

A population-based case-crossover study of polyethylene glycol use and acute renal failure risk in the elderly

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tween polyethylene glycol (PEG) and acute renal failure (ARF) in elderly patients using a health insurance claims database.

METHODS: We conducted a population-based case-crossover study using information obtained from Korean Health Insurance Review and Assessment Service (HIRA) claims from January 1, 2005 to December 31, 2005 (Seoul, Korea). The study population consisted of elderly patients who received PEG prior to experiencing their first ARF-related hospitalization from April 1, 2005 to December 31, 2005. For each patient, one case and two control periods were matched. PEG use in a 2- or 4-wk window period prior to hospitalization for ARF was compared with PEG use in two earlier 2- or 4-wk control window periods. Conditional logistic regression analysis was used to estimate odds ratios (ORs) and 95% CI, adjusting for concomitant uses of diuretics, angiotensin converting enzyme inhibitors, non-steroidal anti-inflammatory drugs, antibiotics, anti-cancer drugs, and contrast media.

RESULTS: Within the HIRA database which contained 1093262 elderly patients, 1156 hospitalized ARF cases were identified. Among these cases, PEG was prescribed to 17 (1.5%) patients before hospitalization. The adjusted ORs when applying the 2- and 4-wk window periods were 0.4 (95% CI: 0.03-5.24) and 2.1 (95% CI: 0.16-27.78), respectively.

CONCLUSION: No increased risk of ARF was found in elderly PEG users. However, based on the limited number of study subjects, further analysis should be performed to confirm these results.

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Key words: Polyethylene glycol; Acute renal failure; Adverse drug reaction; Health insurance claims database; Case-crossover

Abstract

AIM: To evaluate the possibility of an association be-

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INTRODUCTION

Colonoscopy is a common diagnostic or therapeutic procedure. As early detection of colorectal cancer can significantly decrease mortality^[1], regular screening is recommended for those aged 50 years or over^[2]. The success and accuracy of colonoscopy are largely dependent on appropriate cleansing of the colon^[3]. Ideally, a colon preparation would provide safe and rapid cleansing with little or no discomfort to patients^[4]. Currently, polyethylene glycol (PEG) bowel preparation and oral sodium phosphate (NaP) are predominantly used as bowel cleansing agents before colonoscopy based on the fact that they are effective and generally well tolerated^[5-7]. PEG is a non-digestible, non-absorbable, osmotically-balanced laxative lavage solution that does not cause physiologic changes and can even be administered to patients in poor general condition^[8-12].

However, several recent studies have raised concerns about the safety of oral NaP preparations due to their reported association with an increased risk of serious electrolyte disturbances and renal failure^[13]. Conversely, although a large volume of PEG produces discomfort to the examinee, it is considered to be a relatively safe agent. Therefore, there has been a tendency to prescribe PEG more than NaP for renally impaired or elderly patients^[14]. Recently, several studies have shown that the risk of renal impairment is similar between PEG and NaP users^[15,16]. In addition, a case report has raised a possible association between the use of PEG and acute renal failure (ARF)^[17]. The patient in that case was a 55-year-old male without pre-existing renal disease who visited the emergency room with severe abdominal pain and frequent diarrhea after ingesting PEG 2 h earlier as pre-treatment for a follow-up colonoscopy. He was diagnosed as having prerenal ARF and improved after intensive fluid administration. Also, a recent cohort study revealed that following colonoscopy, those over 65 years of age without preexisting renal disease were at risk for impaired renal function^[16]. Unfortunately, most of the evidence for PEG risk to date has been based on a limited number of hospital patients or the case report mentioned.

There have been no quantitative epidemiological studies analyzing a relationship between PEG preparation and the development of ARF using a national health insur-

ance database. Therefore, this case-crossover study was performed to evaluate the risk of ARF following the use of PEG among elderly patients using information gathered from a Korean national health insurance database.

MATERIALS AND METHODS

Data source

We used the Korean Health Insurance Review and Assessment Service (HIRA) database that contains information on all claims including prescribed medications for approximately all 50 million Koreans^[18]. We obtained claims data for elderly patients (age 65 years or older) that had been submitted by healthcare providers based in Seoul between January 1, 2005 and December 31, 2005. Seoul is the capital and largest city of South Korea. A megacity with a population of over 12 million, it is one of the largest cities in the world. The study database contained information on 1 093 262 elderly patients with 11 842 586 prescriptions^[19]. This study was exempted from review by the Institutional Review Board of the Seoul National University College of Medicine/Seoul National University Hospital because researchers only accessed a de-identified database which included age, gender, diagnosis, and a list of prescribed drugs.

Study design

We employed a case-crossover approach, using cases at previous time points as their own controls, thereby eliminating time-invariant confounders between subjects through within-subject difference comparisons^[20]. In this design, only patients experiencing an event of interest were included and their exposures were measured during case- and control-time windows. Accordingly, the number having medication available in the case period (which is the period immediately before the event of interest) is compared with the number having medication available in the control period (which is a period prior to but of the same length as the case period)^[21]. Thus this design eliminates the effects of many potential confounders by keeping characteristics such as age, gender, socioeconomic status, and comorbidity fixed^[21,22].

Study subjects

The study population consisted of patients 65 years of age or older who received PEG prior to their first ARF-related hospitalization (ICD-10 code: N17) from April 1, 2005 to December 31, 2005. The index date was defined as the first hospital admission date for ARF. To identify initial ARF admission patients, we excluded those with pre-existing ARF during the preceding 3 mo, from January 1, 2005 to March 30, 2005.

Case and control periods

For each patient, one case and two control periods were matched to increase the study power and improve the precision of the estimates^[23]. The time windows, of 2 and 4 wk, were used to determine the periods over which as-

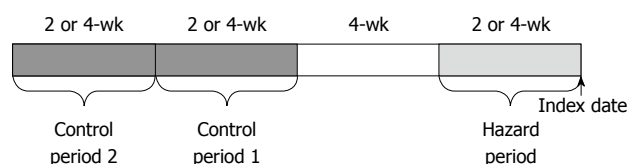


Figure 1 Definition of hazard and control periods in this case-crossover study. Hazard period was defined as the 2- or 4-wk window before the index date. A 4-wk washout period was chosen between the end of the hazard period and the start of the control period. Two consecutive control periods were defined as 2- or 4-wk windows.

assessment of drug exposure occurred. We defined the case period as a 2- or 4-wk window prior to the index date. A 4-wk washout period was chosen between the end of the case period and the start of the control period. Two consecutive control periods were also defined as 2- and 4-wk windows (Figure 1). Accordingly, for each patient, PEG prescription in each window period prior to hospitalization for ARF was compared with PEG prescription in two earlier control-window periods.

Statistical analyses

Descriptive statistics were used to illustrate the characteristics of the first ARF-hospitalized patients by age and gender. For the study population, the distribution of diagnoses on the day of PEG prescription was analyzed. Diagnoses were constructed from records made at the time of PEG prescription and grouped as colorectal cancer (ICD-10 codes: C18-C21, D12), gastric or duodenal ulcer, gastritis or duodenitis, intestinal disorders (K25-K59), renal disease (N03-N20), fibrosis and cirrhosis of the liver (K74), liver cancer (C22), and pancreatic cancer (C25). Conditional logistic regression analysis was used to estimate odds ratios (ORs) and 95% CI. The date of PEG exposure was regarded as the date of PEG prescription in the database. Use of concomitant medications that could induce ARF^[24,25] was included and evaluated in the model. Concomitant drugs included diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, β -lactams, sulfonamides, anti-viral agents, antimycotics, anti-cancer drugs, and contrast media. We assessed PEG prescriptions and uses of concomitant drugs included in the case- or control-window periods. Exposure to PEG and other concomitant drugs was considered as a dichotomous variable in the model (exposed at least once during each specific time window: yes or no). Statistical analysis was performed using the SAS statistical application program (Release 9.1, SAS Institute Inc., Cary, NC, USA).

RESULTS

The total number of elderly patients who had at least one claim for any healthcare service in Seoul between January 1, 2005 and December 31, 2005 was 1 093 262. Their mean age was 71.0 ± 6.1 years and 59.9% were female.

Table 1 Characteristics of elderly patients who had at least one claim for any healthcare service in Seoul between January 1, 2005 and December 31, 2005 and those who were hospitalized for acute renal failure among the population *n* (%)

| | Total of elderly patients | Patients hospitalized for ARF |
|---------------|---------------------------|-------------------------------|
| Age (yr) | | |
| mean \pm SD | 72.0 \pm 6.1 | 75.9 \pm 7.3 |
| 65-69 | 472 614 (43.2) | 270 (23.4) |
| 70-74 | 297 348 (27.2) | 260 (22.5) |
| 75-79 | 179 562 (16.4) | 272 (23.5) |
| 80-84 | 96 131 (8.8) | 197 (17) |
| ≥ 85 | 47 607 (4.4) | 157 (13.6) |
| Sex | | |
| Male | 438 795 (40.1) | 587 (50.8) |
| Female | 654 497 (59.9) | 569 (49.2) |
| Total | 1 093 262 (100) | 1156 (100) |

ARF: Acute renal failure.

Table 2 Characteristics of elderly patients with polyethylene glycol prescription prior to hospitalization for acute renal failure

| | <i>n</i> (%) |
|--|----------------|
| Age (yr) | |
| mean \pm SD | 70.6 \pm 4.6 |
| 65-69 | 8 (47.1) |
| 70-74 | 5 (29.4) |
| 75-79 | 3 (17.6) |
| 80-84 | 1 (5.9) |
| Sex | |
| Male | 14 (82.4) |
| Female | 3 (17.6) |
| Diagnoses on the day of PEG prescription | |
| Colorectal cancer | 6 (35.3) |
| Gastric or duodenal ulcer, gastritis or duodenitis, intestinal disorders | 6 (35.3) |
| Renal disease | 3 (17.6) |
| Fibrosis and cirrhosis of liver | 2 (11.8) |
| Liver cancer | 1 (5.9) |
| Pancreatic cancer | 1 (5.9) |
| Total | 17 (100) |

PEG: Polyethylene glycol.

Among them, we identified 1156 patients hospitalized for ARF with a mean age of 75.9 ± 7.3 years. Patient sex was split relatively equally with males accounting for 50.8% of cases (Table 1). Among the cases of ARF, 17 (1.5%) had received PEG prior to their hospitalization. Their mean (SD) age was 70.6 (4.6) years and 82.4% (14 cases) of them were male. The most frequent diagnoses on the day of PEG prescription were colorectal cancer (35.3%), gastric or duodenal ulcer, gastritis or duodenitis, or intestinal disorders (35.3%) (Table 2). Using the 2- and 4-wk windows, the crude ORs for ARF were 0.7 (95% CI: 0.07-6.41) and 1.3 (95% CI: 0.22-7.99), respectively. After adjusting for the use of concomitant drugs the adjusted ORs applying the 2- and 4-wk windows were 0.4 (95% CI: 0.03-5.24) and 2.1 (95% CI: 0.16-27.78), respectively (Table 3).

Table 3 Association between polyethylene glycol and the risk of acute renal failure with respect to time-window periods by matched ratio of case and control period

| Time-window period | Case period (<i>n</i> = 17) | Control period (<i>n</i> = 34) | Crude OR (95% CI) ¹ | Adjusted OR (95% CI) ² |
|--------------------|---------------------------------|------------------------------------|-----------------------------------|--------------------------------------|
| 2 wk | | | | |
| PEG non-users | 16 | 31 | 1 | 1 |
| PEG users | 1 | 3 | 0.7 (0.07-6.41) | 0.4 (0.03-5.24) |
| 4 wk | | | | |
| PEG non-users | 15 | 31 | 1 | 1 |
| PEG users | 2 | 3 | 1.3 (0.22-7.99) | 2.1 (0.16-27.78) |

¹Calculated by conditional logistic regression; ²Calculated by conditional logistic regression adjusted for use of nephrotoxic drugs (diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory drugs, aminoglycoside, β -lactams, antiviral agents, antimycotics, anti-cancer drugs, and contrast media). PEG: Polyethylene glycol; OR: Odds ratio.

DISCUSSION

This population-based case-crossover study showed that PEG did not increase the risk of ARF in elderly patients. When several different time-window periods were applied, the use of PEG was not associated with ARF risk. This study supports findings of previous reports which have suggested that PEG does not increase the risk of ARF^[12,26-29]. Known PEG-associated common adverse effects include volume-related symptoms of abdominal fullness, nausea, and bloating, with minimal discomfort^[26]. Also, previous results of a prospective, randomized, multicenter, controlled trial comparing PEG plus ascorbic acid to NaP solution in 352 patients had shown that PEG use was associated with fewer adverse events and no clinically relevant changes in laboratory values^[27]. In a study addressing age, 557 patients were stratified into two groups, > 60 years and \leq 60 years of age, all of whom received either PEG or a cathartic preparation for colonoscopy, barium enema, or elective colon surgery^[28]. Patients in the older age group reported significantly fewer cramps ($P < 0.05$) and no differences in overall discomfort compared to their younger PEG counterparts, confirming the generally accepted understanding that PEG is safe and tolerable^[12,29].

In our study, we excluded patients admitted with a diagnosis of ARF 3 mo before the study starting date; therefore we could infer that PEG did not increase the risk of ARF among patients without recent worsening of renal function. However, because decreased renal function is extremely common in elderly persons^[30], the study population might have asymptotically decreased renal function. Further studies should be performed to examine the possibility that PEG could worsen existing renal impairment and hasten its progression to ARF. Moreover, although the study results did not show a statistically significant risk for ARF in PEG users, it may be desirable to ensure adequate hydration before, during, and after PEG bowel preparation and provide renal function monitoring before and after colonoscopy in high risk patients.

We applied a case-crossover design optimal for evaluating short-term effects after transient exposures, particularly by removing time-invariant between-subject confounding factors^[31]. Results of clinical trials are sometimes difficult to generalize to clinical practice and rarely detect adverse event incidents because they include only small numbers of highly selected patients. Also, the estimates of adverse drug effects derived from observational studies are vulnerable to unmeasured or unknown confounding factors, associated with both the exposure and the outcome^[20]. Actually, a previous cohort study which aimed to compare the risk of renal dysfunction related to the use of PEG and NaP mentioned that its results could be affected by potential selection bias^[11]. The cohort study was conducted using clinical records of patients undergoing colonoscopy in one hospital. Accordingly, the baseline patient characteristics might have affected which drugs were prescribed and the two groups were not comparable^[32,33]. In the present study, using the case-crossover technique, only cases with incident renal failure were considered and their PEG exposures were compared during two different time-windows. Since inherent confounders remain invariant over time, the case-crossover design which is optimal for transient exposures with short-term effects has an advantage in that it can minimize between-subject confounding and assure an optimal sample size^[31].

This study has several strengths. Firstly, we evaluated patients from an entire target population of over one million elderly derived from the national health insurance claims database in Seoul, South Korea, rather than use a sample population. Therefore, our results reflect unbiased real world conditions. Nevertheless, we identified only 17 cases of ARF following PEG use. This means that there is little possibility the PEG would increase the risk of ARF. Secondly, this study included elderly patients who are not usually involved in clinical trials or safety studies, but are at high risk of renal failure related to bowel preparations. Thirdly, although we controlled unmeasured confounders which were stable over time by using a case-crossover design, we further adjusted for other medication use which could affect the development of ARF such as diuretics, ACE inhibitors, ARBs, β -blockers, NSAIDs, aminoglycosides, β -lactams, anti-viral agents, antimycotics, anti-cancer drugs, and contrast media^[24,25].

However, our results should also be interpreted with caution. Although ARF is generally defined as an abrupt and sustained decline in the glomerular filtration rate (GFR)^[34], we defined incident cases of ARF as hospitalization with diagnosis of ARF in the HIRA database. Since the database did not contain laboratory test results such as GFR, a validation study was used to compare the diagnosis derived from the HIRA database with the actual diagnosis in the patients' medical records. The overall positive predictive value of the diagnoses was 81.8% in cases of hospitalized patients^[35]. Also, ARF as defined in this study only included symptomatic and serious events requiring hospitalization. We defined the date of PEG exposure as the prescription date of PEG; however, there could be a

difference of several days or more between the date of prescription and actual administration. Nonetheless, the date of PEG administration followed the prescription, so the period from the actual PEG exposure date to ARF hospitalization might in fact be shorter than calculated.

In this study, PEG was found not to be associated with an increased risk of ARF in elderly patients. However, further studies should be conducted to confirm an association or lack thereof.

COMMENTS

Background

Polyethylene glycol (PEG), a commonly used solution for colonoscopy bowel preparation, is regarded as effective and tolerable. Recent reports have cited an increased risk of acute renal failure (ARF) in the elderly. Until now there have been no quantitative population-based epidemiological studies analyzing a possible relationship between PEG and ARF.

Research frontiers

Colonoscopy is a common diagnostic or therapeutic procedure. The success and accuracy of colonoscopy are largely dependent on appropriate cleansing of the colon. Ideally, a colon preparation would provide safe and rapid cleansing with little or no discomfort to patients. Currently, PEG bowel preparation and oral sodium phosphate (NaP) are predominantly used as bowel cleansing agents before colonoscopy based on the fact that they are effective and generally well tolerated.

Innovations and breakthroughs

Several recent studies have raised concerns about the safety of oral NaP preparations due to their reported association with an increased risk of serious electrolyte disturbances and renal failure. There have been no quantitative epidemiological studies analyzing a relationship between PEG preparation and the development of ARF using a national health insurance database. Therefore, this case-crossover study was performed to evaluate the risk of ARF following the use of PEG among elderly patients using information gathered from the Korean national health insurance database.

Applications

No increased risk of ARF was found in elderly PEG users. However, based on the number of study subjects, further analysis should be performed to confirm an association or lack thereof.

Peer review

This is very well constructed paper regarding the possibility of an association between PEG and ARF in elderly patients.

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