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Biochemical and Physiologic Changes Following Sodium Phosphate Preparation for Colonoscopy

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ABSTRACT

Background: Sodium phosphate (NaP) is widely used for endoscopic bowel preparation. Acute phosphate nephropathy associated with nephrocalcinosis and a reduced glomerular filtration has been increasingly reported after NaP bowel preparation. The aim of this study was to evaluate biochemical and physiologic changes following NaP bowel preparation.

Methods: Patients with normal renal function (creatinine level ≤1.5 mg/dl) who were scheduled for colonoscopy were enrolled in the study. Two doses of 45 ml NaP (phosphate 373.5 mEq/45 ml) followed by 2 liters of water were taken with 12 hours interval apart. Clinical data and blood chemistry were collected at baseline, 24 hours after taking NaP, and 3 days later. Twelve hour urine was collected prior to NaP taking, and after each dose of NaP. Patients with acute elevation of serum creatinine ≥0.3 mg/dl was defined as having acute kidney injury (AKI), and their data were compared with those of the entire group.

Results: There were 30 patients with age (mean ± SD) of 58.9 ± 12.6 years. Twenty-four hours after NaP taking, serum phosphate level increased sharply, contrasting with reducing serum calcium, sodium, potassium, chloride and magnesium levels. Urine acidosis and increased urine excretion of phosphate occurred nearly at the same time. Elevated serum phosphate level returned to baseline 3 days later. There was no change in serum creatinine and parathyroid hormone levels. Two patients developed transient AKI without any other biochemical changes far from the whole group.

Conclusions: After NaP taking, transient hyperphosphatemia, hypocalcemia, phosphaturia with urine acidosis occurred. Urine acid excretion may be the physiologic response to acute phosphate loading in order to enhance renal phosphate excretion and prevent phosphate nephropathy. Hypocalcemia without increased urine calcium loss may be the effect of calcium-phosphate binding product following hyperphosphatemia. No significantly different parameters were identified in patients who developed AKI. Further study is needed to confirm our observation in this study.

Key words : Colonoscopy, Sodium phosphate, Nephropathy

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INTRODUCTION

The medical knowledge concerning colorectal cancer has expanded rapidly. As advance stages of colorectal cancer are associated with poor clinical outcomes, early detection of colorectal cancer is best to improve clinical outcomes. Colonoscopy is a widely used method for evaluating the large and the distal small intestines, especially regarding colorectal screening. Bowel preparation is very important before performing colonoscopy, and the quality of bowel preparation is correlated with mucosal abnormality detection rate[1]. Widely accepted agents for colonoscopic bowel preparation include polyethylene glycol (PEG) and sodium phosphate regimen (NaP). Both agents have comparable efficacy[2-4]. However, fewer side-effects, especially nausea and/or vomiting, and better tolerability were reported with the sodium phosphate regimen[5].

In recent years, many studies have reported renal failure after colonoscopy with NaP bowel preparation[6,7,10-12]. Renal pathology demonstrated sodium-phosphate crystal deposits in the renal parenchyma, a condition termed "nephrocalcinosis", and the situation is referenced to as "Phosphate Nephropathy"[6,7]. Many hypotheses were generated for explaining the pathogenesis of this occurrence, such as dehydration, rapid and high phosphate load, parathyroid hormone (PTH) related, and the acid-base status of the urine[8]. However, data concerning the body response after NaP ingestion is limited. The primary purpose in this study was to compare the parameters of phosphate homeostasis and creatinine levels before and after NaP ingestion, and the secondary purpose was to demonstrate the association between phosphate parameter and acute renal dysfunction.

MATERIALS AND METHODS

Subjects

A prospective, descriptive analytic study was conducted between August 15th, 2008 and November 30th, 2008. Patients with differing indications for colonoscopy were recruited to enter the study. The inclusion criteria is included; age 18-80, patients undergoing elective colonoscopy, history of normo-tension in the previous 2 weeks, creatinine ≤1.5 mg/dl, and no serious medical illnesses such as active SLE, symptomatic HIV, congestive heart failure, diabetes with proteinuria, etc. The exclusion criteria is included; emergency colonoscopy especially gastrointestinal bleeding, exposure to contrast media in the previous 4 weeks, use of NSAIDs, diuretics or sulfamethoxazole-trimethoprim within 2 weeks, adjusted ACEI or ARB doses in the previous 2 weeks and patient who refusal to participate in the study.

Methods

The study protocol was approved by the Ethical Committee, Ramathibodi Hospital, Mahidol University. All participants gave informed consent before entry into the study. A total of 30 patients were enrolled. Baseline parameters including demographic data (age, sex, weight, height, body mass index or BMI, alcohol status, presence of diabetes/hypertension, indication for colonoscopy), clinical and laboratory parameters (serum electrolyte, creatinine, calcium, inorganic phosphate, albumin, magnesium and serum parathyroid hormone or PTH) were obtained. Glomerular filtration rate (GFR) was determined by the Cockcroft-Gault method. Patients were thereafter scheduled to colonoscopy, and were assigned to receive 2 doses of 45 ml sodium phosphate solution (each dose consisting of monobasic sodium phosphate 21.6 grams, dibasic sodium phosphate 8.1 grams with total phosphate 373.5 mEq) followed by 2 liters of water in the evening before the procedure day and in the morning of the procedure day (12 hours interval). Three 12-hour urine specimens were collected, the first specimen from pre-sodium phosphate ingestion, the second from post-1st dose sodium phosphate ingestion and the third post-2nd dose sodium phosphate ingestion. Standard routine colonoscopy was then performed. The collected urine specimens were sent for determination of urine volume, pH, creatinine, electrolyte, calcium, inorganic phosphate and magnesium. Serum biochemistry was collected again before the patients were discharged from the endoscopy room (24 hours from the first dose of sodium phosphate) and at day-3 following colonoscopy (except the serum parathyroid hormone which was collected only at day-3 after colonoscopy, see Figure 1). The risk of acute kidney injury (AKI) was defined by on elevation of serum creatinine over 0.3 mg/dl from baseline, or serum creatinine rising more than 1.5 times from baseline (based on RIFLE criteria)[9].

Statistical Analyses

This study was a pilot study. For short of relevant data from any previous study, we estimated the

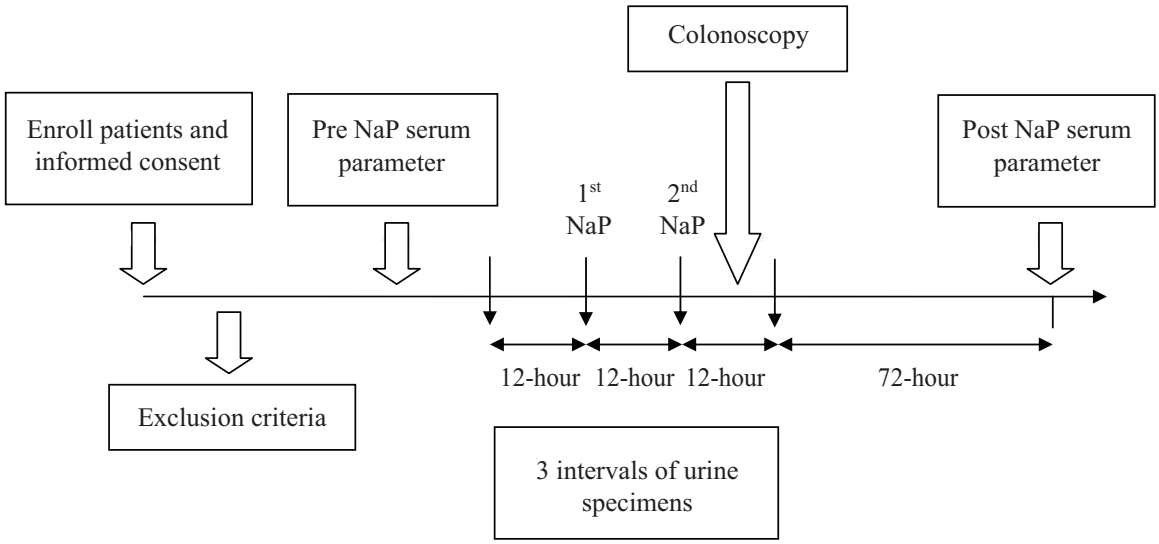

Figure 1. Illustrated the study design

total number of patients to be about thirty. Patient demographic data were summarized in frequencies (or percentages) for categorical variables and as means ± SD for continuous variables. Paired t-test was used to compare difference between pre-NaP and post-NaP biochemical parameters. The analysis was done by SPSS statistical software version 13. A *p*-value of less than 0.05 was accepted as statistically significant.

RESULTS

There were 36 patients initially recruited to the study. Five patients were withdrawn because of inconvenience with specimen collection and one patient died of unrelated cases before the scheduled data of colonoscopy. The remaining 30 patients completed the protocol, and none were lost to follow up. Most patients underwent colonoscopy for colorectal screening (50%). Other indications included anemia, chronic abdominal pain, and bowel habit changes. The mean age (SD) of the total group was 58.9 (12.6) years, with the male to female ratio of 1:1. Baseline demographic and clinical characteristic data of the patients are presented in Table 1. 4 patients (13.3%) were diabetics, 6 patients (20%) had underlying hypertension and 3 patients (10%) concurrently used angiotensin converting enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB).

Sequential serum and urine biochemical parameters after sodium phosphate ingestion are presented in Table 2 and Table 3. After 2 doses of NaP ingestion, serum phosphate increased sharply (from 3.64 to 5.39 mg/dl, $p = 0.000$). This was in contrast with the reduction of serum sodium, potassium, chloride, bicarbonate, calcium, magnesium and albumin. However, the elevated serum phosphate and the decreased serum electrolytes all returned to baseline three days later. There were no changes in serum creatinine and parathyroid hormone levels. Regarding urine parameters, we adjusted phosphate excretion by calculating the fractional excretion with creatinine (the average urine phosphate divided by average urine phosphate at the specific interval time). For urine calcium and magnesium, we calculated in the same manner. Sharply elevated phosphate excretion in contrast with slightly decreased

Table 1. Baseline demographic and clinical characteristic data of the patients.

Characteristic	Results
Male/Female[b] (n, %)	15 (50%)/15 (50%)
Mean age[a] (yrs.)	58.87 (12.56)
Diabetes[b] (n, %)	4 (13.3%)
Hypertension[b] (n, %)	6 (20%)
ACEI/ARB use[b] (n, %)	3 (10%)
Alcohol[b] (n, %)	7 (23.3%)
Weight[a] (kg)	63.05 (14.17)
Height[a] (m)	1.64 (0.96)
BMI[a] (kg/m^2)	23.32 (4.09)

[a]Mean (SD), [b]Frequency (%)

Table 2. Mean serum biochemical changes after sodium phosphate bowel preparation.

	Pre-NaP	Post-NaP	*p*-value[a]	3 days Post-NaP
Creatinine (mg/dl)	1.01	0.96	0.62	0.95
GFR (ml/min)	67.65	74.45	0.018	72.96
Sodium (mEq/l)	140.53	136.67	0.000	139.73
Potassium (mEq/l)	4.13	3.45	0.000	4.10
Chloride (mEq/l)	103.23	99.77	0.001	103.00
Bicarbonate (mEq/l)	28.39	27.17	0.071	28.63
Calcium (mg/dl)	9.11	8.65	0.000	9.03
Phosphate (mg/dl)	3.64	5.39	0.000	2.86
Magnesium (mg/dl)	2.12	1.87	0.000	2.05
Albumin (g/l)	41.20	39.07	0.000	39.41
PTH (pg/ml)	47.01	-	-	43.15[b]

[a]Comparison between Pre-NaP and Post NaP

[b]Comparison between Pre-NaP and 3 days Post-NaP, $p = 0.179$

Table 3. Mean urine biochemical changes after sodium phosphate bowel preparation.

	Pre-NaP	Post 1st NaP	*p*-value[a]	Post 2nd NaP
Urine volume (ml)	1444.48	889.66	0.001	794.83
Specific gravity	1.012	1.015	0.125	1.018
pH	6.18	5.71	0.000	5.48
Creatinine (mg/dl)	53.52	50.70	0.74	57.89
Sodium (mEq/l)	65.87	64.83	0.892	54.23
Potassium (mEq/l)	19.13	19.93	0.834	21.43
Chloride (mEq/l)	72.70	52.97	0.018	42.97
Calcium (mg/dl)	6.82	3.35	0.006	2.13
Phosphate (mg/dl)	31.59	113.03	0.000	138.27
Magnesium (mg/dl)	2.93	1.42	0.002	0.76
Calcium/Creatinine	0.15	0.11	0.018	0.07
Phosphate/Creatinine	0.59	2.97	0.000	3.64
Magnesium/Creatinine	0.06	0.03	0.000	0.02

[a]Compared between Pre-NaP and Post 1st NaP

calcium and magnesium excretion was demonstrated. Urine acidosis (decrease in urine pH) occurred at the same time. Two patients developed transient AKI. One patient was a 54 year-old man with diabetes, hypertension, on ACEI inhibitor, who underwent colonoscopy for colorectal cancer screening (creatinine increasing from 1.3 to 1.6 mg/dl). The other patient was a 34-year-old man without underlying disease, no concurrent medication, who underwent colonoscopy for rectal bleeding (creatinine rising from 1.1 to 1.4 mg/dl). Serum creatinine returned to the baseline at day 3 of follow up in both patients, however. No other biochemical parameters of both patients differred from the entire group.

DISCUSSION

Many cases of acute and chronic renal failure after sodium phosphate bowel preparation have been reported[6,7,10-12]. A possible mechanism is a high phosphate load presented to the renal tubules after ingestion of sodium phosphate. In our study, the sequential collection of both serum and urine in patients undergoing colonoscopy demonstrated a transient elevation of serum phosphate (from 3.64 to 5.39 mg/dl) concomitant with an increase of urine phosphate excretion (phosphate/creatinine ratio from 0.59 to 2.97). This phenomenon would support the hypothesis of phosphate loading to the kidney and enhanced phosphauria

after sodium phosphate ingestion. In this study, the level of serum phosphate after 2 doses of 45 ml. sodium phosphate for bowel preparation in patients with normal renal function was evaluated. Although serum creatinine did not significantly change after phosphate load, in patients with nephrocalcinosis (as in reported cases), some other factors may potentiate calcium-phosphate precipitation in the renal tubules. Future study is needed to confirm this hypothesis. Increased urine acidity is likely to be the body response to maintain normal homeostasis. Other serum electrolytes showed transient reduction after NaP ingestion without an increase in urine excretion. A simple explanation of these events is that NaP induces diarrhea and increases gastrointestinal loss. Replacement therapy for these conditions was controversial and requires future study evaluation. The unchanged level of serum PTH at day-3 could be due to a short follow up interval, or these changes could have been transient and insufficient to stimulate a PTH response. In the two cases of transient AKI, many factors could have potentiated the elevated serum creatinine, such as dehydration, but no phosphate parameters could have explained these events.

In conclusion, elevated serum creatinine can transiently occur after sodium phosphate bowel preparation. Causative factors may be to multifactorial, including dehydration. Nephrocalcinosis, a deposition of calcium-phosphate crystal in the renal tubules leading to persistent renal failure, is uncommon following NaP bowel preparation. Nephrocalcinosis appears to require other special co-factors to develop. Further study with a larger sample size and a longer study duration is needed to confirm this hypothesis.

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