ORIGINAL RESEARCH

The Effect of Niacinamide Supplementation on Phosphate Concentrations in Dutch Dialysis Patients: A Randomized Crossover Trial

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Objective: Hyperphosphatemia is a common complication in patients with kidney failure, despite the use of phosphate binders. Vitamin B3, either in the form of niacin or niacinamide (NAM), shows potential as "add-on" treatment to reduce serum phosphate concentrations in this population. NAM seems to lack many of the side effects that are observed with niacin. The aim of this study was to investigate whether NAM is an effective and acceptable treatment in reducing serum phosphate concentrations in patients with kidney failure.

Methods: DiaNia was a double-blind placebo-controlled randomized crossover trial, comparing NAM (250-500 mg/day) to placebo as "add-on" treatment to an individual treatment with approved phosphate binders for 12 weeks in patients receiving hemodialysis. The primary outcome was serum phosphate concentrations, and the secondary outcomes were platelet counts as well as drop-outs due to side effects. Data were analyzed using both per-protocol and intention-to-treat analyses.

Results: Mean age of the per-protocol population (n = 26) was 63.6 ± 17.2 years and 53.8% were men. NAM treatment significantly reduced serum phosphate with 0.59 mg/dL (p = .03). Linear mixed-effects models demonstrated superiority of 12 weeks NAM over 12 weeks placebo with a between-treatment difference of 0.77 mg/dL (95% CI 0.010, 1.43; *P* = .03). Similar results, although not significant, were found in the intention-to-treat population. We found no between-treatment differences in platelet counts and during the NAM treatment we observed 3 drop-outs due to side effects (8.6%).

Conclusion: NAM is effective in reducing serum phosphate concentrations in patients with kidney failure receiving hemodialysis. In addition, NAM is well-tolerated and seems not to increase the risk of thrombocytopenia. Thus, NAM can be valuable as "add-on" treatment to combat hyperphosphatemia in patients with kidney failure. However, more research in larger populations is needed to confirm this.

Keywords: Hemodialysis; hyperphosphatemia; niacinamide; thrombocytopenia

Introduction

HYPERPHOSPHATEMIA, DEFINED AS serum phosphate levels > 4.5 mg/dL, is a common complication in patients with kidney failure receiving hemodialysis, with a prevalence of 72.3% in 2020.[1] Hyperphosphatemia in dialysis patients is associated with an increased risk of both all-cause and cardiovascular mortality.[2] Cardiovascular disease occurs in 76% of the patients with kidney failure receiving hemodialysis, and accounts for over half of the deaths.[1] The potential role of hyperphosphatemia in mortality of patients with kidney failure prompts for approaches to reduce serum phosphate levels in this population.

Currently, the clinical strategies for managing hyperphosphatemia in kidney failure involve dialytic removal, limiting dietary phosphate intake, and the use of phosphate binders (PBs).[3] Despite 90% of patients with kidney failure being prescribed PBs, only 50% reach the recommended serum phosphate concentrations.[4] This low percentage can be partly attributed to poor adherence to PBs of patients

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with kidney failure.[5] Dialysis patients are instructed to ingest a certain number of PBs with each meal or snack depending on its phosphate content.[6] Besides this complex intake regimen, PBs have a high pill count and often cause side effects.[7,8] These factors may all contribute to the burden experienced by patients with kidney failure, resulting in nonadherence rates to PBs ranging from 22 to 74%.[9]

Daily supplementation with vitamin B3 may reduce the number of PBs that needs to be taken per day. Vitamin B3, either in the form of niacin or niacinamide (NAM), inhibits intestinal transport of dietary phosphate.[10,11] Consequently, the number of PBs that is needed to achieve normal phosphate concentrations could be reduced. In return, vitamin B3 does not need to be taken with every meal and has a lower pill count when compared to PB medication.[12,13] Thus, considering the advantages of vitamin B3 over PBs and its effect on the phosphate absorption pathway, vitamin B3 shows potential as "add-on" treatment in patients with resistant hyperphosphatemia.

Although a meta-analysis of 9 randomized controlled trials concluded NAM to be safe and effective for improving phosphate concentrations in hemodialysis patients, current guidelines do not yet recommend prescription of vitamin B3 as part of the treatment of hyperphosphatemia.[3,14] In 2013, we performed an open-label efficiency study with niacin in 21 dialysis patients, in which 66% of the patients stopped taking the pills due to side effects (unpublished data). We found a marked decrease in serum phosphate in patients who were able to tolerate the niacin. In fact, for some of these patients PB medication could be reduced. The well-established side effect profile of niacin is presumably the reason why niacin has not been integrated in the current guidelines. Studies on the vitamin B3-analog NAM to treat hyperphosphatemia in dialysis patients suggest NAM to lack many of the side effects that are observed with niacin.[14] Therefore, we performed a randomized crossover trial to investigate whether NAM is a feasible, effective and well-tolerated treatment in reducing serum phosphate concentrations in patients with kidney failure receiving hemodialysis.

Methods

Trial Design

DiaNia was a double-blind placebo-controlled randomized 12-week crossover trial. As our study period was long enough for phosphate concentrations to return to baseline in the placebo period, we decided to not include a washout period between the treatments. Figure 1 shows an overview of the trial design. The first 4 weeks participants orally ingested one tablet daily, corresponding to 250 mg NAM or placebo. After these 4 weeks, participants took two NAM or placebo tablets for the remaining 8 weeks, corresponding to a total dose of 500 mg.

Our trial is an investigator-initiated study. The study protocol was approved by both the Medical Ethics Committee of Wageningen University (METC-WU) (NL50499.081.14) and by the regional ethical board (Gelderse Vallei Hospital, Ede). The trial was conducted in accordance with the Declaration of Helsinki and registered in the Dutch registry for clinical studies and trials (https://www.toetsingonline.nl).

Participants

We informed hemodialysis patients from the dialysis unit in Gelderse Vallei Hospital, Ede, the Netherlands about the study. The research nurse or nephrologist notified eligible patients about the study and provided them with an information letter about the study from the university researchers. Patients who were interested to take part in the study could read further information in the Patient Information Folder. We included patients when they were > 18 years old, had a well-functioning shunt, were treated with PBs according to standard protocols established by Kidney Disease: Improving Global Outcomes (KDIGO),[15]

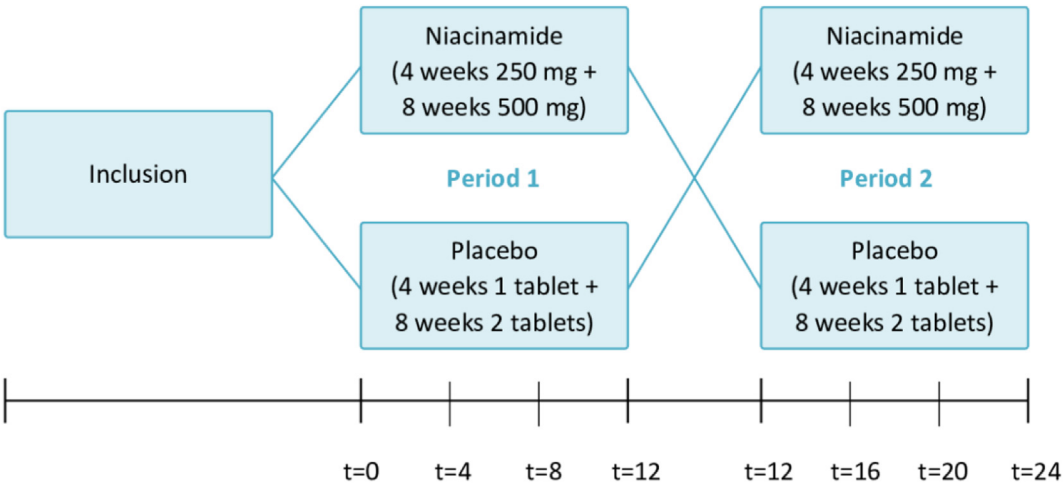

Figure 1. Schematic overview of the 2 × 12 weeks crossover study design of the DiaNia trial in 35 hemodialysis patients.

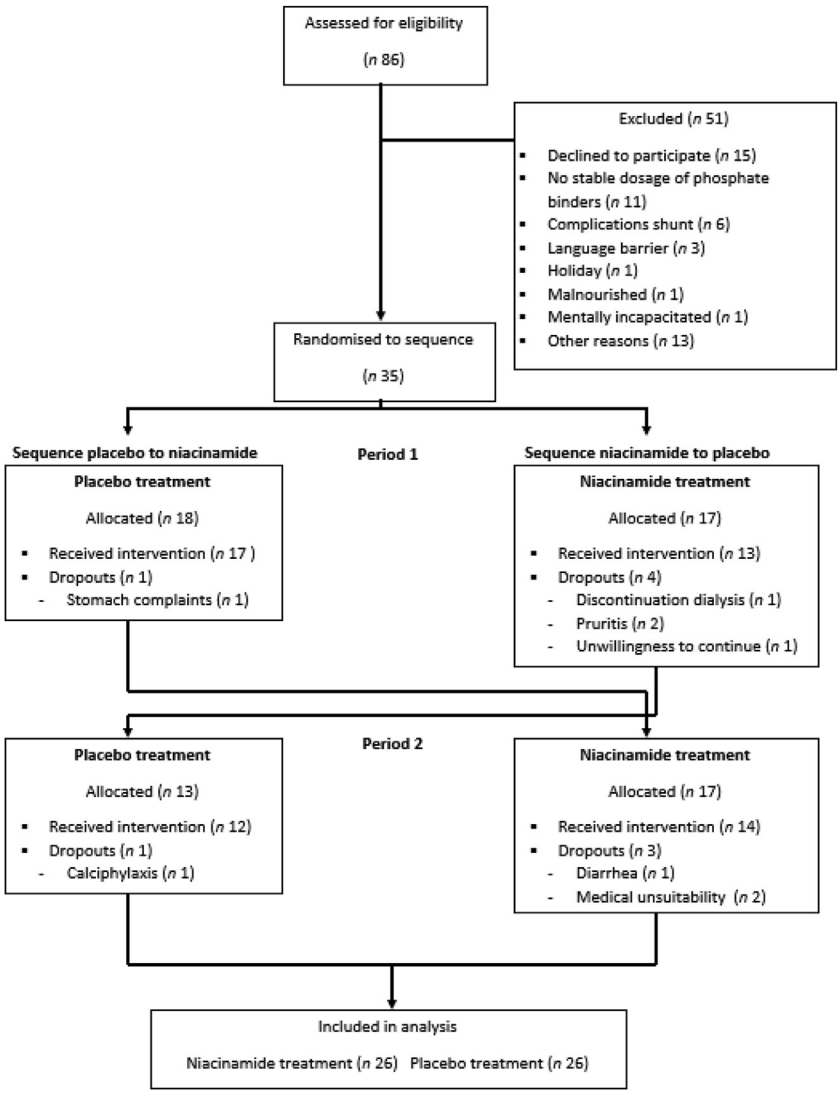

Figure 2. Flow diagram of the DiaNia study [based on the CONSORT (Consolidated Standards of Reporting Trials) statement[21]]. Participants were randomly assigned to 1 of the 2 sequences: NAM-Placebo or Placebo-NAM. NAM, niacinamide.

and were in a stable dialysis state (at least 6 months hemodialysis) as measured at baseline. We excluded patients when severely malnourished (as diagnosed by the department's dietitian), when treated with overnight dialysis or when not able to understand Dutch language. We obtained written signed informed consent from all participants.

Randomization and Blinding

We randomly allocated participants 1:1 to the treatment order by an individual study number, which corresponded to either NAM-placebo or placebo-NAM. For this purpose, we used a random number generator (https://www.randomizer.org/). Both researchers and participants were blinded to the group allocations.

Investigational Product

The investigational product was the food supplement NAM 250 mg of Orthica (hazard analysis and critical control points-certified). The pharmacy of Gelderse Vallei Hospital provided placebo tablets with identical appearance, which were free of calcium, magnesium, and aluminum to avoid phosphate binding. To reduce pill burden and side effects we decided to limit the final dose of NAM to 500 mg, which is slightly lower than the dose in previous studies.[16–22] Number and dosing of PBs remained unchanged during the intervention period *unless* serum phosphate concentrations became too low according to the treating nephrologist. The research nurse noted changes in medication.

Outcomes

The primary outcome is defined as the absolute change in serum phosphate concentrations during the use of NAM versus placebo. We considered a reduction in serum phosphate of at least 10% or 0.46 mg/dL to be clinically

Table 1. Baseline Characteristics in the PP Population[a]

Characteristics	NAM-Plac (n = 12)	Plac-NAM (n = 14)	Total (n = 26)
Age (in years)	62.7 ± 19.2	64.4 ± 16.1	63.6 ± 17.2
Sex (men), n (%)	3 (25.0)	11 (78.6)	14 (53.8)
BMI (kg/m^2)	27.9 ± 7.2	27.5 ± 6.3	27.7 ± 6.6
Diabetes, n (%)			
Type I	0 (0.0)	2 (14.3)	2 (7.7)
Type II	3 (25.0)	4 (28.6)	7 (26.9)
History of cardiovascular events†, n (%)	4 (33.3)	7 (50.0)	11 (42.3)
Months since start dialysis, median (IQR)	29.0 (26.5)	35.5 (32.8)	31.5 (32.8)
Serum phosphate (mg/dL)‡	4.46 ± 0.90	4.74 ± 0.90	4.61 ± 0.90
nPNA (g/kg lb)	1.21 ± 0.22	1.18 ± 0.15	1.19 ± 0.19
Subjective Global Assessment (SGA), n (%)			
3-5 (mild malnourished)	1 (8.3)	1 (7.1)	2 (7.7)
6-7 (well nourished)	11 (91.7)	13 (92.9)	24 (92.3)
Daily medication usage			
No. different types of medications	16 (4.5)	12 (1.8)	13 (4.0)
Phosphate binders, no. per participant	7 (4.3)	8 (4.5)	7 (4.0)
Total pills, no. per participant	15 (8.5)	15 (7.8)	15 (9.0)

BMI, body mass index; IQR, interquartile range; NAM, niacinamide; nPNA, normalized Protein Nitrogen Appearance; PP, per-protocol; SD, standard deviation.

*Results presented as mean ± SD, median and interquartile range (IQR) or number (percentage).

†History of cardiovascular events include coronary artery bypass grafting, abdominal aortic aneurysm, left ventricular hypertrophy, aortic valve sclerosis, myocardial infarction, transient ischemic attack, percutaneous transluminal angioplasty, endovascular aorta repair, non-ST elevation myocardial infarction, severe aortic stenosis, supraventricular tachycardia, cardiomyopathy and coronary disease.

‡Conversion factor for serum phosphate in mg/dL to mmol/L, x0.3229.

relevant. Despite this apparently small reduction, 0.46 mg/dL may be helpful to lower phosphate toward the normal range as defined by KDIGO.[15] In addition, it can possibly reduce the high pill burden of hemodialysis patients.

Secondary outcomes included the tolerability of NAM (defined as a dropout due to side effects less than 20%), supplement-related complaints (including nausea, diarrhea, and pruritis), and change in platelet count to determine whether NAM treatment increases the risk of thrombocytopenia in hemodialysis patients.[14]

Data Collection

At the start of study enrollment, we collected demographic and baseline clinical data from the patient file. These data included age, sex, body mass index, duration since start of hemodialysis, daily medication usage and comorbid conditions, including diabetes and cardiovascular events. We obtained serum phosphate concentrations at baseline during routine measurements. During the study, we monitored drop-outs and noted reasons for drop-out.

Nutritional Status

The renal dietitian monitored nutritional status using the Subjective Global Assessment.[23] Taking into account the association between hyperphosphatemia and protein-energy wasting, the renal dietitian monitored protein intake and body weight.[24] We monitored protein intake by means of protein nitrogen appearance normalized to lean body mass.

Laboratory Assessments

Serum phosphate concentrations are measured every 4 weeks as part of routine medical care. This resulted in a total of 7 consecutive serum phosphate measurements (t = 0, t = 4, t = 8, t = 12, t = 16, t = 20, and t = 24) during the intervention period. Platelet counts were measured once in 3 months. This resulted in a platelet count measurement at baseline, the end of period 1 (week 8/12) and at the end of period 2 (week 20/24) for each participant. All laboratory analyses were performed at the Clinical Chemistry lab of Gelderse Vallei Hospital, Ede, the Netherlands.

Statistical Analysis

We analyzed data in both the per-protocol (PP) population and the intention-to-treat (ITT) population. First, we conducted independent t-test for an effect of sequence ("NAM-Plac" vs. "Plac-NAM") on serum phosphate levels and platelet counts. With paired t-tests we compared the differences in serum phosphate and platelet counts before and after treatment (NAM or placebo). For this purpose, we log-transformed the data of platelet counts. To compare the overall difference of serum phosphate and platelet counts between the 2 groups, we used linear mixed-effects models (LMMs). Treatment group (NAM or placebo), time (0,4,8, and 12 weeks), and treatment-by-time interaction represented the fixed effects, and participants the random effect. We employed an autoregressive covariance structure for the repeated factor of time. We performed the statistical analyses using IBM SPSS Statistics

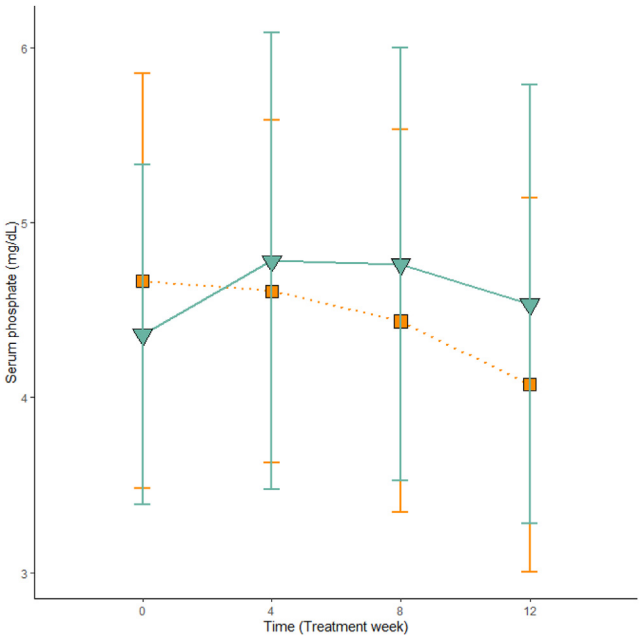

Figure 3. Mean serum phosphate concentrations at baseline and at 4, 8, and 12 weeks in the PP population after initiating treatment: NAM (□) versus Placebo (▽). Data are given as mean ± SD. Conversion factor for serum phosphate in mg/dL to mmol/L, x0.3229. NAM, niacinamide; SD, standard deviation.

(version 29; IBM Corp., Armonk, NY, USA), and R software (version 4.2.1; https://www.r-project.org). We considered a significance level of 0.05 as statistically significant. Data are expressed as means ± standard deviation (SD), median (interquartile range) or frequency, as appropriate.

Sample Size Calculation

Based on a pilot study (unpublished data) and results from literature we decided a difference of 0.46 mg/dL (0.15 mmol/L) in serum phosphate to be the minimal desired effect.[16,22,25,26] The SD of similar changes in serum phosphate in patients in Gelderse Vallei Hospital was 0.53 mg/dL (0.17 mmol/L). Considering an SD of 0.62 (0.20 mmol/L), 19 participants were required to detect a minimal difference of 0.46 mg/dL with a power of 80% at an α level of 0.05. To correct for a 30% dropout during the study, we aimed to recruit a total of 30 participants.

Results

Patient Population

Between September 2015 and June 2016, we screened a total of 86 patients on the dialysis ward in Gelderse Vallei Hospital for eligibility. After excluding 51 of these patients, we randomized 35 individuals (NAM-Plac: n = 17; Plac-NAM: n = 18) into the study (Figure 2).[27] The proportion of study completers was 71% in the NAM-Plac and 78% in the Plac-NAM group. Reasons for exclusion and study discontinuation are summarized in Figure 2. Baseline characteristics are shown in Table 1 and Table S1 for the PP and ITT population, respectively. In the PP population, there were substantially more men in the Plac-NAM group (78.6%) than in the NAM-Plac (25.0%). Among the 26 participants in the PP population, the mean (±SD) age was 63.6 ± 17.2 years, 53.8% were men, and the mean body mass index was 27.7 ± 6.6 kg/m^2. Mean serum phosphate was 4.61 ± 0.90 mg/dL with a median and interquartile range daily PB use of 7 (4.0).

Serum Phosphate

Treatment sequence (NAM-Plac vs. Plac-NAM) neither affected serum phosphate levels in the PP population (P = .86) nor in the ITT population (P = .47). Figure 3 shows the time course of serum phosphate in the PP population. Twelve weeks of NAM significantly decreased serum phosphate concentrations with 0.59 mg/dL (P = .03) in the PP population, while 12 weeks of placebo slightly increased

Table 2. Baseline and Week 4, 8, and 12 Values for Serum Phosphate in the ITT and PP populations*

	NAM		Placebo	
Serum Phosphate (mg/dL)†	ITT Population (n = 35)	PP Population (n = 26)	ITT Population (n = 35)	PP Population (n = 26)
Week 0	4.88 ± 1.34	4.67 ± 1.18	4.69 ± 1.36	4.36 ± 0.97
Week 4	4.74 ± 1.34	4.61 ± 0.98	5.00 ± 1.36	4.78 ± 1.30
Week 8	4.68 ± 1.34	4.44 ± 1.09	5.12 ± 1.36	4.76 ± 1.23
Week 12	4.55 ± 1.36	4.07 ± 1.07	4.73 ± 1.36	4.53 ± 1.25
Change‡	−0.33	−0.59§	0.046	0.17
Difference in change compared to placebo	0.38 (−0.28, 1.05)	0.77 (0.010, 1.43)‖	-	-

ITT, intention-to-treat; NAM, niacinamide; PP, per-protocol; SD, standard deviation.
*Values are presented as mean ± SD or as mean (95% CI).
†Conversion factor for serum phosphate in mg/dL to mmol/L, x0.3229.
‡Total change over the 12-week intervention period.
§Significant change over the 12-week intervention period, $P < .05$ (paired t-test).
‖Significantly different from placebo treatment, $P < .05$ (LMMs).

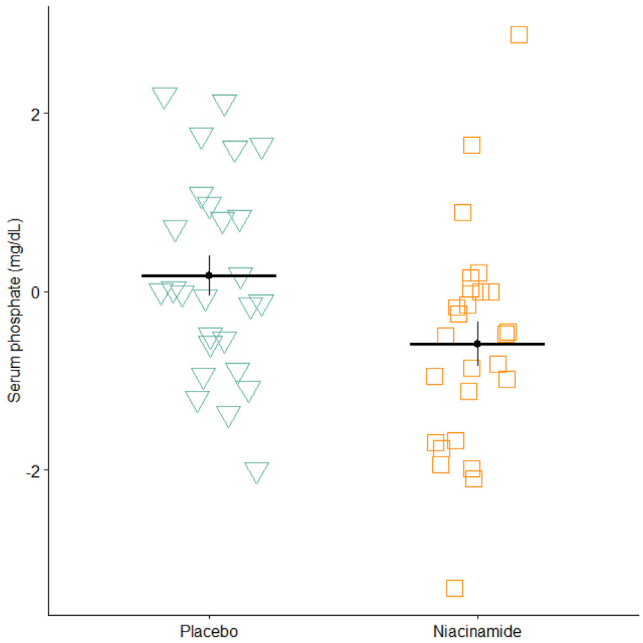

Figure 4. Change in serum phosphate concentration over the 12-week intervention period in response to treatment (NAM (□) versus Placebo (▽)) in the PP population. Conversion factor for serum phosphate in mg/dL to mmol/L, x0.3229. NAM, niacinamide; PP, per-protocol.

serum phosphate concentrations with 0.17 mg/dL ($P = .44$) (Table 2). LMMs demonstrated superiority of 12 weeks NAM over 12 weeks placebo in the PP population with a between-treatment difference of 0.77 mg/dL (95% CI 0.010, 1.43; $P = .03$) (Figure 4). We found similar results, although not significant, in the ITT (n = 35) population (Figure S1, Figure S2 and Table 2).

Platelet Count

Treatment sequence (NAM-Plac vs. Plac-NAM) neither affected platelet counts in the PP population ($P = .76$) nor in the ITT population ($P = .81$). For platelet counts, we found no significant changes upon both the NAM ($-19.8 \times 10^3/\mu L$; $P = .07$) and placebo treatment ($-16.1 \times 10^3/\mu L$; $P = .18$) in the PP population. We found a nonsignificant difference in change of $3.7 \times 10^3/\mu L$ between the 2 treatments (95% CI -17.2, 24.7; $P = .72$). Similarly, we found a nonsignificant difference of $0.68 \times 10^3/\mu L$ between the 2 treatments (95% CI -17.9, 16.5; $P = .94$) in the ITT population.

Tolerability

We reported 7 (20.0%) drop-outs during the NAM treatment, of which 3 (8.6%) were because of side effects. The reported side effects included diarrhea (n 1) and pruritis (n 2). The remaining four drop-outs were reported as a consequence of discontinuation of dialysis (n 1), septic shock (n 1), kidney transplantation (n 1) and language barrier (n 1). During placebo treatment, we reported 2 (5.7%) additional drop-outs due to stomach complaints (n 1) and calciphylaxis (n 1).

Serious Adverse Events (SAEs)

We reported 2 SAEs during the study period. One participant (allocated to NAM-Plac) was transferred to intensive care because of a septic shock. Another participant (allocated to Plac-NAM) died after discontinuation of dialysis. Both these SAEs occurred during NAM treatment but were not related to the study.

Discussion

To the best of our knowledge, this is the first randomized crossover trial that investigated the efficacy and tolerability of NAM as "add-on" treatment to reduce serum phosphate concentrations in Dutch hemodialysis patients. Four weeks of 250 mg NAM followed by 8 weeks 500 mg NAM significantly reduced serum phosphate concentrations in patients with kidney failure receiving hemodialysis compared to placebo treatment. The drop-out rate due to side effects was low and we found no significant changes in platelet counts in response to NAM.

Our results suggest that NAM is a well-tolerated "add-on" treatment to combat hyperphosphatemia in patients with kidney failure receiving hemodialysis. Regarding the decrease in serum phosphate concentrations by NAM, our results confirm previous studies in patients with kidney failure.[16–22] These studies used doses starting from 500 mg NAM up to 2000 mg/day[16–20] or similar doses multiple times per day.[21,22] They all found a significant effect of NAM on serum phosphate concentrations in a similar order of magnitude we found in our study.[16–22] The relatively low dose of NAM in DiaNia could explain the low drop-out rate due to side effects we found in our study. Whereas studies using higher doses of NAM observed complaints such as thrombocytopenia, nausea and diarrhea,[16–22] we found only 1 case of diarrhea and 2 cases of pruritis upon NAM treatment. In addition, in 4 participants of the NICOREN study, a fall in platelet counts <70 000/μL was demonstrated after 4-8 weeks of 1000 mg NAM/day.[20] In line with this, 25% of the patients in the study of Shahbazian and colleagues developed thrombocytopenia after 8 weeks of 500-1000 mg NAM/day.[16] Contrarily, in none of our participants platelet counts decreased significantly in response to 12 weeks of NAM. Therefore, it can be speculated that the 250-500 mg/day of NAM we used in DiaNia is optimal for patients with kidney failure to reduce serum phosphate concentrations while preventing its adverse effects and the development of thrombocytopenia.

Interestingly, we demonstrated a phosphate-lowering effect of NAM in a patient population with baseline serum phosphate within the normal range (4.61 ± 0.90 mg/dL) according to KDIGO guidelines.[3] Controlled serum phosphate concentrations in our population, together with the

small sample size and short duration of the study, potentially affect its generalizability to the wider dialysis cohort. Namely, about 50% of the hemodialysis patients seems to achieve these KDIGO guideline targets regarding serum phosphate.[4] An even more striking effect of NAM could be expected among patients with persistent hyperphosphatemia despite treatment.

Whereas one-quarter (n = 9) of the randomized patients dropped out of this trial, only 3 drop-outs (8.6%) could be attributed to side effects of NAM. When comparing this drop-out rate of 8.6% to the drop-out rate due to side effects of 66% in our previously performed open-label study with niacin, we can conclude that NAM is much better tolerated than niacin in patients with kidney failure. For instance, NAM does not produce one of the most prominent side effects of niacin: flushing. This can be explained by the fact that NAM is, in contrast to niacin, not a vasodilator.[28] Consequently, NAM does not stimulate prostaglandin D2 and E2 secretion, which causes the flushing upon niacin.[29] Thus, taking the side effect profiles into account, the use of NAM is preferred over the use of niacin to reduce serum phosphate in patients with kidney failure receiving hemodialysis.

To date, research on the underlying mechanism of NAM in reducing hyperphosphatemia is limited to experimental animal models. In rodents, NAM reduces hyperphosphatemia through an effect on the gastrointestinal sodium-dependent phosphate transporter NaPi2b.[11,30] Approximately 50% of the phosphate absorption is mediated through this cotransporter.[30] NAM seems to inhibit phosphate absorption through reducing the NaPi2b expression.[11] Interestingly, dietary and pharmacological phosphate restriction leads to a maladaptive upregulation and increased activity of NaPi2b in several animal models.[31-34] Therefore, the use of NAM as NaPi2b inhibitor in addition to PBs seems an acceptable approach to manage serum phosphate in patients with kidney failure. However, it should be kept in mind that the mechanism is not yet fully understood and should be confirmed by human trials.

Before advocating more research on strategies to lower phosphate concentrations, beneficial effects of reduced serum phosphate in hemodialysis patients need to be confirmed by trials. At present, the evidence regarding serum phosphate and (cardiovascular) mortality is limited to associations. Large clinical trials are necessary to demonstrate whether lowering serum phosphate truly leads to beneficial outcomes in dialysis patients. Fortunately, such valuable clinical trials, PHOSPHATE (NCT03573089) and HiLo (NCT04095039), are now being performed.

A limitation of our study is that compliance was not objectively measured. Nevertheless, dietitians and research nurses involved in the trial and dialysis treatment of these patients closely monitored compliance and affirmed an overall good compliance. In addition, a carry-over effect could have been expected, since no washout period was integrated in our crossover design. However, the presence of a carry-over effect can be (partly) refuted by no significant effect of treatment sequence on both serum phosphate and platelet counts. Besides, the crossover design allows comparison of the treatment effect within participants, since each participant served as his or her own control. This is an advantage of our study, since individual patient variability plays a role in several determinants of phosphate control. Namely, dialytic removal, phosphate absorption and PB efficacy may all differ between patients.[35] Similar results in the ITT and PP population strengthen our study as well, since analyzing data using an ITT protocol reduces confounding due to nonrandom drop-out.

It should be mentioned that PB medication is not without side effects either. For example, the use of sevelamer, lanthanum, and iron-based binders may lead to gastrointestinal complaints and gastrointestinal mucosal injury.[8,36] Additionally, sometimes different PBs are combined to allow prescribing lower doses to reduce side effects of the medication. However, there is hardly any research investigating the safety of the use of a combination of PBs. Considering these aspects of PBs and the good tolerability of NAM we found in our study, the implementation of NAM in the treatment of hyperphosphatemia seems a rational resolution.

Nonetheless, the current guidelines only recommend further research on NAM as "add-on" treatment in patients with resistant hyperphosphatemia.[3] Acknowledgment of NAM as treatment of hyperphosphatemia might encourage payment models to reimburse NAM in the future. In the long term, partial replacement of PBs by NAM could save costs. Furthermore, when the number of PBs can be reduced as a result of NAM, this will lower the high burden patients experience and presumably increase adherence to their pill regimen. DiaNia provides more evidence on the efficacy and safety of NAM, which encourages the integration of NAM in the guidelines as treatment of hyperphosphatemia.

In conclusion, with DiaNia we demonstrate that 250-500 mg NAM per day effectively reduced serum phosphate concentrations in patients with kidney failure receiving hemodialysis. Moreover, NAM is well-tolerated and seems not to increase the risk of thrombocytopenia in this population. However, further research should establish an "optimal dose" of NAM to reduce serum phosphate concentrations while avoiding its possible adverse effects, including the development of thrombocytopenia. Besides, future studies should assess the long-term safety of NAM.

Practical Application

Our study provides evidence that 250-500 mg NAM per day can be safely integrated in the treatment of

hyperphosphatemia in patients with kidney failure. This dose is sufficient to reduce serum phosphate concentrations while it seems not to come with side effects or an increased risk of thrombocytopenia. The use of NAM as "add-on" treatment may lower the number of PBs and with that the burden patients experience. Consequently, side effects of PBs will be avoided and adherence to the pill regimen will be increased in patients with kidney failure. Moreover, (partial) substitution of PBs by NAM could eventually save costs.

CRediT authorship contribution statement

Lara Schepers: Formal analysis, Writing – original draft, Visualization. **Inez Jans:** Conceptualization, Data curation, Investigation, Writing – review & editing. **Gerda K. Pot:** Writing – review & editing. **Arend-Jan Smilde:** Conceptualization, Project administration. **Julia M. Hofstra:** Formal analysis, Writing – review & editing. **Nicole M. de Roos:** Methodology, Conceptualization, Formal analysis, Writing – review & editing.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1053/j.jrn.2024.02.005.

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