A Comparison of Ionic, Monomer, High Osmolar Contrast Media with Non-ionic, Dimer, Iso-osmolar Contrast Media in ERCP

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Objective: Pancreatitis is the most common and serious complication of endoscopic retrograde cholangiopancreatography (ERCP). Several studies have compared contrast media (CM) with different osmolalities, but the results are conflicting. We conducted this study to clarify the difference between 2 CM used in ERCP.
Methods: Five hundred and seventy-six patients were examined by using ERCP in our hospital during 2010. Out of these, 56 patients were enrolled in this study. We investigated the incidence of post ERCP pancreatitis (PEP) and hyperamylasemia. Serum amylase levels were compared in the 2 groups.
Results: Twenty-seven patients were treated with iodixanol and 29 with diatrizoate meglumine Na. The rate of PEP in the diatrizoate meglumine Na group and iodixanol group was 0% (0/29) and 7.4% (2/27), respectively (P = 0.228). The rate of hyperamylasemia was 10.3% (3/29) and 14.8% (4/27), respectively (P = 0.70). There were no significant differences between two groups for amylase levels pre-procedure (P = 0.082), 3 h post procedure (P = 0.744), or next morning (P = 0.265).
Conclusions: There were no significant differences in the rates of PEP or hyperamylasemia between CMs in ERCP. We believe it is unnecessary to use the more expensive low osmolality CM in ERCP to prevent PEP.

Key words: Contrast media, ERCP, Pancreatitis, Osmolality

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is used for the diagnosis and treatment of a variety of hepatobiliary and pancreatic disorders. However, this procedure has a higher potential for serious complications than any other standard endoscopic technique. Complications of ERCP include pancreatitis, bleeding, infection, and perforation. Among these, pancreatitis is the most frequent, occurring in 1%−9% of cases [1−6]. Several studies have identified the following risk factors for overall complications: difficulty of cannulation, biliary sphincterotomy, precut sphincterotomy, sphincter of Oddi dysfunction, parapapillary diverticulum of the duodenum, and cirrhosis [3, 7−10]. Post-ERCP pancreatitis (PEP) occurs in about 40% of cases depending on the presence of these risk factors [1−3, 6−8, 11−19]. Several studies have confirmed that pancreatic duct stent placement or pharmacological agents can prevent PEP [20, 21]. In addition, the possibility of the contrast media (CM) irritating the pancreatic ductal epithelium has been reported [22−24], and several studies have compared the frequency of PEP between different CM. The osmolality of CM has been implicated as a contributing factor to the development of PEP [25]. CM are classified into 2 groups depending on their ionic properties (ionic or non-ionic) and 3 types according to their osmolality (high, low, or iso-osmolar) [26]. The image quality appears to be similar when comparing high osmolality CM (HOCM) and low osmolality CM (LOCM) [27]. However, there is a considerable controversy regarding the role of osmolality of CM in the development of PEP and the results of clinical trials are conflicting. One randomized cross-over study [28] and 4 randomized control trials [29−32] have suggested a benefit from LOCM, while 10 others have not [27, 33−41]. In our study, we investigated the difference in serum amylase levels after ERCP and the frequency of PEP between diatrizoate meglumine Na (ionic HOCM, Urographin® 60%) and iodixanol (iso-osmolar, non-ionic dimer CM, Visipaque® 270) in ERCP.

MATERIALS AND METHODS

Five hundred and seventy-six patients underwent ERCP in our institution from January to December 2010. We used diatrizoate meglumine Na (Urographin®60%) and iodixanol (Visipaque® 270) on alternate days during this year. Fifty-six of these patients who underwent ERCP but did not undergo brushing cytology, biopsy, intraductal ultrasound, or pancreatic duct stenting were included in the study. We investigated the incidence of PEP and hyperamylasemia (defined as 3 times higher than the upper limit of normal in our institution) and compared with the serum amylase level pre-procedure, 3 h post-procedure, and the next morning in 2 CM groups (Urografin® group and Visipaque® group). The investigation conformed to the principles outlined in the Declaration of Helsinki.

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Table 1 Properties of the two contrast media

Contrast media	Ionic properties	Osmolality (osm/kg H_2O)	Viscosity (mPa・s) (37°C)	pH	Cost(¥/ml)
Diatrizoate meglumine Na (Urografin®60)	ionic	1500	4.0	6.0～7.7	27.05
Iodixanol (Visipaque®270)	non ionic	290	5.8	6.7～7.7	112.8

Table 2 Patient characteristics

	Urografin® (N = 29)	Visipaque® (N = 27)	*p* value
Age – year mean ± SD	65.21 ± 10.63	65.19 ± 11.98	0.994
Sex –Female/Male	15/14	14/13	0.992
Diagnosis- No(%)			
CBD stone	11 (37.9)	8 (29.6)	0.512
pancreatic tumor	5 (17.2)	6 (22.2)	0.639
bile duct tumor	4 (13.8)	8 (29.6)	0.149
pancreaticobiliary maljunction	4 (13.8)	1 (3.7)	0.353
AIP	2 (6.9)	1 (3.7)	1
normal	2 (6.9)	1 (3.7)	1
pancratic cyst	1 (3.4)	2 (7.4)	0.605
Procedure – No(%)			
only pancreatography	15 (51.7)	16 (59.3)	0.571
EST	10 (34.5)	8 (29.6)	0.698
IDUS (in the CBD)	4 (13.8)	3 (11.1)	1

CBD: Common bile duct; AIP: Autoimmune pancreatitis; EST: Endoscopic Sphincterotomy; IDUS: Intraductal ultrasound.

Definitions

The definition of PEP was based on Cotton's criteria [10], with a modified definition of severity. Instead of the number of hospital days, however, we evaluated the degree of severity of pancreatitis as the number of days before resuming feeding. PEP was defined as pancreatic pain and hyperamylasemia within 24 h post-procedure. Pancreatic pain was defined as persistent pain in the epigastric or periumbilical region. Hyperamylasemia was defined as a serum amylase level greater than 3 times the upper limit of normal in our hospital.

Contrast media

Urografin® is a ionic monomer, high osmolar, radiographic CM. It contains a mixture of sodium amidotrizoate and meglumine amidotrizoate in a proportion of 10:66 in an aqueous solution (formed from amidotrizoic acid or diatrizoic acid – 3, 5-bis-acetamido-2, 4, 6-triiodobenzoic acid). Visipaque® – 5, 5'-[(2-hydroxy-1, 3-propanediyl) bis (acetylimino)] bis[N, N'-bis(2, 3-dihydroxypropyl)-2, 4, 6-triiodo-1, 3-benzenedicarboxamide] – is a non-ionic dimeric, iso-osmolar, radiographic CM. Urografin® has an osmolality about 5 times higher than Visipaque® but costs only about a quarter as much (Table 1).

Statistical analysis

χ^2 test or Fischer's exact test were used to evaluate proportional differences. Student's *t* test was used to compare continuous variables. All statistical analyses were performed with IBM SPSS Statistics software version 21.

RESULTS

Patient characteristics

Table 2 shows basic patient characteristics, final diagnoses, and procedures in both groups. In the Urografin® group, the mean age (± standard deviation) was 65.21 ± 10.63 years and the male:female ratio was 14:15. In the Visipaque® group the mean age was 65.19 ± 11.98 and male:female ratio was 13:14. There were no significant differences between groups with regard to age, sex, final diagnosis, or type of endoscopic procedure (Table 2).

Post-endoscopic retrograde cholangiopancreatography pancreatitis

The overall rate of PEP was 3.6% (2/56). The rate of PEP in the Urografin® and Visipaque® groups was 0% (0/29) and 7.4% (2/27), respectively ($P = 0.228$, Fisher's exact test). The severity of pancreatitis was mild in both cases. The rate of hyperamylasemia in the Urografin® and Visipaque® group was 10.3% (3/29) and 14.8% (4/27), respectively (P = 0.70, Fisher's exact test) (Table 3).

Serum amylase level

There were no significant differences between two groups for the amylase level pre-procedure ($P = 0.082$), 3 h post-procedure ($P = 0.744$), or next morning after the procedure ($P = 0.265$) (Table 4 and Figure).

Table 3 Incidence of post-endoscopic retrograde cholangiopancreatography and hyperamylasemia

	Urografin®(N = 29)	Visipaque®(N = 27)	*p* value
Post ERCP pancreatitis	0 (0)	2 (7.4)	0.228
Hyperamylasemia	3 (10.3)	4 (14.8)	0.70

ERCP: Endoscopic retrograde Cholangiopancreatography.

Table 4 Serum amylase levels in the two groups

	Urografin®(N = 29)	Visipaque®(N = 27)	*p* value
Pre procedure	72.83 ± 28.04	92.22 ± 51.23	0.082
After 3 hours	197.93 ± 388.89	227.56 ± 270.29	0.744
Next morning	195.41 ± 328.70	304.41 ± 394.88	0.265

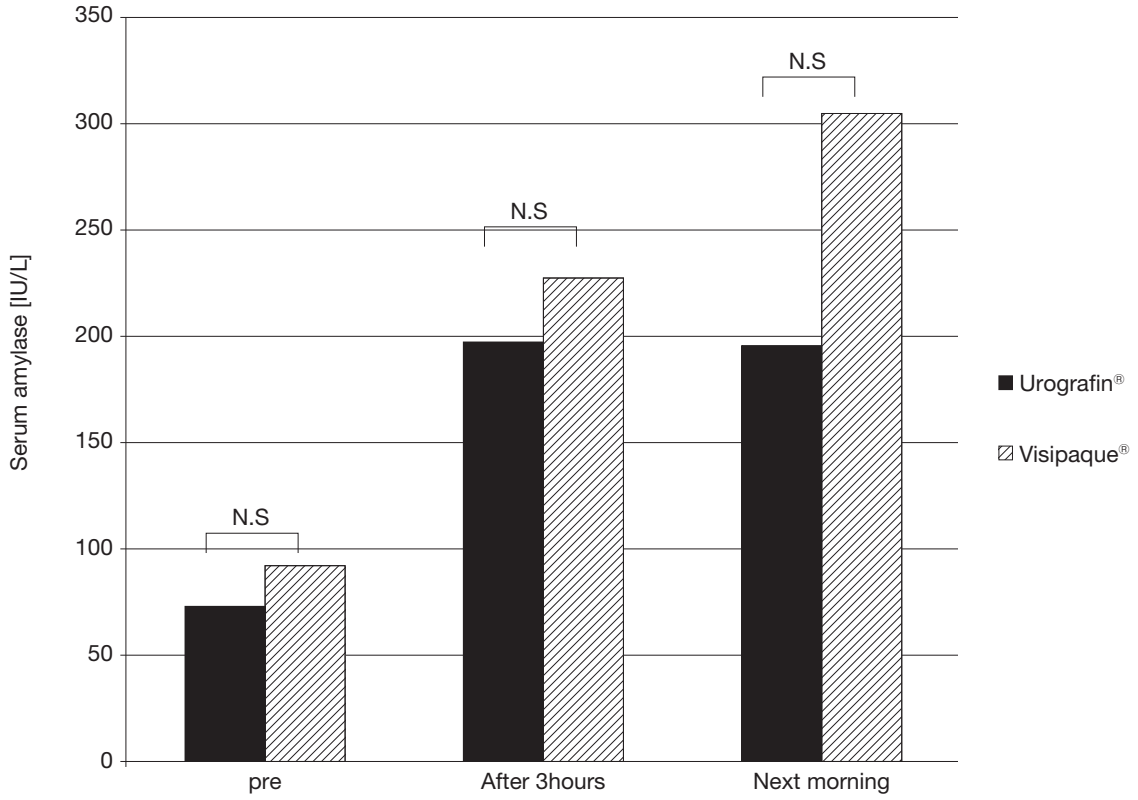

Figure Comparison of two groups with serum amylase levels.

DISCUSSION

Acute pancreatitis is the most common serious complication of ERCP [1]. It results in morbidity and occasional mortality. The overall rate of PEP was 3.6% in this study. This was consistent with reported rates of PEP, ranging from 1% to as high as 40% in patients with relevant risk factors [1–4, 6–8, 12–19]. The osmolality of the CM has been implicated as a contributing factor for the development of PEP [25]. It has been reported that a non-ionic CM significantly reduces the frequency of severe and potentially life-threatening adverse drug reactions to CM at all levels of risk in intravascular administration [23]. It is also known that a major factor in the toxicity of ionic monomers is their high osmolality, which is responsible for injection site pain, heat sensation, and nausea [42]. As a result, the non-ionic LOCM is considered superior to the ionic HOCM for intravascular injection. Furthermore, isoosmolar CM such as Visipaque®, which has a lower osmolality (290 mOsm/kg H_2O) than LOCM (770 mOsm/kg H_2O), is thought to cause fewer immediate reactions such as nausea and vomiting, but mild skin reactions such as rash are more frequent in comparison with LOCM [43]. Systemic absorption of CM during ERCP is common and well documented. However, adverse reactions such as nausea, vomiting, and skin reactions to CM administered during ERCP are exceedingly rare [44]. Morphologic changes in the pancreatic duct epithelium shortly after injection with CM have been shown in cats. Less damage was noted after injection with LOCM [45]. Thus, the osmolality of CM has been suggested to be a risk factor in the development of PEP. George *et al.* [25] determined the

incidence of PEP associated with HOCM and LOCM in a meta-analysis: in reviewing relevant studies, they found that the definition of PEP has not been standardized. In addition, clinical pancreatitis was evident by elevation of pancreatic enzymes and by pain. The results of their study indicated that there was no significant difference between HOCM and LOCM with regard to clinical pancreatitis [25]. Mäkelä *et al.* found no difference in the incidence of hyperamylasemia between diatrizoate meglumine (ionic HOCM) and iohexol (non-ionic LOCM) groups [37]. Our study is in accordance with this finding in that no significant difference was noted between the iso-osmolar CM and HOCM in the serum amylase level and PEP. In conclusion, we consider that there is no need to use the more expensive LOCM in ERCP to prevent PEP.

The authors state that they have no conflict of interest (COI).

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