学位論文

「Nafamostat Mesylate is Not Effective in Preventing Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis」（ナファモスタットメシル酸塩は内視鏡的逆行性膵胆管造影後膵炎の予防に有効ではない）

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著者の宣言

本学位論文は、著者の責任において実験を遂行し、得られた真実の結果に基づいて正確に作成したものに相違ないことをここに宣言する。

論文要旨

論文題目「Nafamostat Mesylate is Not Effective in Preventing Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis」
（ナファモスタットメシル酸塩は内視鏡的逆行性膵胆管造影後膵炎の予防に有効ではない）

【背景】
内視鏡的逆行性胆管膵管造影（endoscopic retrograde cholangiopancreatography，ERCP）の偶発症の一つとしてERCP後膵炎（post ERCP pancreatitis，PEP）が知られている．PEPはときに致死的なものとなることより，この偶発症への対策は重要な課題である．これまでにもPEPの予防におけるプロテアーゼ阻害剤の有用性の評価がなされてきたが，その効果は一定でない．プロテアーゼ阻害剤の1つであるnafamostat mesylate（NM）のPEPの予防効果を示す単施設による無作為化比較研究が複数報告されているが，多施設での検討は我々の知る限りこれまでにない．本臨床研究ではNMのPEPに対する予防効果を多施設共同無作為化比較研究により検証し，さらにNMの投与開始時期の差異によるPEPの発症頻度を比較した．
【対象と方法】
2012年12月から2019年3月の間に，4つの医療施設で，膵胆道疾患の診断や治療のためにERCPを要した20歳以上の患者を対象とした．目標症例数はNM（20mg）投与群400例（ERCP前投与群200例，ERCP後投与群200例），NM非投与群400例の計800例とした．
患者は年齢（39歳未満か40歳以上）と性別を調整因子として，NM非投与群またはNM投与群のいずれかに無作為に割り付けられた．無作為割り付けは独立した第三者機関で行われた．欧州消化器内視鏡学会のガイドラインを参考に，7項目（history of previous pancreatitis, previous PEP, suspected sphincter of oddi dysfunction, female sex, difficult cannulation, pancreatic double-guidewire technique, pancreatic injection）のうち，1項目以上を有した症例をhigh-risk group，それ以外の症例はlow risk groupに分類した．
主要評価項目はNM非投与群とNM投与群におけるPEPの発生率と重症度とした．副次的評価項目は，NM投与別（ERCP前後）にみたPEPの発生率，PEPの危険因子，NMの安全性とした．統計比較は，カテゴリー変数に対してFisher's exact testとMann–Whitney U testを，PEPの危険因子の抽出にはロジスティック回帰分析を用いた．$p<0.05$の場合，統計学的有意と定義した．
【結果】
研究実施期間中に441名が登録された（NM非投与群：n＝149、NM投与群：n＝292［ERCP前投与群：n＝144、ERCP後投与群：n＝148］）．患者背景は，NM後投与群はNM前投与群に比べて膵管挿管が目的に含まれた症例が有意に多かった（p =0.04）が，その他の項目に差はみられなかった．PEPは，NM非投与群では15例（10%）に発症し，重症度はmild/moderate/severe：10（7%）/4（3%）/1（1%）であった．一方で，NM投与群では25例（9%）に発症し，重症度はmild/moderate/severe：16（5%）/6（2%）/3（1%）であった．2群間でPEPの発症率に差は

みられず，NM の PEP に対する予防効果はみられなかった．また NM 投与群におけるサブ解析では，PEP は NM 前投与群では 17 例（12%）に発症し，重症度は mild/moderate/severe：10（7%）/5（3%）/2（1%）であったのに対して，NM 後投与群では 8 例（5%）に発症し，重症度は mild/moderate/severe：6（4%）/1（1%）/1（1%）であった．NM 前投与群は後投与群に比べ PEP の発症頻度が高い傾向がみられた（p =0.06）が，重症例に限ると発症頻度に有意差はみられなかった（p =0.62）．PEP の high risk 群（355 例，80%）における NM の PEP に対する予防効果は示されなかった（p =1.00）．一方で，low risk 群（86 例，20%）では NM 投与群において PEP の発症頻度が低い傾向がみられた（p =0.10）．

多変量解析では，pancreatic double-guidewire technique（オッズ比: 3.05, 95%信頼区間: 1.41-6.61, p < 0.01）および pancreatic injection（オッズ比: 2.56, 95%信頼区間: 1.11-5.88, p = 0.03）が各々PEP の独立した危険因子であった．NM に関連した有害事象は，高カリウム血症が 2 例（0.7%）認められたが，保存的治療により軽快した．

【結論】

NM の投与時期にかかわらず PEP に対する NM の予防効果を示すエビデンスは得られなかった．

目次

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is an important technique that has been performed clinically since 1969, and it is currently used throughout the world to investigate and treat pancreaticobiliary diseases. Complications of ERCP include pancreatitis, bleeding, cholangitis, cholecystitis, and perforation. Of these complications, post-ERCP pancreatitis (PEP) is the most frequent, with a global incidence of 2–15% [1–3].

Protease inhibitors have the potential to prevent PEP by inhibiting the conversion of trypsinogen to trypsin in pancreatic acinar cells and preventing subsequent inflammation. Various protease inhibitors, such as gabexate mesylate, nafamostat mesylate, and ulinastatin, have been evaluated clinically for their utility in preventing PEP, with various outcomes reported [4–13]. Randomized controlled trials (RCTs) have shown that the protease inhibitor nafamostat mesylate (FUT-175: 6-amidino-2-naphthyl p-guanidinobenzoate di-methane-sulfonate; NM) has efficacy when used prophylactically against PEP [8, 10, 11]. However, the RCTs showing that NM is effective for the prevention of PEP were performed at a single center, and a consensus on the efficacy of NM for the prevention of PEP is lacking.

To our knowledge, the efficacy of NM is yet to be evaluated simultaneously across multiple centers. In this study, we describe the first multicenter RCT to assess the prophylactic efficacy of NM against PEP. This study also evaluated the incidence of PEP in patients who began NM treatment compared with that in patients who did not. Furthermore, the efficacy of NM was evaluated in patients stratified into low- and high-risk groups.

Methods

Trial Design

This was a multicenter prospective RCT. All patients provided written informed consent for participation in the study, which was approved by the Kitasato University Institutional Review Board based on its ethical, scientific, and medical validity (NO. C12-737). The study is registered at http:// www.umin.ac.jp (UMIN000009027).

Participants

All patients who underwent ERCP at Kitasato University Hospital, Kitasato University East Hospital, Isehara Kyodo Hospital, and Hiratsuka Kyosai Hospital for the diagnosis and/or treatment of pancreaticobiliary disease between December 2012 and March 2019 were recruited. Patients aged ≥20 years who had a planned ERCP with hospitalization were included. Patients were excluded if they were pregnant; had acute pancreatitis, severe cardiopulmonary disease, or a duodenal obstruction; were not naïve for major duodenal papilla (for example, post-endoscopic papillectomy, post-endoscopic sphincterotomy, or post-endoscopic papillary balloon dilatation); had a history of Billroth-II and total gastrectomy, allergy to iodine-based contrast agents or NM, or serious mental disorder; had received a protease inhibitor within the prior week; or were deemed unsuitable for the study by an investigator for any other reason.

Interventions

Patients administered NM before ERCP (pre-ERCP NM group) received 20 mg of the study drug dissolved in 500 mL of 5% glucose by intravenous drip infusion over 6 h, commencing 0.5–2.0 h before ERCP (and continuing throughout the ERCP procedure). Patients who received NM after ERCP (post-ERCP NM group) were administered the same dose by intravenous drip infusion over 6 h commencing within 1 h after ERCP. Patients in the non-NM group were administered 500 mL of 5% glucose by intravenous drip infusion over a period of 6 h commencing 0.5–2.0 h before ERCP. Patients who did not receive NM in accordance with the methods described above were excluded from the analysis.

Patients abstained from food beginning from the morning of the procedure, and fluid replacement was provided as appropriate, starting before surgery. ERCP was performed with the patient under sedation (pethidine 50 mg and midazolam 3–10 mg). Scopolamine butylbromide and glucagon were administered as required to inhibit gastrointestinal peristalsis. The first endoscopist to perform the ERCP was selected by an experienced endoscopist; those with≤6 years of experience performing ERCPs were classified as inexperienced, and those with≥7 years of experience were classified as experienced. Notably,

each experienced endoscopist had completed over 300 ERCP procedures. When the first endoscopist was inexperienced and unable to achieve successful cannulation within 10 min or after 5–10 attempts, an experienced endoscopist then completed the procedure. JF-260 V and TJF-260 V (Olympus Medical Systems, Tokyo, Japan) duodenoscopes were used for ERCP. A conventional ERCP catheter (PR-4Q-1; Olympus Medical Systems; and S01-20-70-1; MTW Endoskopie Manufaktur, Wesel, Germany) or a papillotomy knife (Clever Cut 3 V; Olympus Medical Systems) was used to cannulate the bile duct and/or pancreatic duct and inject contrast media. The initial decision between wire-loaded and wire-guided cannulation was made by the experienced endoscopist. Either a 0.025- (G-240-2545A, VisiGlide1, VisiGlide2; Olympus Medical Systems) or 0.035-inch disposable guidewire (RFGA35403, Radifocus; Terumo Corporation, Tokyo, Japan) was used. If cannulation was difficult with a guidewire, then the double-guidewire technique was used, or precutting was performed with a needle knife (Single Use 3-Lumen Needle Knife V; Olympus Medical Systems). The experienced endoscopist decided whether to insert a pancreatic duct stent to prevent pancreatitis. Patients who received a pancreatic duct stent during ERCP to prevent pancreatitis and those who were observed during ERCP without any devices contacting the duodenal papilla were excluded from the analysis. The presence of subjective and objective symptoms was assessed by the attending physician, and blood biochemical tests were performed 3 h after ERCP and the following morning. If necessary, imaging examinations were performed to evaluate potential symptoms of PEP and incidental symptoms related to ERCP. Appropriate treatment was initiated immediately following a diagnosis of PEP.

Outcomes

The primary outcome was the incidence and severity of PEP in patients who were not administered NM (non-NM group) compared with those who were administered NM (NM group). The secondary outcomes were PEP incidence according to the timing of NM initiation (before or after ERCP), determination of risk factors for PEP, and adverse events related to NM.

The following variables were recorded before ERCP: patient characteristics; medical history of previous pancreatitis (including PEP); medical history of suspected sphincter of Oddi dysfunction (SOD); purpose of ERCP (diagnosis or treatment); target duct (bile duct and/or pancreatic duct whether the pancreatic duct was cannulated intentionally or inadvertently); and general blood tests.

The following variables were evaluated after ERCP: experience of the endoscopist (experienced endoscopist or inexperienced endoscopist); number of attempts to cannulate the duodenal papilla (≤ 4 or ≥ 5); pancreatic injection; method of successful cannulation; rate

of successful target duct cannulation; treatment of duodenal papilla (endoscopic sphincterotomy, endoscopic pancreatic sphincterotomy, endoscopic papillary balloon dilation); intraductal ultrasound; general blood tests; and adverse events during hospitalization.

PEP was diagnosed when new-onset abdominal pain or abdominal pain with increased intensity lasted for more than 24 h and was associated with increased serum amylase and lipase levels (at least three times higher than the normal limit) approximately 24 h after the procedure. Severity was graded based on Cotton's criteria [14] and considered mild when hospitalization lasted for 2–3 days; moderate when hospitalization lasted for 4–10 days; and severe when hospitalization lasted for more than 10 days or when any of the following occurred: hemorrhagic pancreatitis; pancreatic necrosis; pancreatic pseudocyst; or the need for percutaneous and/or endoscopic drainage or surgery. Difficult cannulation was defined as more than five attempts, including failure of cannulation. Based on the European Society of Gastrointestinal Endoscopy (ESGE) Guideline [15], patients with at least one of the following risk factors were classified as high risk: previous pancreatitis; previous PEP; suspected SOD; female sex; difficult cannulation; pancreatic doubleguidewire technique; and pancreatic injection. All other patients were classified as low risk.

Sample Size

Based on the previously reported incidence of PEP [8, 10, 11], we assumed a PEP incidence of 4% in the NM group and 10% in the non-NM group. With a statistical power of 80% and significance level (α) of 0.05, the required sample size was calculated to be 316 patients per group. Taking dropouts into account, a target sample size of 400 patients per group was chosen, i.e., 800 patients in total.

Randomization

The study aimed to enroll a total of 800 patients: 400 patients in the NM group (pre-ERCP NM group, n=200; post-ERCP NM group, n=200) and 400 patients in the non-NM group. The patients were randomly assigned to the non-NM, pre-ERCP NM, or post-ERCP NM groups (2:1:1 ratio). Age ($\leq$39 vs$\geq$40 years) and sex (male vs female) were used as adjustment factors at the time of random assignment to avoid extreme bias. The patients were randomized to one of the three groups by Kitasato Clinical Research Center, an independent third-party organization.

Statistical Methods

Statistical comparisons were performed using Fisher's exact probability test and the

Mann–Whitney U test for categorical variables. Risk factors for PEP were included in a logistic regression model for multivariate analysis of independent risk factors for PEP. Factors with $p<0.20$ in the univariate analysis were further assessed using multivariate analysis. Statistical analyses were performed using SPSS Statistics version 23.0 (IBM Japan, Ltd., Tokyo, Japan); p values <0.05 were considered statistically significant.

Results

A total of 481 patients were enrolled in the study, of whom 40 were excluded (Fig. 1), resulting in a final study population of 441 patients. Thus, we failed to enroll the target sample size. Of the 441 patients included in the analysis, 149 were randomized to the non-NM group and 292 to the NM group (pre-ERCP NM group: 144, post-ERCP NM group: 148).

Patient characteristics are shown in Table 1. There were no significant differences in baseline patient characteristics such as sex, median age, history of previous pancreatitis, history of SOD, reason for ERCP (diagnosis or treatment), and target duct (bile duct and/or pancreatic duct) between the non-NM and NM groups. The most common indication for diagnostic ERCP was for obtaining pancreatic juice cytology ± intraductal ultrasound (IDUS). The second most common indication was for obtaining bile juice cytology (or biopsy) ±IDUS. Only contrast injection into the pancreatic or biliary duct was performed in one case in the non-NM group, three cases in the pre-NM group, and two cases in the post-NM group. Among the patients who received NM, the pancreatic duct was included in 41 (28%) patients in the pre-ERCP NM group compared with 60 (41%) patients in the post-ERCP NM group. ERCP was performed for cannulation of the pancreatic duct in a significantly greater number of patients in the post-ERCP NM group than in the pre-ERCP group ($p=0.04$). Most indications for cannulation of the pancreatic duct were based on pancreatic juice cytology because of suspected pancreatic neoplasms, which occurred in 35 cases in the non-NM group, 31 cases in the pre-ERCP NM group, and 49 cases in the post-ERCP NM group. The other reason for cannulation of the pancreatic duct was pancreatic duct drainage because of chronic pancreatitis, occurring in six cases in the non-NM group, three cases in the pre-ERCP NM group, and four cases in the post-ERCP NM group.

The outcomes of ERCP are shown in Table 2. The first endoscopist was inexperienced for 105 patients (70%) in the non-NM group and 203 patients (70%) in the NM group. Five or more attempts were made to cannulate the duodenal papilla in 80 patients (54%) in the non-NM group compared with 131 patients (45%) in the NM group. Pancreatic duct injection was performed in 71 (48%) patients in the non-NM group and 166 (57%) patients in the NM group. The inadvertent pancreatic injections occurred in 24 (16%) patients in the non-NM group and 65 (22%) patients in the NM group (40 patients in the pre-ERCP NM group and 25 patients in the post-ERCP NM group). In the non-NM group, cannulation was performed successfully using the wire-loaded or wire-guided technique in 116 patients (78%), the doubleguidewire technique in 13 patients (9%), and precutting in nine patients (6%). In the NM group, cannulation was performed successfully using the wire-loaded or wire-guided technique in 237 patients (81%), the double-guidewire technique in 32 patients (11%), and precutting in nine patients (3%). The rate of successful cannulation of the target

duct was 93% in the non-NM group and 95% in the NM group; the duodenal papilla was treated in 86 patients (57%) in the non-NM group and 185 patients (63%) in the NM group. There was no statistically significant difference in the outcomes of ERCP between the groups. A further breakdown of the NM group showed that the first endoscopist was inexperienced for 97 patients (67%) in the pre-ERCP NM group and 106 patients (72%) in the post-ERCP NM group. At least five attempts were made to cannulate the duodenal papilla in 60 patients (42%) in the pre-ERCP NM group compared with 71 patients (48%) in the post-ERCP NM group. Pancreatic duct injection was performed in 81 patients (56%) in the pre-ERCP NM group and 85 patients (57%) in the post-ERCP NM group. In the pre-ERCP NM group, cannulation using the wire-loaded or wire-guided technique in 115 patients (80%), the double-guidewire technique in 17 patients (12%), and precutting in four patients (3%) was successful. In the post-ERCP NM group, cannulation was successful using the wire-loaded or wire-guided technique in 122 patients (82%), the double-guidewire technique in 15 patients (10%), and precutting in five patients (3%). The rate of successful cannulation of the target duct was 94% in the pre-ERCP NM group and 96% in the post-ERCP NM group, and 96 (67%) patients received treatment for duodenal papilla in the pre-ERCP NM group compared with 89 patients (60%) in the post-ERCP NM group. There was no statistically significant difference in the outcomes of ERCP between the groups.

PEP outcomes are shown in Table 3. Overall, PEP occurred in 40 of 441 patients (9%), including 15 patients (10%) in the non-NM group. Among these, the severity was considered mild, moderate, and severe in 10 (7%), four (3%), and one (1%) patient, respectively. In comparison, PEP occurred in 25 patients (9%) in the NM group, among whom the severity was mild, moderate, and severe in 16 (5%), six (2%), and three (1%) patients, respectively. There was no difference in the incidence of PEP between the groups, and no evidence for a prophylactic effect of NM against PEP. Further breakdown of the NM group revealed that PEP occurred in 17 patients (12%) in the pre-ERCP NM group, among whom the severity was mild, moderate, and severe in 10 (7%), five (3%), and two (1%) patients, respectively. In comparison, PEP occurred in eight patients (5%) in the post-ERCP NM group, among whom the severity was mild, moderate, and severe in six (4%), one (1%), and one (1%) patient, respectively. Considering all grades of severity, the incidence of PEP tended to be higher in the pre-ERCP NM group than in the post-ERCP NM group ($p=0.06$); however, there was no significant difference when only severe cases were compared ($p=0.62$). Among those who developed severe PEP, three patients received continuous regional arterial infusion of concomitant NM and antibiotics. PEP was resolved in all patients, and no deaths were reported during the study period.

Overall, 355 patients (80%) were considered at high risk for PEP and 86 patients (20%) at low risk. NM showed no prophylactic efficacy against PEP in the high-risk group

(p=1.00). Conversely, the incidence of PEP tended to be lower in the NM group among low-risk patients, though the difference was not statistically significant (p=0.10) (Table 4).

The risk factors for PEP were analyzed (Table 5) based on those defined in the ESGE Guideline [15]. Univariate analysis identified pancreatic injection (p<0.01), double-guidewire technique (p=0.01), and difficult cannulation (p=0.01) as significant risk factors for PEP. Multivariate analysis identified pancreatic injection (odds ratio [OR]: 3.05, 95% confidence interval [CI] 1.41–6.61, p<0.01) and the doubleguidewire technique (OR 2.56, 95% CI 1.11–5.88, p=0.03) as independent risk factors for PEP.

NM-related adverse events of hyperkalemia occurred in two patients (0.7%) in the NM group, and all events resolved with conservative treatment.

Discussion

Activation of pancreatic enzymes may be involved in the onset and progression of acute pancreatitis, and protease inhibitors are administered intravenously to inhibit this activation and prevent progression to pancreatitis. NM is a low molecular weight protease inhibitor that inhibits serine proteases, such as trypsin, kallikrein, C1r and C1s, thrombin, and plasmin [16]. Notably, NM has been shown to reduce the incidence of complications [17] and mortality [18–20] in patients with severe acute pancreatitis. Reports have also shown that continuous regional arterial infusion with concomitant NM and antibiotics effectively reduces the rate of pancreatic infection and mortality in patients with severe acute pancreatitis [21–23]. To date, three RCTs have reported the prophylactic efficacy of NM against PEP [8, 10, 11]. All three trials were conducted in a single center in the Republic of Korea, and NM treatment was initiated before ERCP. These trials reported that NM provides prophylaxis against PEP in low-risk patients. However, Park et al. [11] found no prophylactic effect with 20 or 50 mg NM on the incidence of PEP. Kim et al. [24] examined the prophylactic efficacy of 20 mg NM against PEP when dosed continuously for 24 and 6 h but found no difference in the incidence of PEP (2.8 vs 2.1%, p=0.744). To our knowledge, the present study is the first multicenter prospective RCT to evaluate the prophylactic efficacy of NM against PEP and examine whether prophylactic efficacy is affected by the timing of NM initiation (before ERCP vs after ERCP). We found no evidence for a prophylactic effect of NM against PEP, regardless of the timing of NM administration. The effect of the timing of treatment initiation on prophylactic efficacy has been investigated for other protease inhibitors. For example, Manes et al. [7] examined how the timing of treatment affected the prophylactic efficacy of gabexate mesylate against PEP in a multicenter study and found no significant difference in efficacy when NM was initiated before or after ERCP. Similar studies have investigated the use of nonsteroidal anti-inflammatory drugs (NSAIDs), and meta-analyses have concluded that NSAIDs are effective regardless of when they are administered during ERCP [25–27]. In the present study, continuous intravenous infusion of NM began before ERCP and continued during ERCP. We expected NM to reach effective blood concentrations during ERCP when pancreatic enzymes are activated. The response from the patients in the pre-ERCP NM group was compared with that from the post-ERCP NM group; however, the prophylactic efficacy of NM against PEP in the pre-ERCP group was not superior to that in the post-ERCP group.

In a post hoc sub-analysis, the incidence of PEP in low risk patients was lower in those who received NM than in those who did not receive NM; however, the difference was not statistically significant. These findings may be explained by the sample size being smaller than planned and the low proportion of low-risk patients (20%) compared with previous

reports, which have demonstrated the prophylactic efficacy of NM against PEP among low-risk patients (60.7% [8], 56.3% [10], and 40.2% [11]). Thus, it is possible that the patient characteristics and ERCP procedures performed in this study differed from those in previous studies; therefore, the prophylactic efficacy of NM against PEP among low-risk patients requires re-evaluation in a large-scale study.

This study had several limitations. First, the target sample size of 800 patients was not reached. Reports published since the late 2000s have indicated an inhibitory effect of NSAIDs on the onset of PEP [26–29]. Then, in 2015, the "Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015" were published [30], which recommend the rectal administration of NSAIDs for the prevention of PEP in all non-contraindicated patients. We believe that this may explain why it became difficult to obtain consent from patients during the second half of the study. Second, although this study compared the timing of NM administration between pre-ERCP NM and post-ERCP NM groups, the pharmacological parameters related to NM were not examined. Moreover, although "pancreatic guidewire passages>1" is one of the seven risk factors for PEP in the ESGE Guideline [15], it was replaced in the present study with "double-guidewire technique." The ESGE Guideline also states that the "...patients should be considered to be at high risk for post-ERCP pancreatitis when at least one definite or two likely patient-related or procedure-related risk factors are present." However, owing to lack of data, five of the likely risk factors (nondilated extrahepatic bile duct, absence of chronic pancreatitis, normal serum bilirubin, end-stage renal disease, and failure to clear bile duct stones) could not be used to stratify risk (high or low) or be included in a statistical analysis of PEP risk factors. Nevertheless, the risk factors for PEP extracted from the available data are acceptable.

In conclusion, in this multicenter RCT, NM demonstrated no prophylactic efficacy against PEP. However, it is necessary to re-evaluate the prophylactic efficacy of NM in patients with low risk for PEP in a larger study. Additionally, commencing NM before or after ERCP did not affect the prophylactic efficacy of NM against PEP.

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Figures and Legends

Figure.1 Patient enrollment and reasons for exclusion.

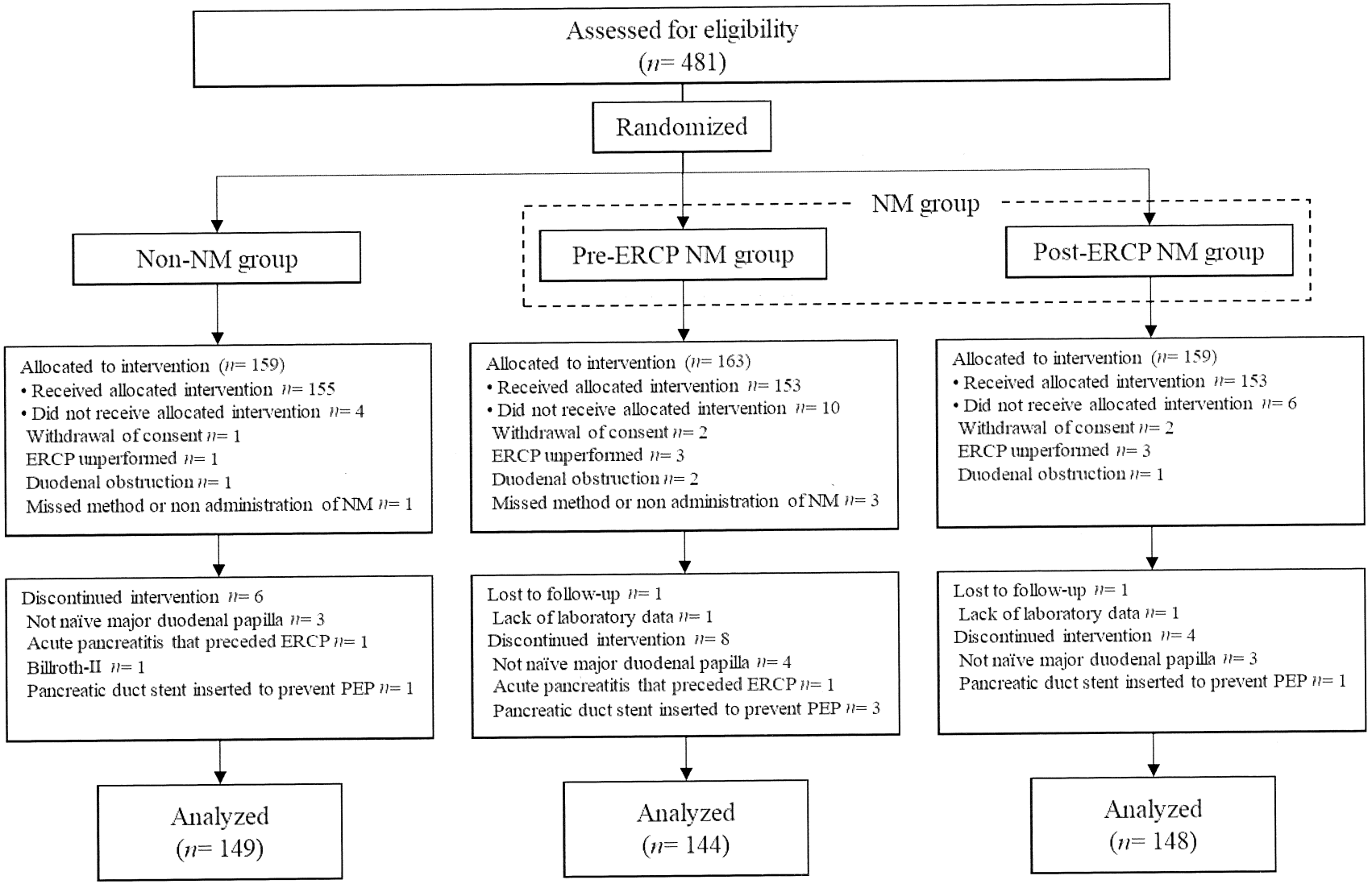
Assessed for eligibility
(n= 481)
Randomized
NM group
Non-NM group
Pre-ERCP NM group
Post-ERCP NM group
Allocated to intervention (n= 159)
• Received allocated intervention n= 155
• Did not receive allocated intervention n= 4
Withdrawal of consent n= 1
ERCP unperformed n= 1
Duodenal obstruction n= 1
Missed method or non administration of NM n= 1
Allocated to intervention (n= 163)
• Received allocated intervention n= 153
• Did not receive allocated intervention n= 10
Withdrawal of consent n= 2
ERCP unperformed n= 3
Duodenal obstruction n= 2
Missed method or non administration of NM n= 3
Allocated to intervention (n= 159)
• Received allocated intervention n= 153
• Did not receive allocated intervention n= 6
Withdrawal of consent n= 2
ERCP unperformed n= 3
Duodenal obstruction n= 1
Discontinued intervention n= 6
Not naïve major duodenal papilla n= 3
Acute pancreatitis that preceded ERCP n= 1
Billroth-II n= 1
Pancreatic duct stent inserted to prevent PEP n= 1
Lost to follow-up n= 1
Lack of laboratory data n= 1
Discontinued intervention n= 8
Not naïve major duodenal papilla n= 4
Acute pancreatitis that preceded ERCP n= 1
Pancreatic duct stent inserted to prevent PEP n= 3
Lost to follow-up n= 1
Lack of laboratory data n= 1
Discontinued intervention n= 4
Not naïve major duodenal papilla n= 3
Pancreatic duct stent inserted to prevent PEP n= 1
Analyzed
(n= 149)
Analyzed
(n= 144)
Analyzed
(n= 148)

Figure.1

Tables

Table 1. Patient characteristics

	Non-NM group (n = 149)	NM group (n = 292)	p value[a]	NM group		p value[b]
				Pre-ERCP (n = 144)	Post-ERCP (n = 148)	
Sex, n (%)			0.75			0.81
Male	101 (68)	193 (66)		94 (65)	99 (67)	
Female	48 (32)	99 (34)		50 (35)	49 (33)	
Median age, yrs [range]	71 [31–89]	72 [28–96]	0.68	74 [32–93]	71 [28–96]	0.75
Previous pancreatitis, n (%)			0.55			0.50
Yes	0 (0)	2 (1)		0 (0)	2 (1)	
No	149 (100)	290 (99)		144 (100)	146 (99)	
Suspected SOD, n (%)			0.55			0.50
Yes	0 (0)	2 (1)		0 (0)	2 (1)	
No	149 (100)	290 (99)		144 (100)	146 (99)	
Reason for ERCP, n (%)			0.61			0.63
Diagnosis	56 (38)	118 (40)		56 (39)	62 (42)	
Treatment	93 (62)	174 (60)		88 (61)	86 (58)	
Target duct, n (%)			0.59			0.04
Bile duct	102 (68)	191 (65)		103 (72)	88 (59)	
Including pancreatic duct	47 (32)	101 (35)		41 (28)	60 (41)	

Abbreviations: NM, nafamostat mesylate; SOD, sphincter of Oddi dysfunction; ERCP, endoscopic retrograde cholangiopancreatography.

p values were determined using Fisher's exact probability test or the Mann-Whitney U test.

[a] Non-NM group vs NM group.

[b] Pre-ERCP NM group vs post-ERCP NM group.

Table 2. Outcomes of endoscopic retrograde cholangiopancreatography

	Non-NM group (n = 149)	NM group (n = 292)	p value[a]	NM group		p value[b]
				Pre-ERCP (n = 144)	Post-ERCP (n = 148)	
First endoscopist, n (%)			0.91			0.48
Experienced	44 (30)	89 (30)		47 (33)	42 (28)	
Inexperienced	105 (70)	203 (70)		97 (67)	106 (72)	
Number of cannulations attempts to duodenal papilla, n (%)			0.09			0.29
≤ 4	69 (46)	161 (55)		84 (58)	77 (52)	
≥ 5	80 (54)	131 (45)		60 (42)	71 (48)	
Pancreatic injection, n (%)			0.07			0.91
Yes	71 (48)	166 (57)		81 (56)	85 (57)	
No	78 (52)	126 (43)		63 (44)	63 (43)	
Successful cannulation method, n (%)			0.45*			0.55*
Wire-loaded or wire-guided	116 (78)	237 (81)		115 (80)	122 (82)	
Double-guidewire technique	13 (9)	32 (11)		17 (12)	15 (10)	
Precutting	9 (6)	9 (3)		4 (3)	5 (3)	
Failure of cannulation	11 (7)	14 (5)		8 (6)	6 (4)	
Successful cannulation to target duct, %	93	95	0.28	94	96	0.59
Treatment of duodenal papilla, n (%)			0.26			0.28
Yes	86 (57)	185 (63)		96 (67)	89 (60)	
EST	76 (51)	162 (55)		85 (59)	77 (52)	
EPBD	8 (5)	13 (4)		5 (3)	8 (5)	
EPST	2 (1)	10 (3)		6 (4)	4 (3)	
No	63 (42)	107 (37)		48 (33)	59 (40)	

Abbreviations: NM, nafamostat mesylate; EST, endoscopic sphincterotomy; EPBD, endoscopic papillary balloon dilation; EPST, endoscopic pancreatic sphincterotomy.

p values were determined using Fisher's exact probability test.

[a] Non-NM group vs NM group.

[b] Pre-ERCP NM group vs post-ERCP NM group.

*p value comparing "conventional contrast, wire-loaded or wire-guided," and "double-guidewire technique, precutting and failure of cannulation".

Table 3. Effects of nafamostat mesylate prophylaxis on post-endoscopic retrograde cholangiopancreatography pancreatitis

	Non-NM group (n = 149)	NM group (n = 292)	p value[a]	NM group		p value[b]
				Pre-ERCP (n = 144)	Post-ERCP (n = 148)	
PEP, n (%)			0.60			0.06
Yes	15 (10)	25 (9)		17 (12)	8 (5)	
Mild	10 (7)	16 (5)		10 (7)	6 (4)	
Moderate	4 (3)	6 (2)		5 (3)	1 (1)	
Severe	1 (1)	3 (1)		2 (1)	1 (1)	
No	134 (90)	267 (91)		127 (88)	140 (95)	

Abbreviations: NM, nafamostat mesylate; ERCP, endoscopic retrograde cholangiopancreatography; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis.

p values were determined using Fisher's exact probability test.

[a]Non-NM group vs NM group.

[b]Pre-ERCP NM group vs post-ERCP NM group.

Table 4. Effects of nafamostat mesylate on post-endoscopic retrograde cholangiopancreatography pancreatitis in high- and low-risk groups

	High-risk group (n = 355)		p value[a]	Low-risk group (n = 86)		p value[b]
	Non-NM group (n = 121)	NM group (n = 234)		Non-NM group (n = 28)	NM group (n = 58)	
PEP, n (%)			1.00			0.10
Yes	13 (11)	25 (11)		2 (7)	0 (0)	
Mild	8 (7)	16 (7)		2 (7)	0 (0)	
Moderate	4 (3)	6 (3)		0 (0)	0 (0)	
Severe	1 (1)	3 (1)		0 (0)	0 (0)	
No	108 (89)	209 (89)		26 (93)	58 (100)	

Abbreviations: NM, nafamostat mesylate; PEP, post-endoscopic retrograde cholangiopancreatography pancreatitis.

p values were determined using Fisher's exact probability test.

[a]Non-NM group vs NM group, in the high-risk group.

[b]Non-NM group vs NM group, in the low-risk group.

Table 5. Analysis of risk factors related to post-endoscopic retrograde cholangiopancreatography pancreatitis

	Patients, *n*	Univariate analysis		Multivariate analysis	
		OR (95% CI)	p value	OR (95% CI)	p value
Administration of NM yes/no	149/292	0.84 (0.43–1.64)	0.60		
Suspected SOD yes/no	2/439	10.26 (0.63–167.19)	0.10		
Previous pancreatitis yes/no	2/439	10.26 (0.63–167.19)	0.10		
Female sex yes/no	147/294	1.54 (0.80–2.98)	0.20		
Difficult cannulation yes/no	211/230	2.45 (1.23–4.88)	0.01		
Double-guidewire technique yes/no	45/396	2.94 (1.30–6.67)	0.01	2.56 (1.11–5.88)	0.03
Pancreatic injection Yes/no	237/204	3.26 (1.51–7.03)	<0.01	3.05 (1.41–6.61)	<0.01
Young age < 40/ ≥ 40	9/432	1.26 (0.15–10.34)	0.83		
Precutting yes/no	18/423	3.07 (0.96–9.82)	0.06		
EPST yes/no	12/429	2.06 (0.44–9.74)	0.36		
EPBD yes/no	22/419	0.46 (0.06–3.54)	0.46		
IDUS yes/no	138/303	1.06 (0.53–2.13)	0.86		

Abbreviations: NM, nafamostat mesylate; SOD, sphincter of Oddi dysfunction; EPST, endoscopic pancreatic sphincterotomy; EPBD, endoscopic papillary balloon dilation; IDUS, intraductal ultrasound; OR, odds ratio; CI, confidence interval.

p values were determined using a logistic regression model.

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（Ⅱ）著　書

なし

（Ⅲ）総説・講座

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