A COMBINED, TAILORED PHARMACIST INTERVENTION WITH DOSE OPTIMIZATION OF PHOSPHATE BINDING DRUGS TO IMPROVE PHOSPHATE CONTROL IN PATIENTS ON DIALYSIS

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KEYWORDS

Hyperphosphatemia,
Adherence,
Phosphate binder,
Pill burden,
End-stage Renal Disease,
Hemodialysis

ABSTRACT

Background: Hyperphosphatemia is a common complication in end-stage renal disease (ESRD) patients despite phosphate binder treatment. Low adherence to phosphate binders due to a high pill burden is an important factor. A combined, tailored pharmacist intervention with dose optimization was implemented focusing on therapeutic-related factors and patient-related factors to obtain phosphate control in hemodialysis (HD) patients.

Methods: This study was conducted at a hospital in The Netherlands as a single-centre, intervention study with a within patient pre-post design. In order to identify potential patient adherence barriers, we implemented an individualized intervention. Firstly, multiple pharmacist counselling sessions were performed to identify potential patient adherence barriers with Quick Barrier Scan (QBS), the medication adherence was investigated with the Medication Adherence Report Scale (MARS-5) and the Recognizing and Addressing Limited Pharmaceutical Literacy (RALPH) interview guide was used to explore the patients' health literacy. Secondly, the pharmacist implemented tailored intervention with dose optimization. Finally, the serum phosphate control was evaluated after the intervention.

Results: A total of 28 patients were enrolled in the study for the analysis of serum phosphate level and MARS-5. Mean baseline serum phosphate level was 2.02 mmol/L (SD = 0.45). Serum phosphate level at month 1 decreased to 1.86 mmol/L (SD=0.43). A similar result was found for month 2 and 3 (1.98 mmol/L). However, the paired T-test showed no significant effect in changes in serum phosphate level between pre-intervention and 1,2 and 3 months after intervention ($p = 0.125$, $p = 0.630$ and $p = 0.690$). In addition, the percentage of patients with phosphate regulation (≤ 1.50 mmol/L) increased from 0% (n=28) at baseline, to 21.4%% (n=28) and 17.9% (n=27) and 14.3% (n=28) for 1,2 and 3 months after the intervention respectively. Total MARS-5 scores at pre-intervention resulted in a median (IQR) score of 0.3 (0.0-0.6) and a median (IQR) score of 4.8 (0.4 – 5.0) 3 months after the intervention.

Conclusion: This study highlights the importance of personalized patient counselling sessions in combination with lowering phosphate binder pill burden to positive effects on the serum phosphate levels and phosphate binder adherence. However, the change in serum phosphate level was no significant. Notwithstanding the relatively limited sample size, this study offers valuable insights into personalized intervention with dose optimization to improve phosphate control. Therefore, this study lays the groundwork for future research into personalized intervention strategies.

1 Introduction

Elevated serum phosphate (hyperphosphatemia) is a common complication in end-stage renal disease (ESRD) patients despite available treatments (1,2). Hyperphosphatemia is associated with increased risk of cardiovascular morbidity and mortality, secondary hyperparathyroidism and mineral bone disorders (3,4). Therefore, management of serum phosphate levels is important to improve the prognosis of patients on dialysis. Management of hyperphosphatemia depends on three approaches: pharmacological management with phosphate binders, dietary phosphate restriction, and removal of phosphate through dialysis (5). As dietary restriction and phosphate removal during dialysis alone are inadequate to control serum phosphate levels, phosphate binders are extensively used among patients

with ESRD. Although all three treatments are effective in lowering phosphate levels, an extensive part of hemodialysis (HD) patients continue to suffer from uncontrolled hyperphosphatemia (6). Approximately 45% of all HD patients has serum phosphate levels above the normal range of 0.80 – 1.50 mmol/L (7). Low adherence to phosphate binders is an important factor for uncontrolled hyperphosphatemia (8).
Challenges to phosphate binders adherence include 1) medication-related factors such as high pill burden and medication complexity: the high dosage frequency, specific administration instructions and timing during meals; and 2) patient-specific factors such as limited health literacy, limited knowledge about the importance of taking phosphate binders and forgetfulness (8–11). Especially, the high pill burden seems to be the most important barrier for low phosphate binder adherence (12).

Lower adherence to phosphate binders was reported when the pill burden increased(13,14). Several studies have shown an increase in patient adherence by using multiple interventions targeting therapeutic factors and patient factors (15–19). According to these studies, personal guidance and multiple personal sessions with a pharmacist are important interventions to obtain positive changes in serum phosphate and adherence to phosphate binders among HD patients (13,15). However, the effect of reducing high phosphate binder pill burden among HD patients with hyperphosphatemia on phosphate control remains unknown. In addition, potential barriers which are involved in phosphate binder adherence need more research as well. Therefore, this study investigated a combined, tailored pharmacist intervention strategy.

Aim of the study
The primary aim of this study was to evaluate whether a lower phosphate binder pill burden in combination with personalized patient counselling would improve serum phosphate level in HD patients who suffer from uncontrolled hyperphosphatemia and a high phosphate binder pill burden. Our secondary aims were to investigate (1) the medication adherence before and after the intervention, (2) the pharmaceutical literacy and, (3) potential barriers for medication adherence. We hypothesized that reducing the phosphate binder pill burden in combination with individualized patient counselling would lead to reduced phosphate levels with a minimum of 0.25 mmol/L, due to increasing phosphate adherence (20).

2 Method

Study design
This was a single centre, intervention study with a within patient pre-post design. The study was conducted at the Franciscus Gasthuis & Vlietland (FGV) hospital. Approval was obtained from the Medical research Ethics Committees United (MEC-U). This study does not match the scope of the Dutch Medical Research Involving Human Subjects Act (Dutch: WMO), as the intervention has no risks and patient burden is minimal.

Study population
The study population consisted of patients with ESRD and hyperphosphatemia, who were recruited from the FGV hospital. Patients were considered eligible if they met the following criteria: (1) prescription of 6 or more phosphate binder units daily (as described in *Appendix I*), (2) both a mean serum phosphate level over the last 3 months and the last serum phosphate level higher than 1.50 mmol/L, (3) a minimum age of 18 years or older, (4) medication dispensed by Poli-apotheek Franciscus Gasthuis & Vlietland, (5) intermittent HD for at least 3 months preceding the inclusion date (6) HD during entire follow-up, (7) sufficient language proficiency to comprehend instructions concerning study procedures. Patients were excluded from the study if they were living in nursing home or suffering from cognitive impairment. Based on these criteria, we identified and included patients during monthly screenings of the hospital database HiX.

The intervention
An expert team consisting of pharmacist, nephrologist, sociologist and dietician approved the intervention materials prior to the study. In order to identify potential patient adherence barriers, we implemented an individualized intervention. The intervention consisted of multiple counselling sessions with the pharmacist. These visits were scheduled during HD treatment of the patients to prevent extra hospital visits. The visit schedule for this study consisted of 3 visits; and an extra visit was added when necessary. The pharmacist used the teach-back method to improve information delivery and used shared decision-making regarding preferences of phosphate binders (21,22).

<u>Visit 1: Patient barrier identification</u>
The Quick Barrier Scan (QBS, *Appendix II*) was used for exploring patients' barriers to adherence to medication during the first visit at the HD department. The QBS is a semi-structured interview guide consisting of 15 questions (13 closed and 2 open questions) representing various barriers, such as patients' knowledge, self-motivation, adverse events, forgetfulness, and difficulties with medication (23). Based upon the identified barrier(s), we chose the Intervention Module (IM) according to the Tailored Intervention Guide (TIG, *Appendix III*). This guide consists of five intervention modules for implementation by the pharmacist to overcome patients' barriers to adherence. The QBS and TIG were adapted for HD patients, based upon studies and reviews, since they were primarily designed to inform patients with diabetes and hypertension (23). Next, the Recognizing and Addressing Limited Pharmaceutical Literacy (RALPH, *Appendix IV*) was used to explore pharmaceutical literacy of the patients. Finally, we assessed medication adherence by using MARS-5. This questionnaire comprises five statements of adherence-related behaviour (*Appendix V*) rated on a five-point scale, from 1 (always) to 5 (never). MARS-5 score was determined by summing up the scores, where a high score indicates better adherence.

Visit 2: information and advice

The identified barriers were discussed during the second visit. Visit 2 was scheduled 1-2 weeks after the first visit to discuss: (1) the suitable IM from the TIG, (2) information about hyperphosphatemia, phosphate binders, their use and, (3) patients' beliefs about hyperphosphatemia and its treatment, (4) intervention recommendations, (5) patients' preferences regarding phosphate binders drugs, (6), a dose reduction of phosphate binders to reduce pill burden (*Appendix VI*) (7) written summary of the visit, including the information, recommendations and dose reduction advice.

Visit 3: Follow-up visit

The follow-up visit was scheduled approximately 3 months after the first visit. During this visit patients' experiences with the intervention were discussed. Also, MARS-5 was used to measure the medication adherence after 3 months. After visit 3, patients returned to usual care and no further pharmacist interventions, such as patients visit, were carried out.

Extra visit: encountered problems

We incorporated an extra visit when an increase of at least 30% was observed in the phosphate level or when the phosphate level was higher than 2.0 mmol/L during the first 3 months of follow-up. During this visit, the pharmacist discussed the potential problems patients encountered and the needs of the patients.

Laboratory parameters

Laboratory parameters measured were serum phosphate levels, (corrected) calcium levels, nPCR, PTH and Vitamin D; pre- and post-intervention at month 3 (*Appendix VII*). The primary outcome measure was the difference between the serum phosphate level before and 1,2 and 3 months after the intervention. The secondary outcome measures were: (1) the medication adherence before and after the intervention measured with MARS-5, (2) the pharmaceutical literacy and, (3) potential barriers for medication adherence.

Statical analysis

All the collected data during the study were documented and coded in Castor EDC per patient. This GCP-proof program saves all research data for the standard retention period of 15 years. All analysis was conducted using SPSS (IBM SPSS Statistics version 28, Armonk, New York, USA). For the sample size calculation, we used a standard deviation of 0.5 mmol/L for the phosphate level reduction according to historical data. This led to an effect size of 0.5 based on paired samples T-test, a normal distribution, with a 2-tailed alfa level of 0.05 and 95% power (calculated in G*Power version 3.1, University of Kiel, Germany). For a statistically significant change in the primary outcome, a sample size of 45 patients was necessary.

Descriptive statistics were presented using mean, standard deviation (SD), range and proportion, as appropriate. Comparison of means for continuous variables was analyzed using paired T-test for normally distributed data and Wilcoxon-signed rank test for non-normally distributed data. The differences between the serum phosphate level before the intervention and the serum phosphate level at 1,2 and 3 months after the intervention were analysed with a paired T-test.

We used the Wilcoxon signed-rank test to examine the medication adherence before and 3 months after the intervention. Scores for each MARS-5 item before and after the intervention were summed for total scores, with higher scores indicative for high adherence and lower scores for low adherence. For all analyses, p-values <0.05 were considered significant. Data of patients with uncomplete follow-up, due to e.g. transplantation or death, were analyzed until they were lost to follow-up. Thereafter the data were considered as missing values.

3 Results

Patient characteristics

A total of 44 patients met the study inclusion criteria. Patients with uncomplete follow-up were excluded later in de data analysis process. 44 patients were included into the QBS and RALPH analysis. 16 patients were excluded later because of not completing the 3 months follow-up period and unknown serum phosphate level at month 3 after the intervention. The total sample for the serum phosphate level analysis consisted of 28 patients (62.2% of the sample size calculation) with ESRD and hyperphosphatemia recruited from the FGV hospital. For the MARS-5 analysis 26 patients completed the visit 3 (*Figure 1*). Table 1 shows the baseline characteristics of the study population (n=28 and n=44). Most of the patients included in the study were male (67.9% in n=28 and 63.6% in n=44). In addition, the study population consisted of patients with a mean age (±SD) of 66 (15) years, ranging from 34-86 years old (n=28). The majority of the patients (n=28) were Dutch (50%), followed by Surinamese (25%). The main primary diagnosis of ESRD was hypertension (39.3%, n=28). The study population had a mean serum phosphate level of 2.02 mmol/L at the baseline (n=28), ranging from 1.56-3.45 mmol/L. Total phosphate pill burden was 9.60 units at the baseline (n=28). There were minor differences between the groups of 28 patients and 44 patients in the characteristics.

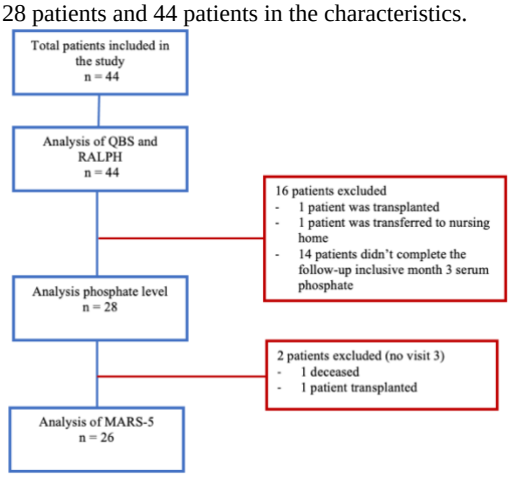

Figure 1. Flow of patients through the study analysis.

Characteristics	n = 28			n = 44		
	Mean	SD	Range	Mean	SD	Range
Year of birth	1957	14.87	1936-1988	1957	16.60	1936-1993
Baseline pre-dialysis weight	81.59	19.08	49.9-124.9	81.39	16.43	49.9-124.9
Baseline biomarkers						
- Phosphate (mmol/L)	2.02	0.45	1.56-3.45	2.05	0.44	1.41-3.45
- Calcium (mmol/L)	2.31	0.20	1.96-2.72	2.26	0.18	1.95-2.72
- Corrected calcium (mmol/L)	2.35	0.23	1.92-3.03	2.29	0.22	1.78-3.03
- PTH (pmol/L)	50.60	46.08	2.2-148.7	59.14	46.08	2.2-212
- Vitamin D (nmol/L)	87.32	25.14	33-168	81.59	23.53	33-168
Phosphate pill burden pre-intervention	9.60	3.63	5-21	8.83	3.07	3-18
		n	%		n	%
Gender						
Male		19	67.9		28	63.6
Female		9	32.1		16	36.4
Country of origin						
Netherlands		14	50.0		27	61.4
Suriname		8	25.0		9	20.5
Turkey		2	7.1		2	4.5
Cabo Verde		2	7.1		2	4.5
Nigeria		2	7.1		3	6.8
Greece		1	3.6		1	2.3
Medication delivery						
Baxter		19	67.9		33	75.0
Independent medication request		9	32.1		11	25.0
Primary renal diagnosis						
Hypertension		11	39.3		17	38.6
Miscellaneous		8	28.6		9	20.5
Diabetes mellitus		4	14.3		8	18.2
Glomerulonephritis or sclerosis		4	14.3		5	11.4
Polycystic kidney disease, adult type		1	3.6		1	2.3
Unknown		0	0.0		4	9.1

Table 1. Baseline characteristics of patients (n=28 and n=44).

Change in serum phosphate levels

First, we examined changes in serum phosphate levels pre-intervention and 1,2 and 3 months after the intervention (*Table 2*). Part of this intervention was dose reduction according to the algorithm (*Appendix VI*), which led to a reduction in phosphate binder units (PBU) compared to the PBU before the intervention. The study population started with a mean PBU of 9.6, ranging from 5-21 PBU per day. After the intervention, PBU was reduced to a mean of 5.3, ranging from 3-10.5 PBU per day.

Baseline serum phosphate level was 2.02 mmol/L (SD = 0.45). Serum phosphate level at month 1 decreased to 1.86 mmol/L (SD=0.43). A similar result was found for month 2 and 3 (1.98 mmol/L). However, the paired T-test showed no significant effect in changes in serum phosphate level between pre-intervention and 1,2 and 3 months after intervention (p = 0.125, p = 0.630 and p = 0.690) (*Table 2*).

After analyzing the change in serum phosphate levels during the intervention, we analyzed the percentage of patients with mean phosphate levels of 1.5 mmol/L or lower, before and 1,2 and 3 months after intervention (*Figure 2*). Patients were split into two groups: patients with serum phosphate regulation or patients without serum phosphate regulation. Regulation of phosphate was defined as serum phosphate levels of 1.5 mmol/L or lower. The percentage of patients with phosphate regulation increased from 0% (n=28) at baseline, to 21.4%% (n=28) and 17.9% (n=27) and 14.3% (n=28) for month 1,2 and 3 months after the intervention respectively.

VARIABLE	N	MEAN (mmol/l)	SD	MINIMUM	MAXIMUM	P-VALUE
PHOSPHATE LEVEL PRE-INTERVENTION	28	2.02	0.45	1.56	3.45	
PHOSPHATE M1	28	1.86	0.43	0.99	2.76	Pre-intervention versus phosphate m1: p = 0.125
PHOSPHATE M2	27	1.98	0.55	0.98	3.54	Pre-intervention versus phosphate m2: p = 0.630
PHOSPHATE M3	28	1.98	0.42	1.25	2.99	Pre-intervention versus phosphate m3: p= 0.690

Table 2. Serum phosphate levels before and 1,2 and 3 months after the intervention, with m1= 1 month after intervention, m2= 2 months after intervention and m3= 3 months after intervention. Last column reports the results of paired T-test of change in serum phosphate levels pre-intervention compared to phosphate level 1,2 and 3 months after intervention.

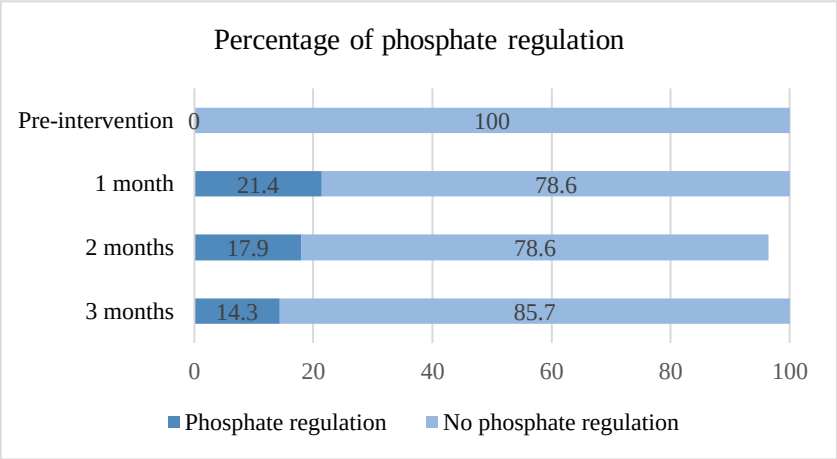

Figure 2. Percentage of patients is controlled (dark blue) and uncontrolled (light blue) pre and 1,2 and 3 months after intervention. Controlled phosphate level is defined as 1.5 mmol/L or lower and uncontrolled phosphate level as > 1.50 mmol/L.

Medication adherence

To assess medication adherence, we analyzed the MARS-5 questionnaire results pre-intervention and 3 months after the intervention. Total MARS-5 scores at pre-intervention resulted in a median (IQR) score of 0.3 (0.0-0.6) and a median (IQR) score of 4.8 (0.4 – 5.0) 3 months after the intervention (*Table 3*). There was a significant improvement in self-reported adherence to phosphate binder after the intervention ($p < 0.001$).

Variable	N	Median	IQR	P value	Z-statistic
Medication adherence pre-intervention	26	0.3	0.0 - 0.6		
Medication adherence 3 months after intervention	26	4.8	0.4 – 5.0	<0.001[a]	-3.905[b]

a. p-value of medication adherence pre-intervention compared to medication adherence after intervention

b. Z-statistic based on negative ranks

Table 3. *Descriptive statistics (Median and IQR) of the medication adherence pre-intervention and 3 months after the intervention. Results of statistical analysis with Wilcoxon signed-rank test of change in medication adherence pre-intervention compared to after intervention.*

RALPH

We explored the patients' pharmaceutical literacy by using RALPH interview guide. Table 4 shows an overview of patients' answers. The RALPH interview guide explores patients' pharmaceutical literacy skills in three domains: (1) Functional skills referring to basic reading and writing skills that allow someone to correctly interpret medication instructions, precaution or warnings (blue box), (2) communication skills referring to skills that allow someone to find understandable (medication) information and to express concerns about the medication (red box) and (3) critical skills referring to more advanced skills that allow someone to critically analyse (medication) information and apply this information to their own situation (green box). By summing up the percentages for each domain, patients had least problems with their communication skills (4.5% + 4.6% + 4.5% + 47.7% = 61.3%), followed by their functional skills (6.8% + 45.5% + 13.6%. + 6.8% = 72.7%) and their critical skills domain (6.8% + 54.5% + 9.1% + 52.3% + 4.5% + 29.5% + 25% = 181.7%).

Sevelamer tablets were discussed for the first 3 questions. Most patients (54.5%) were able to give the correct reason of taking their phosphate binders. In addition, the majority of the patients (75%) would take the initiative to search for correct information in reliable sources when they would receive different information about their medication. However, 52.2% of the patients found it hard to find information about this medicine in words they understood. Also, most of the patients (52.3% and 54.5%) did not look up information about their medication or condition since they claimed to fully rely on the knowledge and the given information of the health care provider. When it came to shared decision making with health care provider about the treatment, 65.9% found it easy to communicate with their health care provider. Only 4.5% of the patients found shared decision making difficult to do.

QBS

QBS was used to investigate the patients' potential barriers for medication adherence. Based on these results, the specific IM, corresponding to the TIG was chosen. The percentage of patients per chosen IM are described in figure 3. The majority of patients were selected for IM 1 (68.2%) which is providing information, followed by IM 5 reducing negative beliefs (59.1%). The open questions of the QBS resulted in several observations. About 75% of the patients reported that they always received support from their social circle and health care providers for taking their medication. However, most of the patients confirmed not to have sufficient knowledge about phosphate and use of phosphate binders.

Health literacy domain		n	%
Functional	Reading medicine label		
	- Yes	3	6.8
	- No	41	93.2
	Indication for use		
	- Yes	24	54.5
	- No	20	45.5
	Instruction for use		
	- Yes	38	86.4
	- No	6	13.6
	Understanding of precaution or warning		
	- Yes	41	93.2
	- No	3	6.8
Communicative	Asking questions		
	- Easy	42	95.5
	- Difficult	2	4.5
	Expressing concerns		
	- Easy	42	95.4
	- Difficult	2	4.6
	Finding understandable information		
	- Easy	21	47.7
	- Difficult	2	4.5
	- Doesn't do it	21	47.7
Critical	Judging reliability of (medication) information encountered in the media or elsewhere		
	- Easy	17	38.7
	- Difficult	3	6.8
	- Doesn't do this	24	54.5
	Judging applicability of this information		
	- Easy	17	38.7
	- Difficult	4	9.1
	- Doesn't do this	23	52.3
	Engagement in shared decision making		
	- Easy	29	65.9
	- Difficult	2	4.5
	- Doesn't do this	13	29.5
	Handling contradictor information	33	75
	- Reliable source	11	25
	- Non-reliable source		

Table 4. An overview of questions and answers of the RALPH questionnaire.

Patients especially struggled with taking the phosphate binders during the meals due to forgetfulness. The negative beliefs about medication in general and high pill burden of phosphate binder was the next barrier which made it difficult for the patients to take their medicine properly. In addition, they experienced practical problems such as opening the baxter medication bags. Some patients experienced different adverse effects such as an itchy skin, diarrhoea and nausea. Therefore, some patients did not take their phosphate binders properly.

4 Discussion

Interpretation of key results and clinical relevance

The primary aim of this study was to evaluate whether a lower phosphate binder pill burden in combination with personalized patient counselling would improve serum

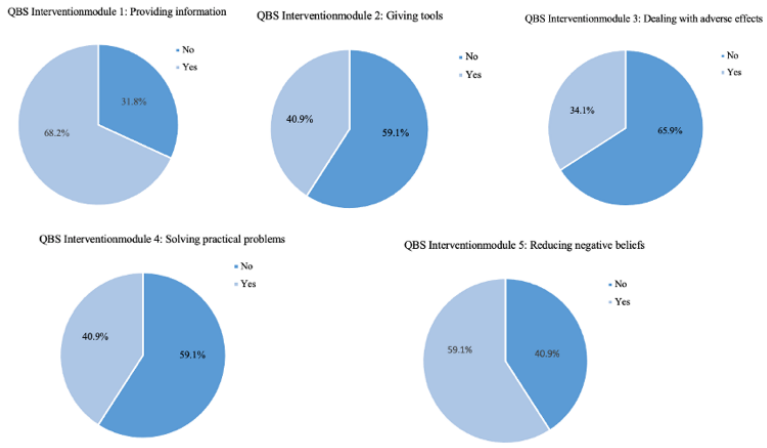

Figure 3. The percentage of patients per chosen Intervention Module (IM) based on the results of the Quick Barrier Scan (QBS). Dark blue stands for the percentage of patients who did not receive the IM and light blue for the percentage of patients who did receive the IM.

phosphate level in HD patients who suffer from uncontrolled hyperphosphatemia and a high phosphate binder pill burden. This study shows that personalized intervention improves the HD patients' mean serum phosphate levels respectively. This positive effect was reflected in decreased serum phosphate levels after the intervention, up to 0.16 mmol/L, although this was not statistically significant. These results reflect those of Van Camp et al. who investigated the effect of a 13-week nurse-led education and counselling on the adherence to phosphate binders. They found that the intervention led to decrease mean serum phosphate levels from 1.58 to 1.38 mmol/L (23). In the first place we expected that combination of reducing the phosphate binder pill burden and individualized patient counselling would lead to reduced serum phosphate level with a minimum of 0.25 mmol/L (20). However, our study showed a lower decrease in serum phosphate levels. The limited effect on serum phosphate level could be due to the power of our study being insufficient (n=28). In addition, an increase was found in phosphate control (1.50 mmol/L or lower) after intervention, especially during the first month after the intervention with an increase of 21,4%. These results reflect those of Hjemas et al, who showed a positive serum phosphate level below the threshold value of 1.80 mmol/L by implementing education and counselling about phosphate binder (13).

Secondary objective was to investigate patient adherence before and after the intervention. Medication adherence of our study population increased after the intervention to a median of 4.8 ($p < 0.001$). This finding is supported by Claxton et al. who showed that the number of doses medication per day is inversely related to adherence and suggested that a lower pill burden would increase medication adherence (24).

RALPH was used to explore the patients' pharmaceutical literacy. According to the RALPH, the patients lacked sufficient knowledge about their phosphate regulation and phosphate binders. Most of the patients fully relied on the judgement of their health care providers. As a result they did not find it important to gain more knowledge about their medication. To conclude, patients encounter the most problems in the critical domain.
Likewise, QBS identified several adherence barriers during our intervention. The main adherence barriers were lack of knowledge about their phosphate binders, negative beliefs about medication, lack of tools and practical problems. Hjemas et al. also showed that specifically individual counselling of the patient revealed lack of knowledge about phosphate binders. In addition, they showed that lack of knowledge plays an important role in poor adherence (13).

Strengths and Limitations
Personalized intervention is a major strength of this study as it is aimed to meet the needs of the patients. All questionnaires were verbally administered which also enabled inclusion of patient with limited reading and writing skills. In addition, multidisciplinary collaboration between the pharmacist, nephrologist, sociologist and dietician made the correct tailored intervention possible. Furthermore, this study enables to include complex non-adherent patients.
Our study also has some limitations. One potential limitation was small sample size. Since we did not reach our sample size, it might have influenced the results of this study to some extent. Increasing the number of patients in a single centre study is difficult, as the patients were included during a limited period of time. Future study should examine the impact of reducing high phosphate binder pill burden with multiple personalized patient counselling sessions with pharmacist in multi-institutional collaborative study to improve the epidemiological quality of data. Other study limitation in this study was the possible Hawthorne effect, whereby people modify their behaviour if they are under supervision for example in a study (25). Patients may have felt the need to give socially desirable responses on the questions, this could for example result in unreliability MARS-5 scores. In addition, the decrease in phosphate levels could not be specifically linked to reducing the pill burden since other factors could play a role as well such as dietary restrictions. Therefore, it is important to adjust for protein intake (nPCR). In this study we didn't adjust for nPCR. However, it should also be noted that the knowledge of the patients improved greatly through the multiple personalized patient counselling sessions according to the evaluations during visit 3. Thus it is hard to attribute the reason for clinical improvement to medication adherence, better knowledge or Hawthorne effect. Finally, our study population consisted of patients with language barrier. The visits revealed that the majority of these people received support from their relatives regarding to their medication and condition. This might suggest that relatives also need to be informed, which did not happen during our intervention.

5 Conclusion

The management of hyperphosphatemia in HD patients is challenging with multidimensional barriers. This study highlights the importance of personalized patient counselling sessions in combination with lowering phosphate binder pill burden to positive effects on the serum phosphate levels and phosphate binder adherence. Although change in serum phosphate level was not significant. Notwithstanding the relatively limited sample size, this study offers valuable insights into personalized intervention with dose optimization to improve phosphate control. Therefore, this study lays the groundwork for future research into personalized intervention strategies.

6 Aknowledgements

I would like to thank dr. F.J. van den Oever and dr. E.S. Koster for guidance and contribution to this study. In addition, I express my sincere appreciation to the staff of

the HD department at the FGV hospital who ensured the data collection.

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Appendix I. Phosphate binder pill units

Phosphate binder	mg	DDD	Chemical element	Phosphate binder units (sevelamer carbonate 800 mg = 1 reference unit)
Calcium carbonate effervescent tablet	1250 mg	3 g	(500 mg Ca)	1
Calcium carbonate chewable tablet	1250 mg	3 g	(500 mg Ca)	1
Calcium carbonate chewable tablet	2500 mg	3 g	(1000 mg Ca)	2
Calcium acetate/ Magnesium carbonate tablet	435/235 mg	6 g	(110 mg Ca, 60 mg Mg)	1
Sevelamer carbonate tablet	800 mg	6,4 g		1
Sevelamer powder for suspension	2400 mg	6,4 g		3
Lanthanum carbonate chewable tablet	500 mg	2,25 g	(500 mg La)	1
Lanthanum carbonate chewable tablet	750 mg	2,25 g	(750 mg La)	1,5
Lanthanum carbonate chewable tablet	1000 mg	2,25 g	(1000 mg La)	2
Lanthanum carbonate powder in sachet	750 mg	2,25 g	(750 mg La)	1,5
Lanthanum carbonate powder in sachet	1000 mg	2,25 g	(1000 mg La)	2
Sucroferric oxyhydroxide chewable tablet	500 mg Fe	1,5 g		1

Appendix II. Quick Barrier Scan

Quick Barrier Scan	**Barrière profiel**	**Interventie module**
1. Kunt u vertellen hoe een gemiddelde dialysedag er voor u uitziet en wanneer u dan uw fosfaatbinders inneemt? Hoe gaat dit op niet-dialysedagen?		
2. Heeft u het gevoel dat u onvoldoende weet over hoog fosfaat bij dialyse of uw medicijnen?		❶
3. Vergeet u weleens om uw fosfaatbinders in te nemen op dialysedagen?		❷
4. Vergeet u weleens om uw fosfaatbinders in te nemen op niet-dialysedagen?		
5. Vergeet u weleens om uw fosfaatbinders in te nemen op bijzondere dagen/periodes, zoals weekendjes weg of vakanties?		❷
6. Heeft u last van bijwerkingen van de fosfaatbinders of andere medicijnen?		❸
7. Bent u weleens bang om bijwerkingen te krijgen?		❸
8. Heeft u weleens moeite met de hoeveelheid fosfaatbinders of de verschillende innamemomenten?		❹
9. Heeft u weleens moeite met het openen van de verpakking of het doorslikken van de pillen?		❹
10. Maakt u zich weleens druk over het nemen van medicijnen in het algemeen? Vindt u bijvoorbeeld dat artsen teveel medicijnen voorschrijven, dat medicijnen meer kwaad dan goed doen en/of dat medicijnen een slechte invloed op het lichaam hebben?		❺
11. Heeft u weleens het gevoel dat u uw medicijnen helemaal niet nodig heeft?		❺
12. Heeft u weleens het gevoel dat uw medicijnen niet werken of meer nadelen dan voordelen hebben?		❺
13. Heeft u zelf nog ideeën over waarom het voor u weleens lastig kan zijn om uw medicijnen in te nemen?		Beoordeel zelf of dit onder een van de interventie modules valt en voer deze dan uit

14. Misschien is het helemaal niet het geval, maar een vraag die ik u toch nog zou willen stellen is: Heeft u op het moment geen zin meer in activiteiten waar u normaal gesproken wel plezier aan beleefde?		❺
15. Ervaart u voldoende steun bij het innemen van uw fosfaatbinders, bijvoorbeeld van dialyseverpleegkundigen, uw familie, nefroloog en/of diëtist?		
Indien er geen duidelijke barrière geïdentificeerd wordt, vertel dan aan de patiënt dat je in het vervolggesprek graag informatie geeft over een hoog fosfaat, de mogelijke gevolgen daarvan en de behandeling met fosfaatbinders.		❶
Toelichting patiënt:		

Appendix III. Tailored Intervention Guide (TIG)

Providing information (IM1)
Providing tools (IM2)
Dealing with side effects (IM3)
Overcoming practical problems (IM4)
Diminishing negative beliefs (IM5)

Appendix IV. Recognizing and Addressing Limited Pharmaceutical (RALPH)

RALPH gesprekshandleiding

Onderstaande vragen kunnen tijdens een gesprek met de patiënt gebruikt worden om meer inzicht te krijgen in de gezondheidsvaardigheden. Vraag bij twijfel of een onduidelijk antwoord altijd door.

Besproken geneesmiddel: .....

Vraagt de patiënt **aan u** of **u** de tekst op het etiket van het geneesmiddel **kunt voorlezen**?

- ❑ Ja
- ❑ Nee

1. Kunt u mij vertellen **waar** u dit geneesmiddel voor gebruikt?
Antwoord: Antwoord klopt? ❑ Ja ❑ Nee ❑ Patiënt weet het niet
2. Kunt u mij vertellen **hoe** u dit geneesmiddel moet gebruiken *(volgens het etiket)*? *Vraag hierbij indien nodig door naar het aantal innamemomenten en het tijdstip van inname*
Antwoord: Antwoord klopt? ❑ Ja ❑ Nee ❑ Patiënt weet het niet
3. *Indien er een speciale gebruiksinstructie/waarschuwing op het etiket staat.* Kunt u mij vertellen in **uw eigen woorden** wat deze gebruiksinstructie/waarschuwing inhoudt?
Antwoord: Antwoord klopt? ❑ Ja ❑ Nee ❑ Patiënt weet het niet

4. Wat doet u als de apotheek u **andere informatie** over dit geneesmiddel geeft dan de huisarts, bijvoorbeeld over hoe vaak u het middel moet innemen?
❑ Patiënt gaat **wel op zoek** naar de juiste informatie in **betrouwbare bronnen** ❑ Patiënt gaat **wel op zoek** naar de juiste informatie maar in **niet per definitie betrouwbare bronnen** ❑ Patiënt gaat **niet op zoek** naar de juiste informatie

5. Stel dat u **een vraag** heeft over dit geneesmiddel, bijvoorbeeld over hoe u het moet innemen, hoe makkelijk of moeilijk vindt u het om deze te stellen aan één van uw zorgverleners (*bijvoorbeeld arts, apotheker of apothekersassistent*)?
❑ Heel erg makkelijk ❑ Best wel makkelijk ❑ Best wel moeilijk ❑ Heel erg moeilijk
6. Stel dat u zich **zorgen** maakt over dit geneesmiddel, bijvoorbeeld over mogelijke bijwerkingen, hoe makkelijk of moeilijk vindt u het dan om dit te bespreken met één van uw zorgverleners (*bijvoorbeeld arts, apotheker of apothekersassistent*)?
❑ Heel erg makkelijk ❑ Best wel makkelijk ❑ Best wel moeilijk ❑ Heel erg moeilijk

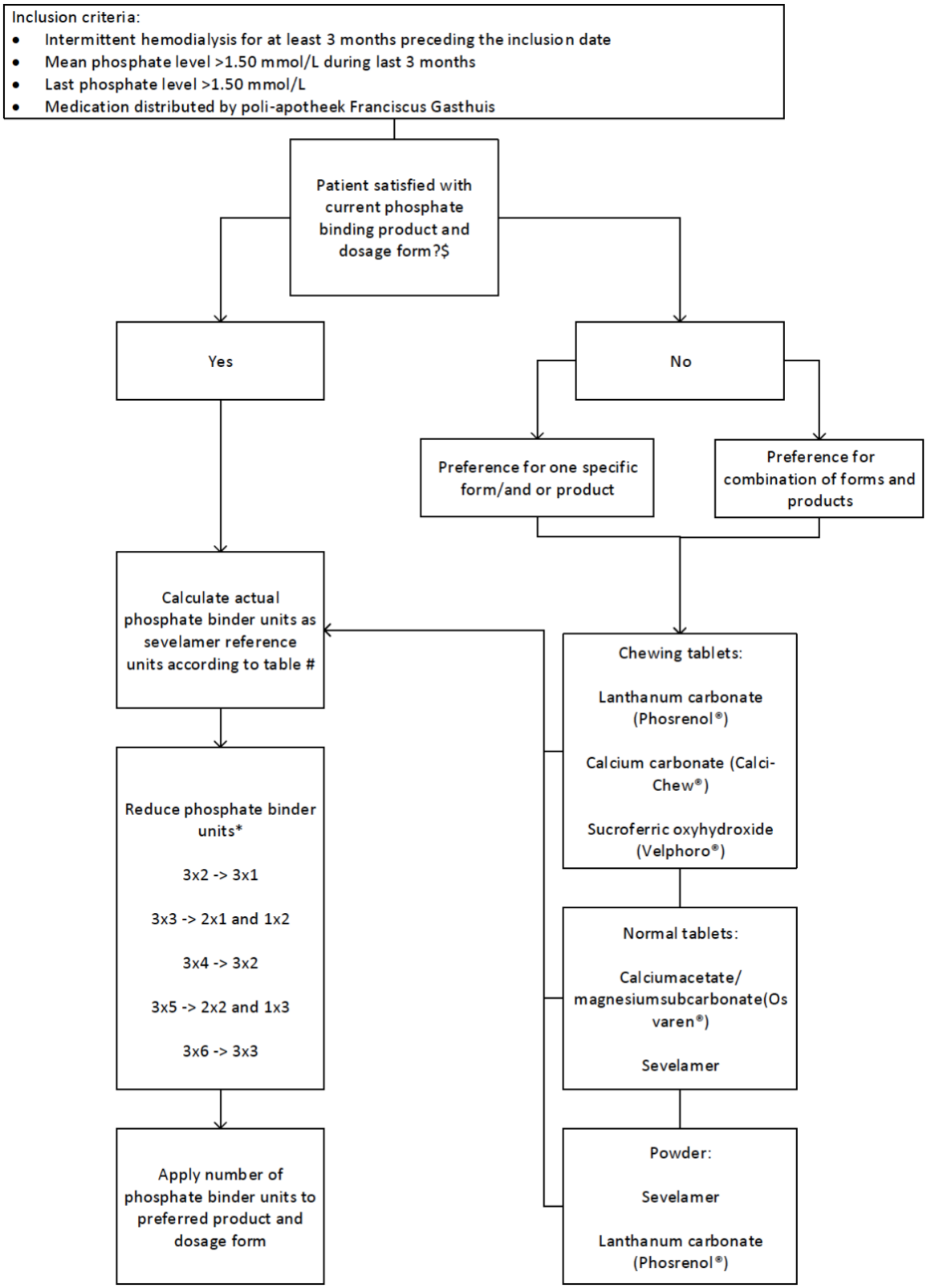
7. Hoe makkelijk of moeilijk vindt u het om informatie over dit geneesmiddel te vinden in **woorden die u begrijpt?** Bijvoorbeeld als u op wilt zoeken of u naast uw geneesmiddel een ander middel dat u bij de drogist haalt (paracetamol of een hoestdrank) mag gebruiken?	
❑ Heel erg makkelijk ❑ Best wel makkelijk ❑ Best wel moeilijk ❑ Heel erg moeilijk	❑ *Patiënt zoekt geen informatie. Reden:*

8. Als u bijvoorbeeld op internet of in de krant informatie over uw aandoening of dit geneesmiddel tegenkomt, hoe makkelijk of moeilijk vindt u het dan om te bepalen of de informatie **op u van toepassing is**?	
❑ Heel erg makkelijk ❑ Best wel makkelijk ❑ Best wel moeilijk ❑ Heel erg moeilijk	❑ *Patiënt ziet geen informatie. Reden:*
9. Als u bijvoorbeeld op internet of in de krant informatie over uw aandoening of dit geneesmiddel tegenkomt, hoe makkelijk of moeilijk vindt u het dan om de **betrouwbaarheid** van die informatie te beoordelen?	
❑ Heel erg makkelijk ❑ Best wel makkelijk ❑ Best wel moeilijk ❑ Heel erg moeilijk	❑ *Patiënt ziet geen informatie. Reden:*
10. Hoe makkelijk of moeilijk vindt u het om **samen** met uw zorgverlener **te beslissen** over de behandeling van uw aandoening, bijvoorbeeld of u een ander medicijn gaat proberen?	
❑ Heel erg makkelijk ❑ Best wel makkelijk ❑ Best wel moeilijk ❑ Heel erg moeilijk	❑ *Patiënt wil niet meebeslissen. Reden:*

Appendix V. Medication Adherence Report Scale (MARS-5)

MARS-5	
I alter the dose of my medicines	never / rarely / sometimes / often / always
I stop taking my medicines for a while	never / rarely / sometimes / often / always
I decide to miss out on a dose of my medicines	never / rarely / sometimes / often / always
I forget to take my medicines	never / rarely / sometimes / often / always
I take less of my medicines than instructed	never / rarely / sometimes / often / always

Appendix VI. Algorithm phosphate binders



Appendix VII. Summary of variables

Variable	When	Measuring instrument	Type of variable plus range
Phosphate levels (mmol/L)	Monthly	Medical record	Continuous variable 0.3-4.00
Calcium serum level (mmol/L) recurrent	Monthly	Medical record	Continuous variable 1.50-4.00
Parathyroid hormone level (pmol/L)	Every 3 months	Medical record	Continuous variable 0.0-300
Vitamin D (25-OH vitamin D) (nmol/L)	Every six months	Medical record	Continuous variable <10 = 9 10-300
nPCR (normalized protein catabolic ratio, g/kg per day)		Medical record Every 3 months	Continuous variable 0.30-2.25
Drug distribution system (medicine sachets)	Visit 1, t=12 months	Medical record	Discrete variable 0 = no 1 = yes
Time since start hemodialysis (months)	Visit 1	Medical record	Continuous variable 0.0-400.0
Age (years)	Visit 1	Medical record	Continuous variable 18.0-99.9
Number of different drugs	Visit 1	Medical record	Discrete variable 0 - 40
Phosphate binder pill burden, pill count (daily number of “pills” for phosphate binding drugs)	Visit 1, Visit 3, t=12 months	Medical record	Discrete variable 0 - 30
Total pill burden, pill count (daily number of all “pills”)	Visit 1,Visit 3, t=12 months	Medical record	Discrete variable 0 - 100
Fluid restriction (milliliters)	Visit 1	Medical record	Continuous variable 800 to 2000 9999 = no fluid restriction
Number of modules selected after Quick Barrier Scan (QBS)	After visit 1	Questionnaire	Discrete variable 0 = no barriers to good adherence, no intervention modules selected 1 = 1 intervention module selected

			2 = 2 intervention modules selected 3 = 3 intervention modules selected 4 = 4 intervention modules selected 5 = 5 intervention modules selected
Selection Intervention Module (IM) 1	After visit 1	Questionnaire	0 = no, 1 = yes
Selection IM 2	After visit 1	Questionnaire	0 = no, 1 = yes
Selection IM 3	After visit 1	Questionnaire	0 = no, 1 = yes
Selection IM 4	After visit 1	Questionnaire	0 = no, 1 = yes
Selection IM 5	After visit 1	Questionnaire	0 = no, 1 = yes
RALPH interview guide	After visit 1	Questionnaire	No problems identified= 0 (Possible) problems identified = 1
RALPH interview guide	After visit 1	Questionnaire	Problems in functional domain = 1 Problems in communicative domain = 2 Problems in critical domain = 3 Problems in functional and communicative domain = 4 Problems in functional and critical domain = 5 Problems in communicative and critical domain = 6 Problems in all domains = 7 No problems identified = 0
MARS-5 at baseline	Visit 1	Questionnaire	Discrete variable 5-25
MARS-5 at 3 months	Visit 3	Questionnaire	Discrete variable 5-25
MARS-5 at 12 months	Visit 3	Questionnaire	Discrete variable 5-25
Low and high adherence at	Visit 1	Proportions	Categorical variable

baseline			
Low and high adherence at 3 months	Visit 3	Proportions	Categorical variable
Number of pharmacist visits		CRF	Discrete variable 0-7
Number of dietician visits		Medical record	Discrete variable 1-6
Extra pharmacist visit		CRF	Discrete variable 0-2