Does the use of low osmolality contrast medium reduce the frequency of post-ERCP pancreatitis? : a comparative study between use of low and high osmolality contrast media

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ABSTRACT

Introduction: A few reports stating that differences in the various types of contrast media injected into the pancreatic duct are related to the onset of Post-ERCP pancreatitis (PEP) have been published, and it was indicated that iodixanol which is a non-ionic iodide radiographic contrast medium with a dimeric (2 dimers) structure may reduce the incidence of PEP. The aim of this retrospective study is to evaluate the usefulness of iodaxanol for prevention PEP in comparison with megulamine amidototrizoate.

Methods: 291 patients were enrolled, and divided into the two groups according to the contrast medium used. 155 patients underwent ERCP with meglumine amidotrizoate, and 136 patients underwent ERCP with iodaxanol. The primary outcome of this study was the incidence of PEP associated with the use of each contrast medium.

Results: In this study, comparison of the meglumine amidotrizoate treatment and iodaxanol treatment groups showed no significant difference with respect to the incidence of PEP. In addition, there was also no difference between the groups with respect to PEP severity.

Conclusion: Our study suggested that iodaxanol does not necessarily contribute to the prevention of PEP in comparison with meglumine amidotrizoate.

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) plays an important role in the diagnosis and treatment of biliopancreatic diseases. Post-ERCP pancreatitis (PEP) is a serious complication that may worsen the patient's condition and even result in death. Impaired pancreatic juice flow (increased pressure in the pancreatic duct) due to papillary edema, insertion of foreign body in the pancreatic duct, direct impairment of the pancreatic tube epithelium/acinar epithelium due to injection of a contrast medium and contamination with exotoxins such as endotoxin, are among the suggested causes of PEP onset. From this viewpoint, various strategies for preventing PEP onset, such as pancreatic stent placement and prophylactic administration of a nonsteroidal anti-inflammatory/analgesic drug have been investigated[1-5].

Recently, a few reports stating that differences in the various types of contrast media injected into the pancreatic duct are related to the onset of PEP have been published. The possibility that osmolality-induced toxicity and ionic toxicity due to contrast media trigger physicochemical effects in the pancreatic duct has been pointed out. Banerjee et al [6] reported that when ERCP was performed using a non-ionic, low osmolality contrast medium, the incidence of PEP tended to be low. Recently, in addition to conventional contrast medium for ERCP, meglumine amidotrizoate (Urografin®), iodaxanol (VISIPAQUE®) which is a non-ionic iodide radiographic contrast medium with a dimeric (2 dimers) structure was introduced and can be used in ERCP procedures. The details of 2 contrast mediums are shown in Table1. The osmolality ratio (ratio to physiological saline) of this radiographic contrast medium is approximately 1 and compared to the conventionally used high osmolality iodinated contrast medium, meglumine amidotrizoate. Thus, its osmotic cytotoxicity to the pancreatic duct is low. Moreover, when used during ERCP, the onset of PEP was likely inhibited[7]. The aim of this retrospective study is to evaluate the usefulness of iodaxanol for prevention PEP in comparison with megulamine amidototrizoate.

PATIENTS AND METHODS

Study design

This was a single-institution retrospective cohort study assessing the onset of PEP due to differences in the contrast media used. This study was approved by the SUBARU Ota Memorial Hospital ethics committee (approval number: OR18007) and was conducted in accordance with the principles of the Declaration of Helsinki and registered on the University Hospital Medical Network Clinical Trials Registry [UMIN R000042246]. The patients were provided the opportunity to opt out instead of omitting informed consent,

which is a way to guarantee the opportunity for research subjects to notify and publish research information on our website.

The primary endpoint was the incidence of PEP associated with the use of each contrast medium, and the secondary endpoints was an increase in pancreatic enzyme (amylase) levels and PEP severity post-ERCP in using each contrast medium.

Patients

At SUBARU Ota Memorial Hospital, the basic contrast medium that was used until May 2016 when performing ERCP was meglumine amidotrizoate. From June of the same year, the contrast medium was switched to iodaxanol. In order to investigate PEP onset associated with the use of a specific contrast medium, we extracted information from the medical records of 975 consecutive patients who underwent ERCP between October 2015 and December 2016. Of these patients, those with items that would have likely affected the investigation of PEP onset according to the type of contrast medium, such as those who had already undergone intervention for duodenal major papilla such as endoscopic sphincterotomy (EST) and endoscopic papillary balloon dilation, those with a malignant tumor, and those who had biliary pancreatitis, patients with surgically altered anatomy, underwent self-expandable metal stent (SEMS) placement, and underwent placement of the pancreatic stent after the ERCP to prevent PEP, were excluded. Finally, 291 patients with naïve papilla were enrolled, and divided into the two groups according to the contrast medium used; 155 patients underwent ERCP with meglumine amidotrizoate from October 2015 to May 2016 (the group A) and the 136 cases in whom iodaxanol was used from June 2016 to December 2016 (the group I) (Figure 1).

Endoscopic procedures and equipment

Prior to performing the ERCP-related procedures, 25 mg diclofenac sodium and ulinastatin (150,000 units) which have been reported to prevent PEP[8, 9], was administered, the former was transanally and the latter was intravenously, to all the patients. The ERCP-related procedures were performed by 2 endoscopists who had the experience of at least 2000 cases of ERCP performed under analgesic/sedative management where appropriate breathing environment system monitoring was performed while pethidine hydrochloride was being administered concomitantly with midazolam.

One type of duodenal endoscope (JF-260V， Olympus Co., Tokyo) was used for all the patients. The contrast mediums were not diluted. The standard ERCP catheter (4Q/10Q， Olympus Co., Tokyo; or ERCP catheter tapered tip, MTW Endoskopie Co., Germany), and a standard 0.025-inch guidewire (Visiglide 2， Olympus Co., Tokyo) were

used. The guidewire was preloaded into the catheter, and the contrast medium-guided cannulation, wherein the catheter was directly inserted after confirming the biliary and pancreatic ducts by injecting a minute amount of contrast medium, was performed. The wire-guided cannulation was not performed for all patients. Moreover, for patients in whom selective insertion to the bile duct was difficult, the pancreatic duct guidewire method[10] or the precut method[11] was performed if contrast imaging of the pancreatic duct had been performed at least twice. In the EST procedure, a standard sphincterotome (Clever Cut 3， Olympus Co., Tokyo) was used and the incision spanned up to the center. In the precut procedure, a standard needle knife (RX Needleknife XL, Boston Scientific Japan Co., Tokyo) was used. If necessary, intraductal ultrasound (IDUS), biopsy and brush cytology were performed.

In patients with choledocholithiasis, stone removal was performed using a basket catheter (Flower Basket V, Olympus Co., Tokyo) or balloon catheter (MULTI-3V PLUS Olympus Co., Tokyo) after the EST. In addition, if necessary, a 7−8.5Fr plastic biliary stent (Flexima, Boston Scientific Japan Co, Tokyo) or a 5-6Fr endoscopic nasal biliary drainage-tube (Silky Pass, Boston Scientific Japan Co., Tokyo) was placed for biliary drainage.

Evaluation of adverse events

Pancreatic amylase level before treatment was the day before or on the day of ERCP. Blood tests and urinalysis were performed at 2 hours post-ERCP to confirm the level of amylase in the blood and urine. When the blood tests and urinalysis at 2 hours post-ERCP confirmed that the pancreatic enzyme level was ≥3 times the normal level, 1000 ml of extracellular fluid was administered. The following day, blood tests were performed, abdominal symptoms evaluated, and a contrast CT was performed, if necessary.

Severity of PEP was evaluated based on the classification proposed by Cotton et al[12]. PEP was diagnosed when the patient had acute pancreatitis, the serum amylase level at 24 hours post-ERCP was increased to ≥3 times the normal level, and hospitalization was required. With regard to the judgement of severity, ‘mild’ was judged when hospital stay was prolonged by 2-3 days, ‘moderate’ when 4-10 days of hospitalization was required, and ‘serious’ when ≥10 days of hospitalization was required. Serious PEP was also diagnosed when a patient had hemorrhagic pancreatitis or pancreatic necrosis/pseudocysts requiring drainage. All adverse events that occurred due to ERCP-related procedures were extracted from the medical records.

STATISTICAL ANALYSIS

IBM SPSS Statistics 21® (IBM Japan, Ltd.) was used for the statistical analysis. The continuous variables such as age, body mass index (BMI), and pancreatic amylase level were analyzed using the Student *t*-test. Parameters such as pancreatic duct findings and pancreatitis were compared using the $\chi 2$ test. Statistical significance was set at $P < 0.05$.

RESULTS

Patients' background data and endoscopic procedures

The age of our 291 patients presented the normal distribution. The median age of all patients was 77 years (range 28-95 years) and there were 144 males and 147 females. By the contrast medium used, the median age of subjects in group A (n = 155) was 75 years (28-94 years) and in group I (n = 136), it was 77 years (28-95 years), showing no statistical difference. Moreover, the preoperative serum amylase level, BMI, and underlying disease also showed no difference between the 2 groups (Table 2). The endoscopic procedure-related parameters, such as pancreatic duct guidewire procedure, frequency of IDUS, EST, choledocholithiasis, frequency of bile duct stone remover use, and bile duct stent placement, showed no difference between the groups. In addition, there was also no difference regarding the frequency of pancreatic duct imaging. The total intervention time was 20.4 and 24.8 min in groups A and I, respectively, showing a slightly longer time for group I; however, this difference was not significant (Table 3).

Post-ERCP pancreatitis / Post-ERCP hyperamylasemia

1) PEP incidence and severity

PEP occurred in 13 of all the subjects with an incidence of 4.5%. In group A, it occurred in 6 patients (3.9%) with all being judged as mild cases, whereas in group I, it occurred in 7 patients (5.1%; 6 cases were mild and 1 was moderate). There was no statistical difference in incidence and severity of PEP between the 2 groups (Table 4,5).

2) pancreatic enzyme levels in the blood post-ERCP

The number of patients who did not meet the PEP diagnostic criteria but had high pancreatic enzyme levels in the blood post-ERCP was significantly high in group I both 2 and 24 hours post-ERCP (group A: 5 (3.2%) patients at 2 hours post-ERCP and 12 (7.7%) at 24 hours post-ERCP; group I: 14 (10.3%) patients at 2 hours post-ERCP and 21 (15.4%) at 24 hours post-ERCP) (Table 4).

DISCUSSION

As above-mentioned, iodaxanol is a non-ionic iodide contrast medium, it is expected

to reduce PEP compared to conventional contrast medium, meglumine amidotrizoate. However, its pharmaceutical prices in national health insurance is high, therefore, if no difference in PEP incidence between the 2 drugs is noted, use of meglumine amidotrizoate is recommended from a medical-economic point of view. Thus, in this study, we investigated the actual efficacy of iodaxanol in preventing PEP incidence retrospectively.

While this investigation was retrospective, the number of subjects was higher than that in previous reports, and the post-ERCP serum pancreas amylase level as well as incidence and severity of PEP could be investigated according to the contrast medium used. Moreover, although this was a retrospective study, there was no difference between the 2 groups with respect to parameters such as patients' background, additional techniques, and frequency of pancreatic duct imaging. Therefore, it is considered that we could show the presented results with many biases related with retrospective study eliminated.

Impaired pancreatic fluid flow and the consequent increased pressure in the pancreatic duct and direct impairment of the pancreatic tube epithelium/acinar epithelium are the suggested causes of PEP onset. These factors suggest that if blood flow is impaired and trypsin is activated, various chemical inhibitors will simultaneously be induced resulting in the disruption of the protective function triggering the onset of PEP [13-17]. Also, the physicochemical action of a high-osmolality contrast medium on the pancreatic duct walls is likely one of the causes of the onset of acute pancreatitis. Moreover, increased pressure in the pancreatic duct worsens PEP. In the development of an experimental pancreatitis model, bile juice and trypsin were injected into the pancreatic duct using excessive pressure and necrotic pancreatitis could be modeled for the first time. Increased pressure in the pancreatic duct was suggested to be involved in the worsening of PEP [13, 18]. Considering these mechanisms, one can predict that use of the non-ionic low osmolality contrast medium, iodaxanol, likely inhibits the incidence and worsening of PEP, and reports mention that its usefulness can be seen in some cases. However, in this study, comparison of the meglumine amidotrizoate treatment and iodaxanol treatment groups showed no significant difference with respect to the incidence of PEP. In addition, there was also no difference between the groups with respect to PEP severity. Thus, the results of this study and the lower national health insurance drug price of meglumine amidotrizoate suggest that meglumine amidotrizoate should be used when performing ERCP, but not iodaxanol.

On the other hand, contrary to initial expectations, the proportion of patients with high pancreatic enzyme levels in the blood post-ERCP was high in the iodaxanol group, fortunately, worsening of acute pancreatitis was not noted in any of the cases. Although

it is difficult to explain this reason clearly, the following can be considered as a hypothesis: there was no difference in the frequency of pancreatic duct imaging between the two groups; however, the volume of the used contrast medium was not evaluated. In other words, as this was not a blinded study, an endoscopist that used iodixanol might inject a large quantity of the contrast medium into the pancreatic duct. The above is a major limitation of this study. Other limitations were 1) its single-institution retrospective design in certain period, 2) the improvement in the skills of the endoscopists with experience as part of the learning curve was not investigated, 3) the factors previously suggested as causes of PEP were not adequately investigated in detail, 4) In this study, we have excluded the patients who were performed the procedure that have an impact on the occurrence of PEP, such as indwelling of the SEMS or pancreatic stent, because the aim of this study was to clarify the effect of the just only contrast medium for PEP. Therefore, considering the frequency of PEP (4.5% in this study), the number of patients was not sufficient for evaluation due to many excluded cases. However, based on the fact that no difference was seen in the incidence of PEP between the 2 groups without any notable difference in the patients' background characteristics, one can conclude that the use of iodaxanol did not contribute to the prevention of PEP. The prevention of PEP onset is crucial for a safe ERCP, and a large-scale prospective study needs to be performed in the future to further validate the findings of this study.

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Statement of Ethics

This study was approved by the SUBARU Ota Memorial Hospital ethics committee (approval number: OR18007) and was conducted in accordance with the principles of the Declaration of Helsinki and registered on the University Hospital Medical Network Clinical Trials Registry [UMIN R000042246]. The patients were provided the opportunity to opt out instead of omitting informed consent, which is a way to guarantee the opportunity for research subjects to notify and publish research information on our website.

Disclosure Statement

The authors declare no conflicts of interest regarding this review article.

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Authorship statement

Kazunori Nagashima and Atsushi Irisawa wrote the manuscript with data analysis. Masashi Ijima and Kouichirou Kimura were performed ERCP and analyzed the data. Eishin Kurihara, Keiichi Tominaga, Koh Fukushi and Akira Kanamori contributed to the analysis of the data from medical chart, and making the tables. Yosuke Otake advised the writing the manuscript and analysis of the all data.

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Figure Legend

Flow diagram of this study