Oral Prostaglandin E1 in Combination with Sodium Bicarbonate and Normal Saline in the Prevention of Contrast-Induced Nephropathy: A Pilot Study

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ABSTRACT

The purpose of this study was to evaluate the use of prostaglandin E1 (PGE1) as a renal protective medication for patients exposed to contrast agents, as well as to demonstrate the safety, efficacy, and low side-effect profile of PGE1. A prospective, randomized, double-blind study was designed to compare combination of intravenous sodium bicarbonate, normal saline, and oral PGE1 200 μg versus the combination and placebo for renal protection from contrast agents. All patients receiving nonionic contrast during their interventional procedure were eligible for enrollment. Creatinine levels were recorded before and after the administration of contrast and renal protective medications. Contrast-induced nephrotoxicity (CIN) was defined as an increase of 0.5 mg/dL or greater in creatinine level, or an increase of 25% or more above baseline. Age, gender, total amount of contrast used, and incidence of renal failure requiring dialysis were recorded. We conducted the study on 41 patients. Of these, 20 patients received PGE1 and 21 received the placebo. The study group comprised 29 males and 12 females. Diabetes mellitus occurred in 41.5% of the cases (including 40% of PGE1 and 43% of placebo patients). Average contrast use was 77.2 mL (range, 15 to 200 mL). Mean age of the groups was 67.2 years. Average baseline creatinine level was 1.17. The differences between the groups were not statistically significant. CIN by definition occurred in one patient, who received the placebo. Incidence of new onset renal failure requiring dialysis was zero. Postcontrast change in creatinine level for the study was 0.11. There was a change in the creatinine level of 0.161 in the PGE1 group and 0.061 in the placebo group; an improvement of 0.10. PGE1 was not effective in significantly altering postcreatinine levels ($p = 0.176$). None of the patients enrolled in the study suffered any side effects from taking the PGE1 tablet. Although preliminary, this study shows that the addition of PGE1 for the prevention of CIN is well-tolerated by patients and is a safe modality. Additional studies are required to evaluate efficacy.

KEYWORDS: Contrast-induced nephropathy, prostaglandin, renal disease, creatinine, angioplasty, artery, hemodialysis, renal failure

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Contrast-induced nephrotoxicity (CIN) is a frequently encountered problem in modern medical practice. Incidence ranges from 2 to 38% in exposed individuals, depending on patient risk factors including elevation of baseline creatinine level and presence of diabetes mellitus.[1] Contrast agents are responsible for 10% of all hospital-acquired renal failure cases.[2] Acute renal failure (ARF) continues to be associated with a substantial inpatient mortality rate.[2] One study showed that the difference in mortality between patients who did or did not develop ARF was 7 versus 34%.[3] CIN is defined as an increase of serum creatinine level of 0.5 mg/dL or an increase of 25% or more above baseline.[4] Occasionally, the onset of CIN will lead to a nonresolving ARF that requires dialysis, with an incidence of 0.7% in contrast-exposed patients.[5] Complications associated with contrast administration are considered an "adverse drug reaction," and have been shown to be a significant financial burden as well.[6]

In a randomized-controlled trial published in JAMA in 2004, intravenous hydration with solutions of sodium bicarbonate is more effective than using normal saline alone.[7] This preventative measure is currently in use at our institution since 2005, and represents the standard of care.

Prostaglandin E1 (PGE1) is an endogenous vasodilatory mediator. It has been studied in vitro and in vivo in regards to prevention of CIN.[8–16] In 1976, a study was conducted that used intra-arterial injection of PGE1 in human subjects who then underwent a contrast nephrogram. The result was a shorter time to the appearance of the contrast in the nephrogram, as well as an increased arterial diameter; both of which suggest an increase in renal blood flow.[9]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are well known to cause nephrotoxicity as a side effect. The likely mechanism of this is the inhibition of prostaglandin (PG) synthesis, and the resultant low levels of PG allows for unopposed vasoconstriction in the kidney; leading to hypoxic damage. Administration of a PGE1 analogue (misoprostol) can prevent/reverse the nephrotoxic side effects of NSAIDs.[13] Hayashida et al found that patients under general anesthesia maintained a greater urine output with PGE1 administration compared with patients receiving placebo.[8] Tabo et al studied PGE1 in patients undergoing hypotensive anesthesia. They concluded that creatinine clearance was preserved in the PGE1 group and was diminished in the control group.[14] In this study, PGE1 outperformed several other proposed renal protective medications such as nicardipine, nitroglycerine, and sodium nitroprusside.

Due to the vasodilatory properties of PGE1, a hypothesized side effect is that it could induce hypotension, thus decreasing renal perfusion pressure and potentially worsening nephrotoxicity. Wutte et al tested this hypothesis in patients with terminal congestive heart failure. They found that even though there was a decrease in blood pressure, creatinine clearance was improved to a degree that achieved statistical significance.[16] They concluded that the direct renal protective benefit outweighs any risk of diminishing renal function secondary to decreased perfusion pressure.

Other studies have established that PGE1 can provide renal-protective benefits even in the face of total renal ischemia. Vargas et al concluded that administration of PGE1 at the time of reperfusion (after total occlusion) ameliorates the expected renal injury, and that delayed treatment was not able to match those results.[15] Paller and Manivel used an in vitro and in vivo rat model to demonstrate the renal-protective effects of PGE1.[11] PGE1-treated rats had a threefold greater glomerular filtration rate than the control group. In addition, there was a direct "cytoprotective" effect found by using misoprostol in a model of renal toxic injury using mercuric chloride.

Paller studied the use of PGE1 in patients receiving cyclosporine, which is known to be nephrotoxic. Using a rat model, the results demonstrated a "substantial reversal" of renal dysfunction by the use of PGE1.[12] This demonstrates that PGE1 is able to aid in renal protection from a non-NSAID, noncontrast toxin source. This suggests that PGE1 may be of benefit to all patients at risk for renal damage from a variety of causes.

Randomized-controlled clinical trials have likewise produced positive results for PGE1 use. In 2000, Koch et al studied 130 patients with a baseline creatinine level of at least 1.5. Either placebo or a variable dose of PGE1 was given before contrast administration. Postprocedure serum creatinine levels were significantly lower in the patients who received PGE1. There were no adverse reactions from intravenous (IV) PGE1 administration.[10] Sketch et al conducted a similar study in 2001, again examining 130 patients with a baseline creatinine level of 1.5 or higher. Using a double blind, randomized, placebo-controlled design, they were able to reproduce the results of Koch et al, by concluding that PGE1 reduced the postprocedure elevation of creatinine level when compared with placebo ($p = 0.03$). Additionally, the authors were able to establish that a dose of 20 μg/kg/min was the optimal dosage in their study.[17]

A large body of literature exists that has attempted to discover a preventative agent or strategy to reduce the incidence and severity of CIN. Past attempts at preventing CIN include use of advanced contrast agents, prophylactic hemodialysis, furosemide, *N*-acetylcysteine, sodium bicarbonate, IV hydration, calcium channel blockers, fenoldopam, nitroglycerin (NTG), and PGE1. This article reviews data from a prospective randomized trial involving PGE1 versus placebo combined with sodium bicarbonate and normal saline in a population of vascular surgery patients in an urban community hospital setting.

METHODS

We enrolled 41 patients for this study. Of these, 20 patients received PGE1 and 21 patients received the placebo. The study group comprised 29 males and 12 females (Table 1). Among males, 12 received PGE1 and 17 received placebo. Among females, eight received PGE1 and four received placebo. The Institutional Review Board of OhioHealth, Columbus, OH approved the prospective randomized, double-blind study comparing oral PGE1(200 μg) versus placebo combined with sodium bicarbonate(150 mEq/1000 mL D5W) at 3 mL/kg/h IV for 1 hour before procedure and 1 mL/kg/h IV for 6 hours after procedure and 500 mL of 0.9% sodium chloride IV before procedure. All patients receiving IV contrast (Visipaque, GE Healthcare) on the vascular surgery service from January 2009 to March 2011 were invited to participate in this study. Inclusion criteria included: all patients receiving IV contrast. Exclusion criteria included: dialysis patients, patients with an allergy to PGE1, and pregnant females. We hypothesized that administration of PGE1 in addition to sodium bicarbonate and IV hydration would provide renal protection beyond that of sodium bicarbonate and IV hydration alone, without any additional risk to the patient. All patients received the standard of care, which is IV hydration and sodium bicarbonate. The experimental group received oral PGE1, and the control group received an oral placebo. The change in the creatinine level after the administration of contrast was observed in both groups. All patients on our vascular surgery service had a measurement of their baseline creatinine level before undergoing a test that involves contrast administration. This was our baseline creatinine level value. All patients enrolled in the group that received IV contrast then had a measurement of the serum creatinine level 24 hours after the contrast was given. This was our postcontrast creatinine level value. We compared the precontrast creatinine levels to the postcontrast creatinine levels to see if they are statistically different. We then compared the control group to the placebo group to see if there was any significant difference between these two groups. The endpoints were the measured difference in creatinine levels between the two groups and comparing pre- and postcontrast values. Side effects and need for dialysis were also recorded. Comparisons were then made between the experimental and control groups. We tested the hypothesis that administration of oral PGE1, in addition to sodium bicarbonate and IV hydration, will provide renal protection beyond that of sodium bicarbonate and IV hydration alone. Descriptive statistics were produced, using means, medians, ranges and standard deviations for numeric variables, and percentages for categorical variables. Independent variables included gender, age, amount of contrast, pre- and postcontrast creatinine levels, reported side effects, and postcontrast dialysis treatment information. Inferential statistics were used to determine statistically significant differences between comparison variables, using independent *t*-tests for normally distributed data. Differences between groups were analyzed for the treatment group (oral PGE1), and the control group (placebo tablet). A chi-square analysis also compared differences between dichotomous variables. Statistical significance was evaluated at an α level of 0.05.

Table 1 Study Population

	Gender		
Count	**Male**	**Female**	**Total**
Prostaglandin E1	12	8	20
Placebo	17	4	21
Total	29	12	41

RESULTS

Mean age of the groups was 67.2 years with the median age of 66 years (range, 48 to 87 years). Of the 41 patients enrolled for the study, 17 (41.5%) had diabetes mellitus. Of the 20 patients who received PEG1, 8 (40%) had diabetes and of the 21 patients who received the placebo, 9 (43%) had diabetes. Average contrast use for the trial was 77.2 mL (range, 15 to 200 mL). Average contrast for PGE1 group was 80.9 mL and for placebo was 73.7 mL. In patients with diabetes mellitus, 86.3 mL of contrast was given in the PGE1 group and 62.9 mL in the placebo group. Mean baseline creatinine level was 1.17 mg/dL (range, 0.60 to 2.60 mg/dL) (Table 2). The differences between the two groups were not statistically significant.

Table 2 Age and Creatinine Levels of the Study Group ($n = 41$)

	Age (in Years)	Precontrast Creatinine Level	Postcontrast Creatinine Level
Mean	67.2	1.17	1.06
Median	66.0	1.10	0.93
Standard deviation	10.21	0.43	0.47
Minimum	48	0.60	0.60
Maximum	87	2.60	3.20

Table 3 Comparison of the Creatinine Levels in Treatment Groups

Treatment Group	Number of Patients	Mean	Standard Deviation	Standard Error Mean
Prostaglandin E1	20	0.1610	0.18926	0.04232
Placebo	21	0.0614	0.26528	0.05789

Mean postcontrast creatinine level was 1.06 mg/dL (range, 0.60 to 3.20 mg/dL). CIN by definition occurred in one patient, who received the placebo. This patient's creatinine level increased from 2.40 to 3.17 mg/dL (an increase of 0.77 mg/dL). An increase of 0.5 mg/dL or greater was considered CIN for this study. This patient did not require postprocedure dialysis. Incidence of new onset renal failure requiring dialysis was zero. Postcontrast mean change in creatinine level for the placebo group was 0.061. The postcontrast mean change for the PGE1 group was 0.161, an improvement 0.10 (Table 3). An independent sample *t*-test was performed on the groups with respect to their level of creatinine change ($p = 0.176$). This value was not significant, showing that in this study PGE1 was not effective in significantly altering postcreatinine levels after contrast administration. There were no patient reported side effects in the PGE1 group.

DISCUSSION

The use of oral PGE1 for renal protection in patients receiving IV contrast shows some promise. It is inexpensive, easy to use, and is well-tolerated orally. PGs have a rather broad side effect profile including diarrhea, abdominal pain, nausea, flatulence, dyspepsia, vomiting, constipation, headache, and menstrual irregularities. Less common reactions described are bronchospasm, anaphylaxis, hypertension, hypotension, myocardial infarction, arrhythmias, thromboembolism, and dehydration. None of the patients who received the experimental medication had any of the previously described side effects. Clearly, any randomized controlled trial will have to compare any experimental drug against normal saline and bicarbonate. During this study, our results may have been less significant due to the use of this combination in our patient population. However, as we know, many patients are highly sensitive to the administration of IV fluids and may not be able to tolerate this preprocedural fluid load. Cases like these will likely be the niche for a drug that can be given as an alternative that will allow the continued flow of blood into the renal medulla and prevent hypoxemic injury. Further study is warranted to delineate the benefit this drug may have. A large-scale prospective, double-blind randomized trial should provide the answer.

CONCLUSION

In modern practice the use of contrast agents for imaging purposes continues to increase. Despite advancements in the manufacturing of less toxic contrast media, there continues to be a distinct risk of postprocedural renal impairment. Individuals at high risk include patients with diabetes and more importantly, those with an elevation of their creatinine level at baseline. Numerous attempts at preventing CIN have been undertaken, most of which have not yielded satisfactory results. As a consequence, currently, there is no standard recommendation for any particular "medicine" to be used as a prophylactic agent. The most widely accepted practice for the prevention of CIN is IV hydration, with or without sodium bicarbonate. Given the substantial morbidity and mortality, if renal failure develops, it would be highly desirable to develop a preventative strategy that would eliminate the incidence of CIN. Dependable prevention of CIN would allow physicians' greater freedom in obtaining diagnostic studies with unlimited frequency and in performing endovascular therapeutic interventions with little or no side effects secondary to contrast use. PGE1 is a promising agent in CIN prevention. This study would add to the assertion that a large-scale trial be completed with our preliminary data showing some improvement in serum creatinine levels without any undue side effects of PGE1.

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