Efficacy and Safety of Nicotinamide in Management of Hyperphosphatemia in Pediatric Patients on Regular Hemodialysis- a Pilot study

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Radwa Maher

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List of abbreviations

ACCP	**American College of Clinical Pharmacy**
ACE	**Angiotensin converting enzyme**
ALT	**Alanine aminotransferase**
ALP	**Alkaline phosphatase**
AST	**Aspartate aminotransferase**
AVF	**Arterial Venous Fistula**
BGL	**Blood glucose level**
BUN	**Blood Urea Nitrogen**
Ca*P	**Calcium- Phosphorus Product**
CAPD	**Continuous Ambulatory Peritoneal Dialysis**
CCPD	**Continuous Cyclic Peritoneal Dialysis**
CKD	**Chronic Kidney Disease**
CV	**Cardiovascular**
ESRD	**End Stage Renal Disease**
FGF	**Fibroblast growth factor**
GFR	**Glomerular Filtration Rate**
GH	**Growth Hormone**
GN	**Glomerulonephritis**
HD	**Hemodialysis**
HDL	**High density lipoprotein**
IGF-1	**Insulin like Growth Factor-1**
IPD	**Intermittent Peritoneal Dialysis**
KDOQI	**Kidney Disease Outcomes Quality Initiative**
LVH	**Left ventricular hypertrophy**
LDL	**Low density lipoprotein**
MNA	**N methyl nicotinamide**
NAM	**Nicotinamide**
NAD	**Nicotinamide adenine dinucleotide**
NADP	**Nicotinamide adenine dinucleotide phosphate**
NKF	**National Kidney Foundation**
NaPi	**Sodium dependent phosphate cotransporter protein**
PARP	**Poly (ADP ribose) polymerase 1**
PD	**Peritoneal Dialysis**
pmp	**per million populations**

PTH	**Parathyroid Hormone**
2 PY	**N methyl 2 pyridone 5 carboxamide**
4 PY	**N methyl 4 pyridone 5 carboxamide**
rhuEPO	**Recombinant Human Erythropoietin**
rhGH	**Recombinant Human Growth Hormone**
TC	**Total cholesterol**
TG	**Triglycerde**
USRDS	**United State Renal Data System**
VUR	**Vesicouretric Reflux**
WBC	**White blood cell**

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Abstract

Abstract

Introduction

Hyperphosphatemia is a significant problem in hemodialysis patients; in fact, renal failure is the main cause of it. Control of serum phosphorus in hemodialysis patients is very important because hyperphosphatemia and the increase in calcium-phosphorus product are associated with overall and cardiovascular mortality in these patients. There are different measures to control hyperphosphatemia such as restriction in dietary phosphorus, dialysis, and using calcium or non-calcium phosphate binders. But none of these can control hyperphosphatemia as recommended. Physicians have been using nicotinamide for different diseases for many years. Nicotinamide inhibits sodium-phosphorus co-transporting (Na/Pi2) in both renal proximal tubules and intestine; as a result, the absorption of phosphorus by related cells is reduced. Recently, nicotinamide has been reported to be effective and safe in controlling hyperphosphatemia in hemodialysis patients, either alone or as an additive therapy.

Aim of the work

The current study was conducted to evaluate the efficacy and safety of nicotinamide addition to calcium based phosphate binder in treatment of hyperphosphatemia in end stage renal disease pediatric patients on regular hemodialysis.

Patients and methods

The study was carried on 60 end stage renal disease pediatric patients undergoing hemodialysis at the Pediatric nephrology and dialysis unit, Ain Shams University Children's Hospital. They were simply randomized to be assigned to either Group I (Control group) who received the calcium based phosphate binder (calcium acetate or calcium carbonate) 500mg 2-3 times daily for 6 months or Group II (Nicotinamide group) who received the calcium based phosphate binder (calcium acetate or calcium carbonate) 500mg 2-3 times daily in addition to nicotinamide tablet for 6 months.

Patients were subjected to full history taking and clinical examination. Biochemical parameters were analyzed by standard clinical laboratory measures. Serum phosphorus and calcium levels were estimated at baseline, month 3 and month 6 prior to HD session and other parameters like complete blood count, blood sugar, parathyroid hormone (PTH), lipid profile, renal profile, and liver function tests were

estimated at baseline and end of the study. Patients were regularly monitored for side effects like gastrointestinal discomfort during the study period.

Results:

The current study has shown that administration of Nicotinamide for 6 months in combination with calcium based phosphate binder was associated with significant decrease (p= 0.0001) in the mean serum phosphorus, the mean serum Ca* P product (p= 0.0001) and in the median serum PTH levels (p=0.02) over the baseline, 3rd month and 6th month measurements. In addition the Nicotinamide group showed a highly significant decrease (p< 0.01) in the mean serum HDL level and in the median serum TG levels (p<0.01). Regarding the side effects 20 patients of the Nicotinamide group experienced the following adverse effects: 24% reported diarrhea, 24% reported flushing, 9% reported diarrhea and flushing, 5% reported flushing and nausea, 19% reported nausea, 9% reported nausea and diarrhea, 5% reported nausea and vomiting and 5% reported nausea, vomiting and diarrhea, moreover the Nicotinamide group showed significant (p=0.014) decrease in the mean platelets count as compared to their baseline values but remain in the normal range and no patients developed thrombocytopenia or bleeding during the study.

Conclusion

In hemodialysis pediatric patients, nicotinamide can effectively reduce serum phosphorus level when administered with calcium based phosphate binder with less potential side effects reported.

Keywords

Nicotinamide – Hemodialysis - Hyperphosphatemia

Review of Literature

Part 1: Renal Insufficiency

I. Definitions

Impairment of normal kidney function is referred as renal insufficiency or renal failure, based on the time course of development, renal failure has been historically divided into 2 broad categories: acute renal failure and chronic renal failure. Chronic kidney disease (CKD) refers to a state of irreversible kidney damage and/or reduction of kidney function, which can be progressive. CKD is now the accepted term in the pediatric nephrology community, replacing the clinical terms of chronic renal failure (CRF) and chronic renal insufficiency (CRI)**. (Mendley et al, 2015)**

Chronic Kidney disease (CKD):

The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline (CPG) for Evaluation and Management of Chronic Kidney Disease revised the 2002 classification of pediatric chronic kidney disease (CKD) by the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guideline for Chronic Kidney Disease and published new definition and classification of CKD in 2013. The KDIGO diagnosis of pediatric CKD is based on fulfilling following clinical criteria: Abnormalities of kidney structure or function (defined by markers of kidney injury or decreased GFR) present for > 3 months with implications for health. *(Either criterion is sufficient for diagnosis.)* **(KDIGO, 2013)**

1. Markers of kidney damage (one or more):
• Albuminuria (AER ≥ 30mg/24hrs; ACR ≥ 30mg/g)
• Urine sediment abnormalities
• Electrolyte and other abnormalities due to tubular disorders
• Abnormalities detected by histology
• Structural abnormalities detected by imaging
• History of prior kidney transplantation
2. GFR < 60 mL/min/1.73m^2

This definition is not applicable to children younger than 2 years because they normally have a low GFR, even when corrected for body surface area.

GFR is equal to the sum of the filtration rates in all of the functioning nephrons and

therefore, can give an estimate of renal function. Interpretation requires a clear understanding that GFR varies according to age, gender, and body size. The normal GFR is much lower in infancy and reaches adult values after one year of age. Despite this, a calculated GFR based upon serum creatinine can be compared to normative age-appropriate values to detect renal impairment even in toddlers and infants with CKD. (Table 1) shows the normal GFR in children and adolescents. (**Jayaranan and Vander voort, 2010**)

Table (1): Normal GFR in children and adolescents

Age	Mean GFR±SD (**ml/min/1.73m^2**)
1 week (males & females)	41 ± 15
2 week (males & females)	66 ± 25
>8 week (males & females)	96 ± 22
2-12 years (males & females)	133 ± 27
13-21 years (males)	140 ± 30
13-21 years (females)	126 ± 22

(**Jayaranan and Vander voort, 2010**)

II. Staging of CKD:

The KDIGO has developed a classification system for the severity of CKD based on GFR and independent of primary renal diagnosis (Table 2).

Table (2): KDIGO classification of the stages of chronic kidney disease

GFR Categories	**GFR (ml/min/ 1.73 m2)**	**Terms**
G1	> 90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased

G5	< 15	Kidney failure or end stage renal disease (ESRD)	
Albuminuria Categories	**AER (mg/24hrs)**	**ACR (mg/g)**	**Terms**
A1	< 30	< 30	Normal to mildly increased
A2	30-300	30-300	Moderately increased
A3	> 300	> 300	Severely increased

(**KDIGO, 2013)**

III. Etiology of CKD:

In children, CKD may be the result of congenital, acquired, inherited, or metabolic renal disease (Table 3), and the underlying cause correlates closely with the age of the patient at the time when the CKD is first detected. CKD in children younger than 5 years is most commonly a result of congenital abnormalities such as renal hypoplasia, dysplasia, and/or obstructive uropathy.

Additional causes include congenital nephrotic syndrome, prune belly syndrome, cortical necrosis, focal segmental glomerulosclerosis, polycystic kidney disease, bilateral renal vein thrombosis, and hemolytic uremic syndrome. After 5 years of age, acquired diseases (various Forms of glomerulonephritis including lupus nephritis) and inherited disorders (familial juvenile nephronophthisis, Alport syndrome) predominate. CKD related to metabolic disorders (cystinosis, hyperoxaluria) and certain inherited disorders (polycystic kidney disease) may present throughout the childhood years. **(Vogt and Avner, 2007)**

Table (3): Etiology of CKD in a group of Egyptian children

Etiology of CKD	Percentage
Urinary tract infection	28.9%
Glomerulopathies	26.7%
Hereditary nephropathies	15.6%
Collagen vascular diseases	15.6%
Miscellaneous (interstitial analgesics nephropathies,	6.6%