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Original Article

# Acute Kidney Injury in Patients Using Polyethylene Glycol as Bowel Cleansing Agent for Colonoscopy

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## ABSTRACT

**Introduction:** The use of polyethylene glycol-based solutions is the gold standard for bowel preparation for colonoscopy. However, polyethylene glycol use might be associated with the risk of acute kidney injury. We aim to find out acute kidney injury and risk factors associated with the development of acute kidney injury in patients using polyethylene glycol for colonoscopy.

**Materials and Methods:** This was an observational study conducted in Department of Nephrology and Gastroenterology, Bir hospital. Patients who underwent colonoscopy using polyethylene glycol were included in the study and assessed for acute kidney injury; its incidence, association of risk factors with acute kidney injury and outcome (complete recovery or no recovery) of acute kidney injury by 3 months.

**Results:** Mean age of the patients was 45.81 ± 18.60 years with the majority of the patients being male (60%). Out of 48 study participants, 4(8%) develop acute kidney injury. Multivariate regression analysis depicted that chronic kidney disease, chronic liver disease, congestive cardiac failure and use of non-steroidal anti-inflammatory drugs, angiotensin receptor blockers, and diuretics drugs were the predictors which significantly influenced the occurrence of acute kidney injury in patients using polyethylene glycol.

**Conclusion:** The evidence strongly suggests that in patients without preexisting renal disease, comorbidities or use of drugs; the risk of renal impairment is low after colonoscopy using polyethylene glycol as a bowel cleansing agent. In the presence of risk factors for renal dysfunction, polyethylene glycol should be used cautiously.

**Keywords:** Acute kidney injury; Non-steroidal anti-inflammatory drugs; Polyethylene glycol

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## INTRODUCTION

Colonoscopy is a procedure performed for diagnosis and follow-up of patients with colon cancer, inflammatory bowel disease (IBD), and gastrointestinal hemorrhage.[1] Bowel preparation with an appropriate bowel cleansing agent is essential for the diagnostic accuracy and safety of colonoscopy.[2] Bowel cleansing agents are isosmotic (Polyethylene glycol-based preparation), hyperosmotic (sodium sulfate-based preparation, sodium phosphate, and combination of sodium picosulfate, magnesium oxide and citric acid), and hyposmotic (low volume Polyethylene glycol (PEG) 3350 with bisacodyl).[3]

Oral sodium phosphate (OSP) preparations are hyperosmoic and prescribed with a much smaller volume of water. It promotes colonic evacuation by drawing 1-1.8 liter of fluid from circulation. It was found to be effective and well-tolerated.[4,5] However, OSP had resulted hyperphosphatemia, electrolyte imbalance and acute kidney injury (AKI) due to acute phosphate nephropathy both in patients with normal kidney function and chronic kidney disease.[6] Transient hyperphosphatemia leads to an increased intratubular phosphate concentration resulting in the precipitation and tissue deposition of calcium phosphate salts that cause luminal obstruction, direct tubular epithelial injury and activation of the immune response.[7,8] Volume depletion from OSP-induced osmotic diarrhea in the setting of reduced oral intake prior to the procedure further worsened the intraluminal calcium phosphate deposition.[9] The risk factors for AKI with OSP as bowel cleansing agents for a colonoscopy include concomitant use of angiotensin converting enzyme (ACEI) angiotensin II receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs), diuretics and presence of comorbidities like hypertension (HTN), diabetes mellitus (DM), chronic liver disease (CLD) and congestive cardiac failure (CCF), dehydration, old age, and female gender.[10] Proper hydration before using OSP and avoiding nephrotoxic drugs could ameliorate AKI in these patients.

The incidence of AKI after colonoscopy using different bowel cleansing agents ranged from 0.3 % to 41.2%.[6,11] According to KDIGO 2012 (Kidney Disease Improving Global Outcome), AKI is defined as any of the following: an increase in Serum Creatinine (S.Cr) by 0.3 mg/dl within 48 hours; or an increase in S Cr to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume<0.5ml/kg/h for 6 hours.[12]

More recently, PEG-based preparation are being used. However, they are associated with some risk for AKI. PEG-based preparations are available as a powder with or without electrolytes and need to be diluted in a large volume of water (up to 4 litre). PEG solution is iso-osmotic that passes through the colon without net absorption or secretion.[3] Overall, PEG preparations were considered to be safe with no shifts of fluid and electrolyte and could be prescribed to patients with electrolyte imbalance, CLD, CCF, and Chronic kidney disease (CKD). However, there have been reports of asymptomatic increases in plasma volume and exacerbations of heart failure and pre-renal AKI related to diarrhea and fluid loss that had improved with fluid replacement.[13] Some of the PEG preparation also contains large amounts of ascorbic acid that enhances the laxative effect. PEG preparation with ascorbic was reported to cause AKI due to the metabolism of absorbed ascorbic acid to oxalate and deposition of calcium oxalate in the renal tubule leading to acute oxalate nephropathy.[14] AKI after bowel preparation with PEG was found in 2.8% patients in a prospective study and risk was high in patients receiving NSAIDs.[15] A case-crossover study had shown an increased risk of AKI in elderly (>50 years) male patients.[16]

Colonoscopy is a regular procedure with 995 cases in the year 2076 in Bir hospital.[17] There are published reports on colonoscopy and biopsy findings from different parts of Nepal with PEG being used for bowel preparation.[18–20] This study aimed to evaluate kidney function before and after colonoscopy, particularly in high-risk groups.

## MATERIALS AND METHODS

This was a hospital-based observational study conducted in the Department of Nephrology and Gastroenterology, National Academy of Medical Sciences (NAMS), Bir Hospital, Kathmandu, Nepal from May 2021 to October 2021. The study was conducted after obtaining ethical approval from the Institutional Review Board (IRB) of NAMS. Informed written consent was obtained from all the study participants before enrollment. A total of 48 patients who underwent Colonoscopy using PEG were included. The sample size was calculated based on the study done by Yoshida N et alwho had reported the rate of renal dysfunction was 14.8% in patients using PEG for colonoscopy.[21] A predesigned proforma was used for data collection. Patients with AKI due to other causes before colonoscopy and on maintenance hemodialysis were excluded from the study. Detail history including age, gender, presence of comorbidities(HTN, DM, CKD, CLD, and CCF), and use of medications (NSAIDs, ACEI/ARBs and diuretics) were recorded. A renal function test was sent one day prior to bowel preparation and previous reports, if present, were also recorded. Bowel preparation was done using Peglec, a PEG preparation containing 118gm of PEG, 2.93gm of sodium chloride, 1.484gm of potassium chloride, 3.370gm of sodium bicarbonate, and 11.360gm of anhydrous sodium sulfate. One packet of Peglec was prescribed as a routine procedure and advised to dissolve in 2 litre water. Patients were asked to drink 2.0 L of Peglec overnight or it was given in two divided doses (1L at night and the remaining 1.0 L a few hours before colonoscopy) if the patient is elderly or hypervolemic and the following day colonoscopy was done using Fujifilm/Pentax model. Patients who underwent colonoscopy using PEG as an enema in the Gastroenterology department were asked to follow up in the Nephrology department with serum creatinine report after 48 hours and after one week following the procedure and recorded. Pre and Post Colonoscopy creatinine were recorded. eGFR (estimated Glomerular Filtration Rate) pre and post-colonoscopy were calculated by CKD-EPI equation.[22] Patients who develop AKI after 48 hours or after 1 week were kept under regular follow-up and were managed as per department protocol.

**Case definition:** AKI was defined by KDIGO 2012.[12] Patients have been diagnosed with diabetes if on antidiabetic drugs or if fasting blood sugar ≥126 mg/dl or HbA1c ≥6.5% and hypertensive if on antihypertensive drug or if BP ≥140/90 mm of Hg.[23] CKD was diagnosis per KDIGO.[22]

Patients were diagnosed as CCF as per complex clinical syndrome identified by the presence of current or prior characteristic symptoms, such as dyspnea and fatigue, and evidence of cardiac dysfunction as a cause of these symptoms (eg, abnormal left ventricular and/or right ventricular filling and elevated filling pressures).[24–26]

Patients were diagnosed with CLD as per progressive destruction of the liver parenchyma over a period greater than 6 months as indicated by abnormal synthesis of clotting factors or nonspecific signs and symptoms such as fatigue, anorexia, weight loss, or complications such as portal hypertension (esophageal varices, ascites), hepatocellular insufficiency (e.g., jaundice, hepatic encephalopathy), and hepatocellular carcinoma or documented by B-mode ultrasound showing increased echogenicity of the liver parenchyma, poor or non-visualization of the diaphragm, intrahepatic vessels and posterior part of the right hepatic lobe.[27]

**Recovery:** complete recovery was defined as a normal renal function as indicated by normal serum creatinine within 3 months after the procedure and no recovery was defined as failure to normalize serum creatinine within 3 months of the procedure.

### Statistical Analysis

Data obtained were entered in MS Excel and statistical analysis was done by SPSS version 16 (SPSS Inc, Chicago USA). Baseline characteristics were represented using appropriate descriptive Statistics. Continuous variables were expressed as mean ± standard deviation and a comparison of serum creatinine and eGFR in patients with and without AKI was done by using an independent t-test. The association of risk factors with AKI was evaluated by multivariate analysis. P value <0.05 was considered statistically significant at 95% confidence intervals.

## RESULTS

A total of 48 patients who underwent colonoscopy using PEG as a bowel cleansing agent were included in the study and assessed for AKI; its incidence and stages, the association of risk factors [age, gender, CKD, CLD, CCF, diabetes, hypertension and use of NSAIDs, ACEI/ARBs and diuretics] with AKI, and outcome (complete and no recovery) of AKI by 3 months.

The clinic-demographic profile of the study population depicted the mean age of the patients as 45.81 ± 18.60years. The study population comprised 60% (n=29) of males and 40% (n=19) of females respectively. The majority of the patients belong to ≤ 65 years [77% (n=37)]. HTN was the most common co-morbidity (39%) followed by DM (15%), and CKD (10%) with the less common being CLD (4%) and CCF (4%). Most of the patients were taking NSAIDs(12.50%) followed by ARBs(10.4%) and Diuretics(8.33%). There was no significant difference in age, co-morbidities, and concomitant drugs used in male and female study populations as shown in Table 1 respectively. Out of the 48 study participants, 4 (8%) develop AKI; out of which 3 were females and 1 was male; and all were in stage 1 AKI.

**TABLE 1: Clinico-demographic Profile of the Study Population**

| Variables | | Total (n= 48) | Male (n= 29) | Female (n=19) | p-value |
|---|---|---|---|---|---|
| Age (Mean ± S.D.) | | 45.81 ± 18.60 | 44.76 ± 18.20 | 47.42± 19.57 | 0.63 |
| Age | ≤ 65 years | 37 (77%) | 22 (76%) | 15 (79%) | 0.54 |
| | ≥ 65 years | 11 (23%) | 7 (24%) | 4 (21%) | |
| Co-morbidities | Hypertension | 14 (39%) | 8 | 6 | 0.50 |
| | Diabetes Mellitus | 7 (15%) | 5 | 2 | 0.42 |
| | CCF | 2 (4%) | 1 | 1 | 0.64 |
| | CLD | 2 (4%) | 1 | 1 | 0.64 |
| | CKD | 5 (10%) | 2 | 3 | 0.30 |
| Concomitant Drugs used | ARBs | 5 (10.4%) | 2 | 3 | 0.30 |
| | NSAIDs | 6 (12.5%) | 3 | 3 | 0.44 |
| | Diuretics | 4 (8.33%) | 1 | 3 | 0.16 |

Mean ±SD of serum creatinine at baseline, after 48hours, and after 7 days in the AKI group were 2.02 ± 2.37, 2.35 ± 2.45, and 2.35 ± 2.51 respectively. These parameters were compared with the non-AKI group and are statistically significant (Table 2).

**TABLE 2: Comparison of serum creatinine and EGFR levels at baseline, 48 hours, and after 7 days in AKI and non-AKI group**

| Variables | AKI (mean±SD) | Non-AKI (mean±SD) | p-value |
|---|---|---|---|
| Creatinine at Baseline | 2.02 ± 2.37 | 0.99 ± 0.59 | 0.02a* |
| Creatinine at 48 hours | 2.35 ± 2.45 | 0.95 ± 0.48 | 0.001 a* |
| Creatinine at 7 days | 2.35 ± 2.51 | 0.98 ± 0.57 | 0.003 a* |
| Baseline eGFR | 81.75 ± 70.36 | 109.75 ± 35.68 | 0.175 * |
| eGFR at 48 hours | 59.00 ± 48.876 | 110.63 ± 32.56 | 0.005 a* |
| eGFR after 7 days | 70.25 ± 56.23 | 111.06 ± 34/53 | 0.03 a* |

*a= Independent t-test; *p value <0.05 is considered statistically significant*

Multivariate regression analysis depicted that the predictors significantly predict the outcome of AKI in patients using PEG and CCF, CLD and CKD (P=0.001, 0.001, 0.05) were the predictors which significantly influenced the occurrence of AKI in patients using PEG. Also, the patients under diuretics, NSAIDs, and ARBs(P=0.001, 0.002, and 0.05) were significantly associated with AKI in patients using PEG as depicted in Table 3 respectively.

**TABLE 3: Multivariate regression analysis showing the association of different risk factors with AKI in patients using PEG**

| Variables | Beta Coefficient | Standard error | T | 95% CI | p-value |
|---|---|---|---|---|---|
| Intercept | 0.34 | 0.53 | 0.640 | | - |
| Age | -0.09 | 0.07 | 0.885 | -0.211-0.08 | 0.38 |
| Gender | 0.10 | 0.05 | 1.11 | 0.16-0.047 | 0.27 |
| Hypertension | 0.11 | 0.08 | 1.40 | -0.28-0.05 | 0.17 |
| DM | 0.12 | 0.15 | 1.20 | -0.08-0.32 | 0.23 |
| CCF | 0.75 | 0.54 | 3.83 | -1.14-0.35 | 0.001** |

| Variables | Beta Coefficient | Standard error | T | 95% CI | p-value |
|---|---|---|---|---|---|
| **CLD** | 0.82 | 0.59 | 6.14 | 0.55-1.10 | 0.001** |
| **CKD** | 0.20 | 0.22 | 1.95 | -0.07-0.40 | 0.05* |
| **ARBs** | 0.19 | 0.22 | 1.99 | -0.40-0.003 | 0.05* |
| **NSAIDs** | 0.27 | 0.33 | 3.32 | 0.109-0.44 | 0.002* |
| **Diuretics** | 0.58 | 0.58 | 4.05 | 0.29-0.87 | 0.001** |

**p value <0.05 - statistically significant, **p-value <0.001 - statistically significant*

Comparing the treatment outcome in the study population revealed that there was no recovery and complete recovery in 1 and 3 patients respectively who develop AKI (P=0.001) as shown in Table 4.

**TABLE 4: Treatment outcome of AKI in 3 months**

| Variables | AKI | Non-AKI | p-value |
|---|---|---|---|
| **No Recovery** | 1 | 0 | 0.001a* |
| **Complete Recovery** | 3 | 44 | |

*a= Chi-Square test; *p value< 0.05 is considered to be statistically significant*

## DISCUSSION

A successful colonoscopy requires an adequate preparation of the large bowel that facilitates clear visualization of the mucosal surface. The effectiveness of bowel preparation is a critical factor related to the safety, diagnostic accuracy, quality, difficulty, and speed of the examination.[28] So, choosing an appropriate bowel-cleansing agent is essential.[29] Previously, OSP and PEG were considered to be the best bowel-cleansing agents. However, previous studies confirmed that OSP is strongly associated with renal dysfunction and severe electrolyte imbalance.[1,11,30]

Reports of acute renal failure after bowel preparation with sodium phosphates have raised concern about its safety.[31,32] The labeling of OSP has therefore been repeatedly updated, and now includes a contraindication for its use in serious renal disease and CCF, and recommends its cautious use in patients with impaired renal function, heart disease, ascites, dehydration, and electrolyte disturbances, as well as in elderly patients.[33,34] These warnings are also supported by previous studies showing that OSP may cause intravascular volume depletion and may increase the calcium phosphate product, providing a plausible pathophysiological hypothesis for the occurrence of nephrocalcinosis and subsequent renal impairment.[35,36]

Therefore, PEG-based solution is now considered to be the gold standard for bowel preparation.[29,37]Although kidney injuries induced by OSP preparations have been often studied, the effects of PEG solutions on renal function are not well known.[5,11,16,30,38,39]However, a recent study showed that the use of PEG-based solution is also associated with the increased risk of renal dysfunction.[16]

Overall, PEG preparations were considered to be safe with no shifts of fluid and electrolyte and could be prescribed to patients with electrolyte imbalance, CLD, CCF, and CKD. However, there have been reports of asymptomatic increases in plasma volume and exacerbations of heart failure and pre-renal AKI related to diarrhea and fluid loss that had improved with fluid replacement.[13] Some of the PEG preparation also contains large amounts of ascorbic acid that enhances the laxative effect. PEG preparation with ascorbic was reported to cause AKI due to the metabolism of absorbed ascorbic acid to oxalate and deposition of calcium oxalate in the renal tubule leading to acute oxalate nephropathy.[14]

Therefore our study aimed to clarify whether impaired renal function after colonoscopy with PEG is an underrecognized problem in clinical practice, and what risk factors may play a role. The current study also identified risk factors for the incidence of moderate or severe renal dysfunction after colonoscopy.

This study revealed 8% of patients who develop AKI underwent colonoscopy using PEG as a bowel cleansing agent. The known risk factors associated with AKI in those patients were CCF, CLD, CKD, and the use of NSAIDs, ARBs, and diuretics. In this study, the mean age of the patients was 45.81 ± 18.60 years. The study population comprised 60% (n=29) of males and 40% (n=19) of females respectively. The majority of the patients belong to ≤ 65 years [77% (n=37)]. Hypertension was the most common co-morbidity (39%) followed by Diabetes mellitus (15%), and CKD (10%) with the less common being CLD (4%) and CCF (4%).

In contrast to our finding, a case-crossover study reported from south Korea in 2013 had shown that the use of PEG was associated with an increased risk of AKI in screening colonoscopy of 1064 patients aged ≥50 years.[16] However, old age was not an independent risk factor in our study. This could be due to the difference in age as their patients were older (68.5±9.5) with significantly increasing age($p<0.05$), while our patients were younger (45.81±18.60 years) with significantly decreasing age($p<0.63$).

A study conducted by Lee SP et al in 2016 revealed that old age and male sex were independent risk factors for renal impairment.[2] However, on the contrary, this study revealed old age and male sex were not independent risk factors. Out of 4 patients who develop AKI; 4 were female($p=0.16$)and concluded that female patients have more kidney injuries than males.

Another study done in Taiwan conducted a Prospective Observational Study to evaluate the risk of renal injury after the Use of PEG for outpatient colonoscopy. In the subgroup analysis, the use of NSAIDs before colonoscopy was statistically associated with the development of AKI (odds ratio, 6.5; 95% confidence interval, 1.2-35.5; P= 0.03) which was similar to this study (odds ratio, 10.0; 95% confidence interval, 1.09-91.44; P= 0.01). This prospective study showed that the use of PEG was associated with a small risk of renal injury. NSAID use was statistically associated with AKI in the context of colonoscopy for which PEG was used for bowel preparation.15 Similarly, in this study NSAIDs were multivariate predictors of renal impairment after colonoscopy. So, it was recommended to evaluate kidney function before and after colonoscopy, particularly in the high-risk group, and discontinue NSAIDs before using PEG and early fluid replacement in dehydration-related AKI.

Ivanovic LF et al 2018,[6] conducted a study to describe clinical complications related to colonoscopy in patients with multiple diseases. The renal injury occurred in 41.2% of the patients. The

use of diuretics was the only independent variable associated with the development of kidney injury in patients with multiple comorbidities who underwent colonoscopy using Bisacodyl and mannitol as bowel cleansing agents which were quite similar to our study. The only difference was the use of different bowel cleansing agents.

Preexisting renal impairment (CKD), CCF, CLD, and use of NSAIDs, ARBs, and diuretics were multivariate predictors of renal impairment after colonoscopy using PEG as a bowel cleansing agent. However, this study didn't show age, sex, DM, and HTN as other risk factors for renal impairment due to PEG preparation.

In this study, all patients with renal injury recovered fully during follow-up except 1 patient with CKD where there was no recovery and the independent risk factor was CKD and the use of diuretics.

In summary, our results indicate that in patients with no comorbidities and no use of drugs (NSAIDs, ARBs, and diuretics) the risk of renal impairment is minimal using PEG as a bowel cleansing agent during colonoscopy. The risk of severe irreversible renal impairment after colonoscopy appears to be very low in patients with or without preexisting renal disease. Therefore, our study does not argue with the causation of impaired renal function in isolated cases, and this may particularly affect patients with comorbidities, the use of NSAIDs, ARBs, and diuretics. Indeed, our results suggest that such risk factors may particularly be an underrecognized problem in clinical practice.

In the presence of risk factors of renal dysfunction, PEG should be used cautiously, and this includes CLD, CCF, and CKD and those taking drugs that affect fluid and electrolyte balance such as NSAIDs, ARBs, and diuretics. In addition, electrolyte and renal function monitoring after the colonic preparation is also strongly recommended regardless of the kind of PEG-based solution used.

The limitation of this study is the use of a non-probability sampling technique and enrollment of all consecutive patients with inclusion criteria during the study period. We have to keep our sample size small as the COVID-19 pandemic was ongoing during that period. No adverse effect of PEG was evaluated as common adverse effects were hyponatremia, hypokalemia, and hypophosphatemia in different studies.[2] We also could not evaluate all other potential risk factors (sepsis, malignancy, drugs such as beta blocker, calcium channel blocker) due to resource constraints.

## CONCLUSIONS

The evidence strongly suggests that in patients without preexisting renal disease comorbidities and CKD or use of drugs (NSAIDs, ARBs, diuretics) risk of renal impairment is low after colonoscopy using PEG as a bowel cleansing agent. In the presence of risk factors for renal dysfunction, PEG should be used cautiously.

**RECOMMENDATION:** This study can be taken as a baseline for a multicenter prospective study to evaluate the independent risk factors associated with the development of AKI in patients using PEG as a bowel cleansing agent during colonoscopy.

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