e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(10); 365-369

Original Research Article

A Randomized, Double‑Blind Clinical Assessment of the Effect of Low‑Dose Nicotinic Acid on Hyperphosphatemia in Patients with ESRD.

Gopal Prasad[1], Kumar Abhinav[2], Sujay Ranjan[3]

[1]Assistant Professor, Department of Nephrology, Patna Medical College and Hospital, Patna, Bihar, India
[2]Junior Resident, Department of Medicine, Patna Medical College and Hospital, Patna, Bihar, India
[3]Junior Resident, Department of Medicine, Patna Medical College and Hospital, Patna, Bihar, India

Received: 10-04-2023 / Revised: 20-05-2023 / Accepted: 24-06-2023
Corresponding Author: Dr. Gopal Prasad
Conflict of interest: Nil

Abstract:

Aim: The aim of the present study was to assess the effect of low-dose nicotinic acid on hyperphosphatemia in patients with ESRD.

Methods: In this randomized, double-blind clinical trial, 100 dialysis patients referred to the Department of Nephrology, Patna Medical College and Hospital, Patna, Bihar, India for the period of six months were evaluated.

Results: The difference in mean age between niacin and placebo groups was not significant. At the end of the first month, the difference between two groups in calcium level was significant. At the end of the second month, the difference between the two groups in terms of phosphorus and calcium levels was significant. At the end of the third month, mean phosphorus level was significantly different between the two groups.

Conclusion: We concluded that niacin (100 mg/day) decreased phosphorus serum level and increased HDL serum level in patients on dialysis.

Keywords: End Stage Renal Disease, High-Density Lipoprotein, Hyperphosphatemia, Nicotinic Acid.

Introduction

Hyperphosphatemia is a frequent complication of end-stage renal disease (ESRD) and principally affects hemodialysis (HD) patients. Elevated serum phosphorus contributes to the development of secondary hyperparathyroidism, chronic kidney disease–mineral bone disorder (CKD-MBD), metastatic calcifications, and calcific uremic arteriolopathy. There is a significant association between hyperphosphatemia and increased morbidity and mortality in ESRD patients including cardiovascular morbidity and mortality, also it is associated with the hospitalization of HD patients. [1] Although there are multiple lines of treatment of hyperphosphatemia in ESRD patients undergoing HD, they are still inadequate. Calcium-containing phosphate binders sometimes cause adverse effects such as hypercalcemia and coronary calcification, the non-calcium-containing phosphate binders, such as sevelamer and lanthanum are expensive. Moreover, aluminum-containing agents are efficient, but no longer used because of their toxicity. Several trials have shown that nicotinamide (NAM) and niacin can reduce serum phosphate levels markedly in patients undergoing HD. [2] Niacin was initially reported to lower plasma cholesterol. [3] The main clinical use of niacin has been to raise high-density lipoprotein (HDL) cholesterol and reduce triglyceride levels with potentially favorable cardiovascular effects. Recently, nicotinic acid and related compounds such as nicotinamide (NAM) have also shown to decrease phosphorus absorption in the gastrointestinal tracts of animals through a unique mechanism other than the traditional phosphate binders. [4]

In prior research, nicotinic acid has been demonstrated to be safe, cheap, and effective in normalizing serum phosphorus and Ca-P product in patients with ESRD. [5] Flushing, a common side effect of nicotinic acid, can be overcome by premedication with aspirin. [6] Although most side effects are reversible, further studies are warranted to investigate the safety profile of this potential therapeutic option. [7] Despite these positive roles of niacin, physicians hesitate to prescribe niacin because of its various adverse effects such as hot flushing, liver function test abnormality and thrombocytopenia. Although some of these adverse effects are mild and easily controlled by symptomatic care, some effects such as hot flushing necessitate cessation of niacin

administration. [8,9] Therefore, it is necessary to judge whether the benefits of low-dose niacin administration outweigh its adverse effects. Edalat-Nejad et al. (2012) suggested that niacin may emerge as a safe and low-cost therapy in combination with other phosphate binders for phosphate control. [10]

The aim of the present study was to assess the effect of low‑dose nicotinic acid on hyperphosphatemia in patients with ESRD.

Materials and Methods

In this randomized, double‑blind clinical trial, 100 dialysis patients referred to the Department of Nephrology, Patna Medical College and Hospital, Patna, Bihar, India for the period of six months were evaluated.

Inclusion criteria were age >18 years, ability to give informed consent, $PO_4 \geq$ 5.5 mg/dl, dialysis duration for more than 3 months, adequate dialysis (Kt/V >1.2) during the study. Exclusion criteria were pregnancy, liver disease, active peptic ulcer disease, taking carbamazepine, history of niacin (or niacin as other drugs' component) sensitivity, and malignancy.

Written informed consent was obtained before randomization, as per the institution's protocol. The study was approved by Ethical Committee. The patients were randomly assigned to either niacinamide or placebo groups. Both participants and the study staff (site investigators and trial coordinating staff) were masked to the treatment. Niacin and placebo were packaged in identical tablets by pharmacy. The patients were prescribed one tablet daily with their meal. Dosages were titrated from 25 mg/day over 12 weeks.

Phosphorus level was measured pretreatment and at the end of weeks 4, 8, and 12. When serum phosphorus levels did not reach the normal reference range (P ≤ 5.5 mg/dl), the dose of nicotinic acid was increased to 50 mg/day at the end of the 1st month and to 100 mg/day at the end of the 3rd month. None of the participants was treated with sevelamer (renagel). Wash‑out period was not permitted by the Ethics Committee, thus, all patients were administered 1500 mg calcium carbonate as phosphate binder during the study. When phosphorus levels exceeded 5.5 mg/dl or decreased to less than 3.5 mg/dl, the dose of phosphate binder was changed in order to continue niacin at the described dose. None of the participants used statins. The patients were followed for 3 months and during this period, serum levels of P, Ca, alanine aminotransferase (ALP), HDL cholesterol, triglycerides (TG), platelet, and parathyroid hormone (PTH) were measured monthly.

Statistical Analysis

Descriptive statistics that used mean and standard deviation are presented as continuous variables. The Chi‑square and Fisher's exact test

were used to compare categorical variables. Mann–Whitney's U‑test and paired t‑test were used to compare continuous variables. For all the tests, (P ≤ 0.05) was considered significant. Data were analyzed using SPSS 20 (SPSS Inc., Chicago, IL, USA).

Results

Table 1: The mean and standard deviation of parameters at the end of first month in two groups (25 mg/day niacin)

Parameters	Niacin	Placebo	P
P (mg/dl)	6.6±0.74	6.5±1.4	0.424
Ca(mg/dl)	8.2±1.5	9.2±1.6	0.005
PTH (pg/ml)	318.2±212	282.8±234.6	0.486
Cholesterol(mg/dl)	143.7±44.6	156.4±32.2	0.088
TG (mg/dl)	132.8±38.8	128.2±28.2	0.785
LDL(mg/dl)	68.2±20.8	69.1±35.5	0.445
HDL(mg/dl)	45±14.6	45.1±12.6	0.932
AST (IU/L)	22.6±6.4	22.1±6.2	0.632
ALT (IU/L)	23.7±12.8	22±6.4	0.535
Bilirubin (mg/dl)	1.05±0.23	1±0.38	0.175
Platelet count, $\times 10^3/mm^3$	21,224.0±50,765.2	23,935.0±61,009.2	0.69

The difference in mean age between niacin and placebo groups was not significant. At the end of the first month, the difference between two groups in calcium level was significant.

Table 2: The mean and standard deviation of parameters at the end of second month in two groups (50 mg/day niacin)

Parameters	Niacin	Placebo	P
P (mg/dl)	1.2±5.4	1.5±6.4	0.001
Ca(mg/dl)	1.4±8.2	1.1±8.1	0.020
PTH (pg/ml)	192.8±316.2	214.6±2275	0.445
Cholesterol(mg/dl)	38±143.7	35.5±154.6	0.224
TG (mg/dl)	44.6±136.4	32.8±132.2	0.445
LDL(mg/dl)	18.2±72.4	17.3±68.2	0.635
HDL(mg/dl)	9.1±42.8	10±43.7	0.785
AST (IU/L)	6.3±18.4	7.4±20.8	0.735
ALT (IU/L)	5.5±18.2	6.6±21.1	0.248
Bilirubin (mg/dl)	0.24±0.96	0.32±1	0.240
Platelet count, $\times 10^3/mm^3$	59894.9±233080	54931.5±242860	0.471

At the end of the second month, the difference between the two groups in terms of phosphorus and calcium levels was significant.

Table 3: The mean and standard deviation of parameters at the end of third month in two groups (100 mg/day niacin)

Parameters	Niacin	Placebo	P
P (mg/dl)	1.2±4.6	0.94±7.1	0.0001
Ca(mg/dl)	0.5±8.2	1.2±8.4	0.325
PTH (pg/ml)	186.8±306.4	201.3±259.7	0.309
Cholesterol(mg/dl)	32.8±146.4	32.6±156.4	0.220
TG(mg/dl)	54.6±136.5	36.2±134.6	0.555
LDL(mg/dl)	22.4±68.2	21.5±72.6	0.634
HDL(mg/dl)	12.8±48.2	11.6±45.5	0.545
AST (IU/L)	6.4±20.5	6.6±22.8	0.151
ALT (IU/L)	6.4±22.08	5.7±24.6	0.242
Bilirubin (mg/dl)	0.18±0.92	0.36±0.94	0.576
Platelet count,$\times 10^3/mm^3$	58785.7±236244	47376.7±243675	0.546

At the end of the third month, mean phosphorus level was significantly different between the two groups.

Discussion

Chronic kidney disease (CKD) is growing worldwide and the incidence of end stage renal diseases (ESRD) is on the rise. [11] Previous studies have reported that hyperphosphatemia results in increased morbidity and mortality among patients with CKD. Serum phosphorus levels more than 6.5 mg/dl increase mortality rate about 27% compared to phosphorus levels <6.5 mg/dl. [12,13] Long‑term inadequate phosphate control leads to secondary hyperparathyroidism, metabolic bone diseases, calcific uremic arteriolopathy, and cardiovascular calcification. Progressive increases in arterial calcification are associated with higher rates of mortality. [14] Management of hyperphosphatemia in patients with ESRD is not adequate. Calcium containing phosphate binders may sometimes result in adverse effects such as hypercalcemia. [15] Noncalcium phosphate binders, such as sevelamer and lanthanum, are expensive. [16] The modest increase in HDL values may be considered as another beneficial effect of this treatment. Its major side effects are vasodilation and flushing, and prostaglandins seems to be the cause, thus can be attenuated by premedication with aspirin. [17]

The global incidence of end-stage renal disease (ESRD) is increasing exponentially. By 2030, the number of individuals on dialysis is projected to reach 5.4 million, with the most growth expected in Asia. [18] Hyperphosphatemia is a potential cause of adverse clinical outcomes in ESRD. In patients on maintenance hemodialysis (HD), the mortality risk increases up to 27% with serum phosphorus levels >6.5 mg/dL compared to serum phosphorus levels ranging from 2.4 to 6.5 mg/dL. [19] Similarly, dismal results have been observed for calcium-phosphorus (Ca-P) product of >45.9 mg2/dL2. Chronically elevated calcium has a predilection for precipitation in myocardium, blood vessels, and heart valves. [20] Therefore, appropriate treatment of hyperphosphatemia in patients with ESRD is imperative to decrease the risk of cardiovascular morbidity as well as renal complications, such as renal failure and renal osteodystrophy. [21]

The difference in mean age between niacin and placebo groups was not significant. At the end of the first month, the difference between two groups

in calcium level was significant. At the end of the second month, the difference between the two groups in terms of phosphorus and calcium levels was significant. At the end of the third month, mean phosphorus level was significantly different between the two groups. In line with the results of this study, Vasantha et al., in an open‑label study on 30 dialysis patients receiving a dose of NAM 750 mg/day, reported reductions in serum phosphorus level (2.3 mg/dl). [22] Rennick et al., in a meta‑analysis reviewed seven studies that evaluated the effect of nicotinamide and nicotinic acid on phosphorus serum level in ESRD patients undergoing dialysis and indicated that in the three studies using nicotinic acid as the therapeutic intervention and four studies using nicotinamide, both nicotinic acid and nicotinamide significantly reduced serum phosphorus level. [23] In the present study, no significant changes in Ca and PTH were detected. Cheng et al., observed insignificant changes in serum calcium and PTH levels in the niacin group. [24] In agreement with Kang et al., statistically significant increases in HDL were observed in the present study. [25]

Results from larger and more significant trials emphasize that the safety profile of nicotinic acid is controversial. [26] A sub-group analysis on a randomized controlled Atherothrombosis Intervention in Metabolic Syndrome with low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial suggested more side effects (flushing) and fewer benefits resulting from nicotinic acid therapy. [27] The study enrolled 3414 cases and used extended-release niacin. A study comparing sevelamer and oral nicotinamide in 100 patients on HD suggested more side effects (major risk of thrombocytopenia) and less clinical effectiveness of nicotinamide. [28] Use of low‑dose niacin is affordable due to low adverse effects and the low cost. Recent studies, suggested that after reducing side effects, nicotinamide can be an in expensive alternative. [29] Therefore, a low dose of niacin may be helpful not only for the control of dyslipidemia, but also for the early prevention of hyperphosphatemia in patients with CKD. Meanwhile, a comparison with baseline revealed increased ALP level after niacin supplementation in our study. Increased ALP level after niacin supplementation was also found in animal and human studies.[30]However, further studies are recommended to examine if it is an acceptable alternative to sevelamer in patients with economic constraints.

Conclusion

We concluded that niacin (100 mg/day) decreased serum phosphorus level and increased serum HDL level in patients on dialysis. The results of our study have confirmed that niacin is an effective drug in reducing serum phosphorus levels in dialysis patients in combination with other phosphate binders. Niacin may be considered as a safe, low-cost therapy, with fewer side effects, and fewer tablets are required to achieve good compliance. The slight elevation in HDL values may be considered as an added beneficial effect.

References

1. El Borolossy R, El Wakeel LM, El Hakim I, Sabri N. Efficacy and safety of nicotinamide in the management of hyperphosphatemia in pediatric patients on regular hemodialysis. Pediatric nephrology. 2016 Feb; 31:289-96.
2. Zahed NS, Zamanifar N, Nikbakht H. Effect of low dose nicotinic acid on hyperphosphatemia in patients with end stage renal disease. Indian Journal of Nephrology. 2016 Jul;26(4):239.
3. Altschul R, Hoffer A, Stephen JD. Influence of nicotinic acid on serum cholesterol in man. Archives of Biochemistry. 1955; 54:558-9.
4. Rennick A, Kalakeche R, Seel L, Shepler B. Nicotinic acid and nicotinamide: a review of their use for hyperphosphatemia in dialysis patients. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2013 Jun;33(6):683-90.
5. Restrepo Valencia CA, Cruz J. Safety and effectiveness of nicotinic acid in the management of patients with chronic renal disease and hyperlipidemia associated to hyperphosphatemia. Nefrología (English Edition). 2008 Feb 1;28(1):61-6.
6. Sampathkumar K. Niacin and analogs for phosphate control in dialysis—perspective from a developing country. International urology and nephrology. 2009 Dec; 41:913-8.
7. Bingley PJ, Mahon JL, Gale EA, European Nicotinamide Diabetes Intervention Trial Group: Insulin resistance and progression to type 1 diabetes in the European Nicotinamide Diabetes Intervention Trial(ENDIT). Diabetes Care. 2008, 31:146-50.
8. Carlson LA. Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review. Journal of internal medicine. 2005 Aug; 258(2):94-114.
9. Bruckert E, Labreuche J, Amarenco P. Meta-analysis of the effect of nicotinic acid alone or in combination on cardiovascular events and atherosclerosis. Atherosclerosis. 2010 Jun 1;210(2):353-61.
10. Edalat-Nejad M, Zameni F, Talaiei A. The effect of niacin on serum phosphorus levels in dialysis patients. Indian journal of nephrology. 2012 May 1;22(3):174.
11. Canadian Institute for Health Information. Canadian Organ Replacement Register Annual Report: Treatment of End‑Stage Organ Failure

in Canada, 2000‑2009. Ottawa, Ont.: CIHI; 2011.
12. Kidney Disease: Improving Global Outcomes (KDIGO) CKD‑MBDWork Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD‑MBD). Kidney IntSuppl 2009:S1‑S130.
13. Melamed ML, Eustace JA, Plantinga L, Jaar BG, Fink NE, Coresh J, Klag MJ, Powe NR. Changes in serum calcium, phosphate, and PTH and the risk of death in incident dialysis patients: a longitudinal study. Kidney international. 2006 Jul 2;70(2):351-7.
14. Block GA, Port FK. Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: recommendations for a change in management. American Journal of Kidney Diseases. 2000 Jun 1;35(6):1226-37.
15. Manns B, Stevens L, Miskulin D, Owen Jr WF, Winkelmayer WC, Tonelli M. A systematic review of sevelamer in ESRD and an analysis of its potential economic impact in Canada and the United States. Kidney international. 2004 Sep 1;66(3):1239-47.
16. Tonelli M, Pannu N, Manns B. Oral phosphate binders in patients with kidney failure. New England Journal of Medicine. 2010 Apr 8;362(14):1312-24.
17. Morrow JD, Parsons III WG, Roberts II LJ. Release of markedly increased quantities of prostaglandin D2 in vivo in humans following the administration of nicotinic acid. Prostaglandins. 1989 Aug 1;38(2):263-74.
18. Liyanage T, Ninomiya T, Jha V, Neal B, Patrice HM, Okpechi I, Zhao MH, Lv J, Garg AX, Knight J, Rodgers A. Worldwide access to treatment for end-stage kidney disease: a systematic review. The Lancet. 2015 May 16;385(9981):1975-82.
19. Qunibi WY. Consequences of hyperphosphatemia in patients with end-stage renal disease (ESRD). Kidney International. 2004 Sep 1;66: S8-12.
20. Six I, Maizel J, Barreto FC, Rangrez AY, Dupont S, Slama M, Tribouilloy C, Choukroun G, Maziere JC, Bode-Boeger S, Kielstein JT. Effects of phosphate on vascular function under normal conditions and influence of the uraemic state. Cardiovascular research. 2012 Oct 1;96(1):130-9.
21. Isakova T, Xie H, Yang W, Xie D, Anderson AH, Scialla J, Wahl P, Gutiérrez OM, Steigerwalt S, He J, Schwartz S. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. Jama. 2011 Jun 15;305(23):2432-9.
22. Vasantha J, Soundararajan P, Vanitharani N, Kannan G, Thennarasu P, Neenu G, Reddy CU. Safety and efficacy of nicotinamide in the management of hyperphosphatemia in patients on hemodialysis. Indian Journal of Nephrology. 2011 Oct;21(4):245.
23. Rennick A, Kalakeche R, Seel L, Shepler B. Nicotinic acid and nicotinamide: a review of their use for hyperphosphatemia in dialysis patients. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2013 Jun;33(6):683-90.
24. Cheng SC, Young DO, Huang Y, Delmez JA, Coyne DW. A randomized, double-blind, placebo-controlled trial of niacinamide for reduction of phosphorus in hemodialysis patients. Clinical Journal of the American Society of Nephrology. 2008 Jul 1;3(4):1131-8.
25. An WS, Kang HJ, Kim KH. Effect of low-dose niacin on dyslipidemia, serum phosphorus levels and adverse effects in patients with chronic kidney disease. Kidney Research and Clinical Practice. 2012 Jun 1;31(2): A16.
26. Drüeke TB, Massy ZA. Lowering expectations with niacin treatment for CKD-MBD. Clinical Journal of the American Society of Nephrology. 2018 Jan 6;13(1):6-8.
27. Aim-High Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. New England Journal of Medicine. 2011 Dec 15;365(24):2255-67.
28. Lenglet A, Liabeuf S, El Esper N, Brisset S, Mansour J, Lemaire-Hurtel AS, Mary A, Brazier M, Kamel S, Mentaverri R, Choukroun G. Efficacy and safety of nicotinamide in haemodialysis patients: the NICOREN study. Nephrology Dialysis Transplantation. 2017 May 1;32(5):870-9.
29. Shin S, Lee S. Niacin as a drug repositioning candidate for hyperphosphatemia management in dialysis patients. Therapeutics and Clinical Risk Management. 2014 Oct 14:875-83.
30. Capuzzi DM, Guyton JR, Morgan JM, Goldberg AC, Kreisberg RA, Brusco OA, Brody J. Efficacy and safety of an extended-release niacin (Niaspan): a long-term study. The American journal of cardiology. 1998 Dec 17;82(12):74U-81U.