that were used as phosphate binder or from $CaCO_3$/$MgCO_3$combination chewable tablets or from both.
$MgCO_3$ (mg/day): Amount of $MgCO_3$ in mg per day from $CaCO_3$/$MgCO_3$combination chewable tablets.
Σ Cost per week: Total cost per week in $/week.

Despite serum $PO4^{-3}$ level decreased significantly in group I by -0.39±0.99 mg/dl after replacing CaCO3 tablets by CaCO3/MgCO3 in equivalent dose, the differences between group I and group II were insignificant (-0.094±0.213). But with a significant lower Σ Cost per week with mean differences of -3.68±0.75 $/week. In contrast to serum Mg^{+2} level, which increased significantly within group I and between the two groups by +0.55±0.36 mg/dl and +0.430±0.089 mg/dl respectively. Neither serum cCa^{+2} nor $cCa^{+2}\times PO4^{-3}$ products were changed significantly either among or between the two groups.

Discussion

There were some studies addressing the adverse effect of H_2-Blockers when combined with phosphate binders especially the most commonly used $CaCO_3$. For example, Tan,*et al*and colleagues conclude that ranitidine has a significant adverse effect on binding of $CaCO_3$to phosphate in patients with renal failure, serum$PO4^{-3}$ levels were significantly higher during the ranitidine than the placebo phase (5.51±1.33 mg/dl versus 4.92±1.52 mg/dl; p<0.001) and there was no significant change in serum c Ca^{+2} [10]. These results were explained depending on the pH effects on dissolution and kinetic binding of $CaCO_3$tablet; the acidity is best for solubility [11] .In contrast $CaCO_3$/$MgCO_3$ combination chewable tablet has no problem in dissolution after either chewing or sucking so that, there is no drug interaction with H_2-Blockers on the dissolution step (rate-limiting step), in addition to that, the higher pH in stomach that is created by H_2-Blockers will potentiate the second step of phosphate binding scenario (binding of Ca^{+2} and Mg^{+2} to the $PO4^{-3}$ in the GIT). In our study, we conclude that there was no significant differences in serum $PO4^{-3}$and $cCa^{+2}$when the H2-Blockers are added to the phosphate binders in both groups may be due improved compliance to CaCO3 tablet intake in group II as described by significant change in serum $PO4^{-3}$ (-0.29±0.35). Despite this insignificant differences, the CaCO3/MgCO3 combination has a total lower cost per week (-3.68±0.75) when compare with CaCO3, which give the advantage of CaCO3/MgCO3 combination chewable tablets. As expected, the serum Mg^{+2} level was increased significantly in this study (+0.430±0.089) as in Delmez, *et al*controlled cross over study when adjusted dose of $CaCO_3$/$MgCO_3$ combination tablets replaced $CaCO_3$ tablets monotherapy group to achieve target serum phosphate concentrations of <6.0 mg/dL and serum calcium concentrations of 9.5–10.5 mg/dl. Serum levels of $PO4^{-3}$,cCa^{+2} were similar in the both phases,serum Mg^{+2} was also similar in both phase due to using 1/3 dialysate Mg^{+2} in the $CaCO_3$/$MgCO_3$ combination tablets phase which means $CaCO_3$/$MgCO_3$ combination tablets can increase serum Mg^{+2} level [12] .

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.
-Cost effectiveness is not constant but variable factor from time to time.

Conclusions

No significant difference was detected between Ca-Mg carbonate chewable tablets and the less expensive Ca carbonate tablets in reducing serum phosphate levels in hemodialysis patients on H2-R blockers.

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