Effects in the Control of Edema of the Papilla of Vater by Epinephrine Saline Irrigation after Endoscopic Retrograde Cholangiopancreatography in an Endoscopy Center in Japan, 2003 to 2007: Exploratory Retrospective Analysis to Evaluate the Characteristics of Eligible Patients with a Focus on Serum Amylase Levels

Konosuke Nakaji¹, Shigeo Suzumura², Yukinori Nakae¹, Kensaku Kojima¹, Mitsutaka Kumamoto¹ and Tomonaga Kozu¹

Abstract

Objective  To evaluate the effects of localized irrigation with epinephrine saline after endoscopic retrograde cholangiopancreatography (ERCP).

Patients and Methods  One hundred and fourteen patients who underwent ERCP in our institute were treated with or without irrigation using epinephrine diluted in saline after ERCP to prevent post-ERCP pancreatitis. The serum amylase levels, white blood cell counts, and urine amylase levels were measured at 24 and 48 hours after ERCP.

Results  The treatment resulted in improvements in all items. A univariate analysis of the explanatory variables between the treatment and untreated groups revealed the treatment to be effective, but not statistically significant. Gender and cannulation of the pancreatic duct were the only variables with significant partial regression coefficients in the multiple regression model with all explanatory variables (p=0.045). When a stratified analysis was conducted using gender as a moderator variable, the treatment became a significant preventive factor (p=0.038), and cannulation of the pancreatic duct was a significant risk factor (p=0.027) in female patients.

Conclusion  We suggest that irrigating with epinephrine saline into the papilla may be effective for preventing pancreatitis in female patients who received ERCP with cannulation of their pancreatic duct.

Key words: endoscopic retrograde cholangiopancreatography, prevention, epinephrine saline irrigation, effects, pancreatitis

(Inter Med 48: 945-952, 2009)
(DOI: 10.2169/internalmedicine.48.1705)

Introduction

We occasionally encounter patients treated with localized irrigation using epinephrine saline after endoscopic retrograde cholangiopancreatography (ERCP) in order to control edema in the papilla of Vater in Japan. Since this is an empirical procedure, any evidence for accurate pancreatitis prevention by controlling edema in the papilla remains unclear. Therefore, in this hospital-based, nested case-control study, we evaluated the possible effects of this procedure, and analyzed eligible patients with a focus on their serum amylase levels.

¹Aishinkai Nakae Hospital Endoscopy Center, Wakayama and ²Division of Epidemiology, Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka
Received for publication September 21, 2008; Accepted for publication March 16, 2009
Correspondence to Dr. Konosuke Nakaji, ko_9.so-pa1bm2is@akk.view21.net
**Patients and Methods**

**Patient characteristics**

There were 128 patients who received an initial diagnostic endoscopic retrograde cholangiopancreatography (ERCP) at Aishinkai Nakae Hospital (a teaching hospital in Wakayama City, Japan) between 2003 and 2007. Ten patients who received endoscopic nasobiliary drainage and 4 patients whose data are partially missing were excluded from the analysis, and thus data from 114 patients were used in this study. There were 63 males and 51 females. The ages of the patients ranged between 29 and 84 years, and the mean age was 66. The underlying diseases consisted of 37 cases of gallstones, 43 cases of chronic pancreatitis, 11 cases of pancreatic cysts, 11 cases of gall bladder adenomyomatosis, 3 cases of tumor-forming pancreatitis, 3 cases with a history of cholecystectomy, 3 cases of enlarged hepatic ducts, and 1 case of pancreatic cancer. Some patients had multiple conditions.

**Diagnostic endoscopy and study design**

The endoscopes used were the JF 200 and TJF 240 (both manufactured by Olympus, Tokyo, Japan), and the contrast agent was injected through a cannula; Tandem XL (Boston Scientific, Natick, MA, USA) or PR-110Q (Olympus). In preparation, a combination of 2 mg - 5 mg of midazolam and 15 mg of pentazocine were given to the patients as a sedative and analgesic. In order to relax the sphincter of Oddi, the patients were given a sublingual administration of nitroglycerin immediately prior to testing. Physicians with more than 10 years of endoscopic experience with credentials as a preceptor certified by the Japan Gastroenterological Endoscopy Society (N.K., N.Y., K.K., or M.K.) performed the ERCP.

The patients were given 500 mL of extracellular fluid and 100 mg of gabaxate mesilate before their examination, and 500 mL of extracellular fluid and 200 mg of gabaxate mesilate with second-generation cephem antibiotics were given from the time when the patients went back to their hospital rooms until midnight. A total of 1,000 mL of extracellular fluid, 300 mg of gabaxate mesilate, and second-generation antibiotics were administered on the following day. From the second day, the patients received 1,000 mL of extracellular fluid, 200 mg of gabaxate mesilate, and second-generation cephem antibiotics. The patients ingested nothing orally on the day of the examination, and water was allowed after the examination if there were no serious changes in the condition of the patient. A liquid diet was started in the evening, and the amount of water in the rice porridge was reduced gradually over the next 2 days. A normal diet was resumed on the 3rd day.

In this study, 63 cases in the treatment group received a 20 mL irrigation with epinephrine diluted to 1:20,000 in saline over the entire papilla, plus the opening with edema, immediately after the ERCP to prevent post-ERCP edema. The 51 control cases received no treatment. To make the analysis easier, the concentration of epinephrine in the saline used for irrigation was kept the same for all patients. Serum amylase levels, white blood cell counts, and urine amylase levels at 24 and 48 hours (days 1 and 2) after the ERCP were compared to the initial level of the patients in the control group.

Written informed consent was obtained from all patients before the ERCP.

**Definitions and diagnostic criteria**

Post ERCP pancreatitis was defined as abdominal pain persisting for at least 24 hours after the procedure, associated with high serum amylase or lipase levels equivalent to at least 3 times the upper limit of normal at 24 hours after the procedure.

Our diagnostic criteria for chronic pancreatitis were abdominal pain, back pain, abnormal serum pancreatic enzyme levels, weight loss, pancreatic exocrine dysfunction as well as abnormalities of the duct system, dilation of the main pancreatic duct and duct branches, and calculi in the ducts by imaging studies.

**Explanatory variables**

The assignment of treatment versus untreated groups, gender and age of the patients, whether a cannula was inserted into the pancreatic duct, the presence or absence of chronic pancreatitis, and the presence or absence of gallstones and cholecystitis were all used as explanatory variables.

**Statistical analysis**

The examination data (serum amylase levels, white blood cell counts, and urine amylase levels) from the time of admission, on the second and third days from both treatment and control groups were then compared. First, the data obtained on days 1 and 2 after the examination of each patient were compared to the data from the time of admission.

Univariate analysis was conducted for between group comparisons of the mean values of each tested item.

Focusing on the serum amylase level on day 1, multiple regression analysis was conducted in order to investigate whether the epinephrine treatment significantly improved the test values.

The outcome variable was the difference calculated in the step explained above, and Dummy variables were used for all variables except for the age of the patients.

A forward selection method was used to select the explanatory variables starting with the smallest t-values of the partial regression coefficients. An F-test was conducted to select the model with a smaller Akaike’s information criteria (AIC) value.

AIC was used to evaluate the appropriateness of the multiple regression models when selecting independent variables. A two-sided 5% significance level was used.

STATMATE-III (ATMS, Tokyo, Japan) software was used.
Results

Univariate analysis

In the comparison of the serum amylase changes after the examination between the two groups, the serum amylase level improved in the treatment group on days 1 and 2 after the examination (Fig. 1). The white blood cell count was also improved on days 1 and 2 after the examination in the treatment group (Fig. 2). The urine amylase level was similarly improved on days 1 and 2 after the examination (Fig. 3). A univariate analysis of the 6 new variables mentioned in the previous section suggested that the treatment was somewhat effective, although it was not statistically significant (Table 1).

Multivariate analysis

The analysis of the correlation between each explanatory variable (the assignment of treatment versus untreated groups, gender and age of the patients, whether a cannula was inserted into the pancreatic duct, the presence or absence of chronic pancreatitis, and the presence or absence of...
Figure 3. Comparison of the changes in post-ERCP urine amylase levels between the epinephrine-treated and untreated groups. B group: epinephrine-treated group; N group: untreated group; SEM: Standard error of the mean

Table 1. Univariate Analysis of the 6 Variables between the Treatment and Untreated Groups

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Time after ERCP</th>
<th>p-value*</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum amylase</td>
<td>Day 1</td>
<td>0.168</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Day 2</td>
<td>0.138</td>
<td>NS</td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>Day 1</td>
<td>0.464</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Day 2</td>
<td>0.186</td>
<td>NS</td>
</tr>
<tr>
<td>Urine Amylase</td>
<td>Day 1</td>
<td>0.182</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Day 2</td>
<td>0.089</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Welch test (two-sided), n=114

ERCP: Endoscopic retrograde cholangiopancreatography, NS: Not significant

gallstones and cholecystitis) revealed that there was a strong negative correlation between the presence of gallstones and the presence of chronic pancreatitis. In addition there were weak but positive relationships between gender and the presence of pancreatitis, and the insertion of a cannula into the pancreatic duct, and treatment and the presence of pancreatitis (Table 2). In the multiple regression model with all explanatory variables, a significant difference was observed between serum amylase change and gender and pancreatic duct cannulation (Akaike’s information criteria=1,415.8, F-test: p=0.045). The t-value of the treatment was not statistically significant at that point (Table 3).

To investigate whether the epinephrine irrigation was effective, a forward selection method was used to select a useful model, and 3 explanatory variables (epinephrine irrigation, gender, and pancreatic cannulation) were selected. Using a forward selection method, variables with the lowest t-value for the partial regression coefficient were removed from the model one by one, thus confirming the decreasing AIC. Although the model showed a trend towards controlling the amylase elevation, it was not statistically significant. Variable selection could not be conducted further based on the epinephrine treatment only.

We therefore hypothesized that gender may be a possible moderator variable, and conducted a stratified analysis. The new model revealed that epinephrine treatment was a significant protective factor of elevation in serum amylase concentration (p=0.038), and that cannulation of the pancreatic duct was a significant risk factor (p=0.027) in female patients (Akaike’s information criteria=715.9, F-test: p=0.012) (Fig. 4).

Using the same explanatory variables, there was no useful model for men, and there was no statistical significance for each standard partial regression coefficient (F-test: p=0.116).

Post-ERCP acute pancreatitis

There were no patients who contracted post-ERCP acute pancreatitis in the control or epinephrine irrigation groups.

Discussion

This study suggested that epinephrine irrigation may be effective for preventing pancreatitis in female patients who received endoscopic retrograde cholangiopancreatography
The serum amylase levels, white blood cell counts, and urine amylase levels were measured on days 1 and 2 after the ERCP, and the epinephrine irrigation in our study resulted in improvements in all items. These results suggest the irrigation helps prevent the post-ERCP pancreatitis caused by the edema around the papilla. However, none of these findings were statistically significant, and the collection of more data is necessary to demonstrate statistical significance. In the clinical setting, we considered the exploration of the practical effectiveness more important than statistical significance, and thus we searched for a useful multiple regression model using the changes in the serum amylase levels as an outcome variable (63 patients in the treatment group and 51 patients in the untreated group).

When a forward selection method with the t-value of each partial regression coefficient was used to select a model, the partial regression coefficient of the treatment was not statistically significant (it seemed to lower the serum amylase level), whereas gender and cannulation of the pancreatic duct were significant. When gender was treated as a moderator variable, the treatment became a significantly protective factor of elevation in serum amylase concentration, and cannulation of the pancreatic duct became a significant risk factor in female patients.

When we searched for studies published between 1992 and 2007 using "post ERCP", "acute pancreatitis", and "prevention" as keywords on Medline, we found a study reported by Ohashi et al (1) on the effectiveness of epinephrine-added saline irrigation on the papilla after endoscopic balloon sphincteroplasty. They administered gabaxate meceline and antibiotics to all patients who underwent endoscopic papillary balloon dilation, and compared the group that received an irrigation of 40 mL - 120 mL (50 mL ± 37 mL) of epinephrine saline (1:1,000,000) to an untreated group, and reported that the elevation in pancreatic enzyme levels was significantly controlled in the treatment group. Although the mechanism responsible for preventing post-ERCP acute pancreatitis by irrigating with epinephrine saline on the papilla remains unknown, it increases the vascular permeability, improves edema, relaxes the muscles in the sphincter of Oddi as well as the muscular layer of the duodenum, leading to the prevention of elevated pressures in the pancreatic duct by blocking drainage of the pancreatic fluid (ERCP) with cannulation of their pancreatic duct.

The serum amylase levels, white blood cell counts, and urine amylase levels were measured on days 1 and 2 after the ERCP, and the epinephrine irrigation in our study resulted in improvements in all items. These results suggest the irrigation helps prevent the post-ERCP pancreatitis caused by the edema around the papilla. However, none of these findings were statistically significant, and the collection of more data is necessary to demonstrate statistical significance. In the clinical setting, we considered the exploration of the practical effectiveness more important than statistical significance, and thus we searched for a useful multiple regression model using the changes in the serum amylase levels as an outcome variable (63 patients in the treatment group and 51 patients in the untreated group).

When a forward selection method with the t-value of each partial regression coefficient was used to select a model, the partial regression coefficient of the treatment was not statistically significant (it seemed to lower the serum amylase level), whereas gender and cannulation of the pancreatic duct were significant. When gender was treated as a moderator variable, the treatment became a significantly protective factor of elevation in serum amylase concentration, and cannulation of the pancreatic duct became a significant risk factor in female patients.

When we searched for studies published between 1992 and 2007 using "post ERCP", "acute pancreatitis", and "prevention" as keywords on Medline, we found a study reported by Ohashi et al (1) on the effectiveness of epinephrine-added saline irrigation on the papilla after endoscopic balloon sphincteroplasty. They administered gabaxate meceline and antibiotics to all patients who underwent endoscopic papillary balloon dilation, and compared the group that received an irrigation of 40 mL - 120 mL (50 mL ± 37 mL) of epinephrine saline (1:1,000,000) to an untreated group, and reported that the elevation in pancreatic enzyme levels was significantly controlled in the treatment group.

Although the mechanism responsible for preventing post-ERCP acute pancreatitis by irrigating with epinephrine saline on the papilla remains unknown, it increases the vascular permeability, improves edema, relaxes the muscles in the sphincter of Oddi as well as the muscular layer of the duodenum, leading to the prevention of elevated pressures in the pancreatic duct by blocking drainage of the pancreatic fluid

---

**Table 2.** Univariate Analysis of the Correlation between Each Explanatory Variable

<table>
<thead>
<tr>
<th></th>
<th>Epinephrine irrigation</th>
<th>Sex*</th>
<th>Age (11 year)</th>
<th>Pancreatic cannulation*</th>
<th>Chronic pancreatitis (Y/N)*</th>
<th>Gall stones*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine irrigation</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex*</td>
<td>0.014</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (11 year)</td>
<td>0.002</td>
<td>0.123</td>
<td>1.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic cannulation*</td>
<td>0.003</td>
<td>0.284</td>
<td>0.018</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic pancreatitis (Y/N)*</td>
<td>0.231</td>
<td>0.326</td>
<td>0.180</td>
<td>0.237</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Gall stones*</td>
<td>0.021</td>
<td>0.081</td>
<td>0.072</td>
<td>0.072</td>
<td>0.503</td>
<td>1.000</td>
</tr>
</tbody>
</table>

* Dummy variables created for the model

**Y:** Presence, **N:** Absence

---

**Table 3.** Multiple Regression Model with All Explanatory Variables

<table>
<thead>
<tr>
<th></th>
<th>Epinephrine irrigation</th>
<th>Sex*</th>
<th>Age (11 year)</th>
<th>Pancreatic cannulation*</th>
<th>Chronic pancreatitis (Y/N)*</th>
<th>Gall stones*</th>
</tr>
</thead>
<tbody>
<tr>
<td>t value for validity of the model</td>
<td>1.47</td>
<td>2.33</td>
<td>0.86</td>
<td>2.31</td>
<td>0.41</td>
<td>0.78</td>
</tr>
<tr>
<td>statistical significance*</td>
<td>ns</td>
<td>*</td>
<td>ns</td>
<td>*</td>
<td>ns</td>
<td>ns</td>
</tr>
</tbody>
</table>

* Akaike information criterion (AIC)=1415.8

**Y:** Presence, **N:** Absence

---

**Figure 4.** Evaluation of the multiple regression models to investigate the effects of the explanatory variables on the serum amylase levels. When a stratified analysis was conducted using gender as a moderator variable, treatment became a significant preventive factor, and cannulation of the pancreatic duct became a significant risk factor in female patients.
and the activation of pancreatic enzymes (2).

In an investigation on the relationship between gender and ERCP, Freeman et al (3) studied 1,963 patients who underwent ERCP and reported that a young age, being female, any functional abnormality of the muscles of the sphincter of Oddi, as well as a history of post-ERCP pancreatitis were all risk factors for ERCP-induced pancreatitis.

Being female was reported as an important risk factor, and all patients who developed severe post-ERCP pancreatitis were female. Freeman et al suggested that this was because functional abnormalities of the muscles of the sphincter of Oddi are more common in women. The results from the present study suggested that epinephrine is effective in female patients undergoing insertion of the cannula into the pancreatic duct.

Since the t-value of the partial regression coefficient for the presence of pancreatitis in the forward selection was small and the t-value for gender was largely unaffected by the removal of the pancreatitis variable, we concluded that there was a negligible effect for multiple collinearity between the pancreatitis and gender variables.

In the present study, all cases also received gabaxate mesilate regardless of which group they were assigned to. Although Andriulli et al (4) in 2007 dismissed the preventive effects of gabaxate mesilate and somatostatin on post-ERCP pancreatitis in their meta-analysis, gabaxate mesilate has been reported to be effective (5). We considered it unethical to not take any preventive measures in case the patients contracted pancreatitis, and decided to administer gabaxate mesilate. We measured the serum amylase levels at 24 and 48 hours after ERCP. However, the serum amylase levels at 6 hours after ERCP have recently been reported to be the most accurate in predicting post-ERCP pancreatitis (6).

ERCP has been used in the diagnosis and treatment of diseases of the biliary tract and pancreas since 1968, and pancreatitis is the most common complications (7). The incidence of patients with post-ERCP pancreatitis throughout Japan is 0.1% (2). The mortality rate of these patients is 0.01% (1); however, it can become fatal if the condition progresses to being serious.

Tsujino et al (8) reported in 2007 that the cost of treating a patient with moderate post-ERCP pancreatitis by Cotton’s classification (9) for 5 days is approximately 299,846 Japanese Yen including inpatient care, and thus this is also an issue of medical economics.

There are several English language reports on the pharmacological prevention of post-ERCP pancreatitis in humans and animals published between 2000 and 2007, and they include epinephrine (1), somatostatin (10, 11), gabaxate (5, 12-14), octreotide (15, 16), allopurinol (17, 18), steroids (18, 19), NK1 receptor agonist (20), indomethacin (21, 22), thalidomide (23), botulinus toxin (24), lidocaine (25), n-acetyl cysteine (26, 27), urinastatin (28), natural β-carotene (29), heparin (30, 31), and nifedipine (32). Various preventative methods are still being tested, including our study.

There are recent studies which reported that the insertion of a guide wire into the biliary duct (33) and the placement of a stent in the pancreatic duct in high-risk patients (34) to be effective in preventing post-ERCP pancreatitis. These techniques are difficult to perform in some cases, and cannot be used in all patients. In contrast, epinephrine irrigation is easy, economical, effective and a non-invasive prophylaxis that can be used at any facility.

The present study has several limitations. Pancreatitis by definition goes along with not only elevated amylase and, more specifically, lipase levels, but also with pain and pancreatic edema. If only elevated serum enzyme levels are observed without pain, hyperamylasemia or hyperlipasemia, then pancreatitis is unlikely. It is therefore not meaningful to extrapolate from the serum enzyme levels to clinically relevant pancreatitis. Moreover, hyperenzymemia does not always correlate with the pancreatitis severity.

Even though the effect of the serum amylase level was not statistically significant in our univariate analysis, we thought the effect might be more significant than the WBC count or urine amylase level. That was why we included the serum amylase model as an independent variable in the multiple regression model. As previously pointed out, the amylase level alone does not explain the protective effect. This is a preliminary analysis, and further studies are needed to evaluate the effects of epinephrine irrigation.

In the same studies, univariate analysis (for example, a t-test) is performed between all “explanatory variables” and the serum amylase level, and then multivariate analysis is performed on the extracted variables. However, in this study, the variables from the univariate analysis and the multivariate analysis are different, so it is difficult to understand the results of this study.

However, the purpose of this study was to identify the characteristics of cases in which epinephrine irrigation was effective, not to explore all of the variables that possibly lower the amylase levels in patients who received ERCP. Therefore, we considered it irrelevant to conduct univariate analyses using all of the variables that could affect the amylase level.

Indeed, an earlier report has suggested that epinephrine may cause pancreatitis (34). One key problem is that only those patients with edema of the papilla received the epinephrine irrigation. Thus, the group may have a selection bias. Since this study was not a randomized controlled trial, biases are possibly present. In order to minimize the effects of possible confounders, we conducted multivariate analyses. We think this minimized the effects of the biases. To date, we can offer no precise explanation as to why the protective effect can only be observed in female patients.

The data are presented in a preliminary form, and statistical analysis may require a larger collection of patients in order to have clearer differences (p<0.045). The amylase levels do not appear to differ between the groups (Fig. 1). Thus, the patient groups should be larger, and epinephrine should also be tested in the normal papilla.

The addition of other substances during the procedure is...
another major flaw. All cases also received gabexate mesilate regardless of which group they were assigned to. This is another problem of the study.

Post-ERCP pancreatitis is relatively rare in pancreatic cancer and chronic pancreatitis. Since there was only 1 case of pancreatic cancer, we believe the overall statistical effect of this case is small. We also included pancreatitis and gallstones as explanatory variables to minimize the biases. However, we also recognize the necessity to evaluate a larger number of patients in order to further understand the effects of those conditions.

Despite these limitations, we report our experience with 114 out of 128 diagnostic ERCPs over four years. We also found a negative correlation between gallstones and pancreatitis, as well as a positive correlation for gender, pancreatic cannulation and treatment with pancreatitis.

This study was not a randomized controlled study, but a retrospective analysis. However, as far as we are concerned, we attempted to minimize any convenience or bias factors in the patient selection. On this basis, we tried the most variant analyses to avoid possible confounders or biased effects.

---

**Conclusion**

Irrigation with epinephrine saline was originally used to improve the edema of the papilla with minor damage to the tissues due to repeated cannulations and deep cannulation during ERCP. The present study suggested that it may be effective for preventing post-ERCP pancreatitis in female patients with cannulation of their pancreatic duct. The design of future studies should be carefully selected, and it is necessary to collect more data, to search for a model using more explanatory variables and to resolve issues surrounding the conditions of the treatment.

**Acknowledgement**

The authors would like to thank Mitsue Kimura and Toyoko Azuma for their excellent technical assistance at the Endoscopic Center, Aishinkai Nakae Hospital. We also thank the nursing staff for data collection and management.

---

**References**


© 2009 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html