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Original

A Prospective, Double-blind, Randomized, Controlled Trial to Compare Nafamostat Mesilate with Gabexate Mesilate in Preventing Post-therapeutic Endoscopic Retrograde Cholangiopancreatography Pancreatitis

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Protease inhibitors (PIs) are effective in preventing post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP); however, the efficacy of low-dose PIs, which are covered by the Japanese national health care insurance, in preventing PEP remains undetermined. In this study, we compared the efficacies of low-dose nafamostat mesilate (NM) and low-dose gabexate mesilate (GM) in preventing pancreatitis after therapeutic ERCP in a prospective, double-blind, randomized controlled trial. Of 166 patients who underwent therapeutic ERCP, 112 patients underwent endoscopic sphincterotomy (EST) and 54 patients underwent endoscopic papillary balloon dilatation (EPBD). Patients were randomized to receive a 1000-ml infusion of 5% glucose solution containing either 20 mg NM or 200 mg GM over a six-hour period beginning one hour before ERCP. The incidence of PEP was 5.8% (5/86) in the NM group and 6.3% (5/80) in the GM group. There were no significant differences in the incidence of PEP, change in serum amylase or lipase levels, or frequency of hyperamylasemia or hyperlipasemia between the EPBD and EST groups at 4 hours or at 18 hours post-ERCP. We conclude that low-dose NM and low-dose GM are equally effective for the prevention of pancreatitis after therapeutic ERCP.

Key Words: post-endoscopic retrograde cholangiopancreatography pancreatitis, nafamostat mesilate, gabexate mesilate, randomized controlled trial, complication

Introduction

Improvements in the relatively non-invasive techniques of computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) now mean that these techniques take precedence over endoscopic retrograde cholangiopancreatography (ERCP). However, in pathological diagnosis, for invasive procedures such as intraductal ultrasonography and peroral cholangiopancreatoscopy, and for biliary drainage, stone removal, and stent insertion, ERCP is still an essential technique. Post-ERCP pancreatitis (PEP) remains the most frequent complication associated with ERCP meaning adequate methods to prevent PEP are therefore important. Protease inhibitors (PIs)[1], pancreatic duct stents[2], and nonsteroidal anti-inflammatory drugs[3] are all useful for the prevention of PEP, and PIs are now widely used for both the prevention and treatment of PEP. However, the efficacy of low-dose PIs, which are covered by the Japanese national health insurance, for the prevention of PEP remains undetermined.

In this study, we compared the efficacy of low-dose nafamostat mesilate (NM) and low-dose gabexate mesilate (GM) in preventing pancreatitis after ERCP in a prospective, double-blind, randomized, controlled trial.

Materials and Methods

Of 380 patients who underwent ERCP at the Tokyo Women's Medical University Yachiyo Medical Center between January 2007 and December 2010,

Table 1 Patient characteristics and indications for ERCP

	Nafamostat (n=86)		Gabexate (n=80)	
Endoscopic procedure	EST (n=58)	EPBD (n=28)	EST (n=54)	EPBD (n=26)
Gender (male : female)	30 : 28	17 : 11	31 : 23	12 : 14
age (mean ± SD)	67 ± 13	65 ± 14	68 ± 13	60 ± 15
Indication for ERCP				
Choledocholithiasis	51	27	49	25
Gallbladder cancer	2	1	1	0
Intrahepatic bile duct cancer	0	0	0	1
Bile duct cancer	1	0	3	0
Pancreatic cancer	4	0	0	0
Chronic pancreatitis	0	0	1	0
Additional therapy				
ENBD tube	30	16	28	5
ERBD stent	13	0	8	0

EST: endoscopic sphincterotomy, EPBD: endoscopic papillary balloon dilatation, ENBD: endoscopic nasobiliary drainage, ERBD: endoscopic retrograde biliary drainage, ERCP: Endoscopic retrograde cholangiopancreatography.

214 underwent diagnostic ERCP and 166 underwent therapeutic ERCP. Patients who underwent diagnostic ERCP were excluded from this study. All patients were given written information about this study and signed a consent form. Approval for the study was obtained from the Tokyo Women's Medical University Hospital Ethics Committee.

The 166 enrolled patients were randomized to receive infusions of either NM or GM. Of these 166 patients, 112 patients underwent endoscopic sphincterotomy (EST) and 54 patients underwent endoscopic papillary balloon dilatation (EPBD).

Table 1 shows the patient characteristics and indications for ERCP at the time of enrollment. In the NM group, 58 patients underwent EST (male:female, 30:28; mean age, 67), and of these patients, 51 had choledocholithiasis, two had gallbladder cancer, one had bile duct cancer, and four had pancreatic cancer. As additional treatment after EST, 30 patients underwent endoscopic nasobiliary drainage (ENBD) and 13 patients underwent endoscopic retrograde biliary drainage (ERBD). Twenty-eight patients in the NM group underwent EPBD (male:female, 17:11; mean age, 65), and of these patients, 27 had choledocholithiasis and one had gallbladder cancer. As additional treatment after EPBD, 16 patients underwent ENBD.

In the GM group, 54 patients underwent EST (male:female, 31:23; mean age, 68), and of these patients, 49 had choledocholithiasis, one had gallbladder cancer, three had bile duct cancer, and one had chronic pancreatitis. As additional treatment after EST, 28 patients underwent ENBD, and 8 patients underwent ERBD. Twenty-six patents in the GM group underwent EPBD (male:female, 12:14; mean age, 60), and of these patients, 25 had choledocholithiasis and one had intrahepatic bile duct cancer. As additional treatment after EPBD, 5 patients underwent ENBD.

Patients fasted on the day of examination and were given 1,500 ml of 5% glucose solution containing electrolytes over a period of 18 hours. NM or GM was administered one hour before the start of ERCP, as previously reported by Xiong et al.[4] and Choi et al[5] Patients in the NM group received a 1,000-ml infusion of 5% glucose solution containing 20 mg NM (Futhan; Torii Pharmaceutical Co., Ltd, Tokyo, Japan) over a 6-hour period. Similarly, patients in the GM group received a 1,000-ml infusion of 5% glucose solution containing 200 mg GM (FOY; Ono Pharmaceutical, Tokyo, Japan) over a 6-hour period. Flunitrazepam, a spasmolytic agent such as hyoscine-N-butylbromide or glucagon (Glucagon G Novo; Novo Nordisk Pharma, Tokyo, Japan), and antibiotics were routinely administered before the start of ERCP.

Testoni et al[6], Thomas and Sengupta[7], and Nishino et al.[8] report that at 4 hours after ERCP, blood tests can be useful as a predictor of PEP occurrence, and Akashi et al[9] reported that PEP occurs within 18 hours of starting ERCP and does not occur after 24 hours. Therefore, we administered blood tests at 4 hours and at 18 hours from the start of ERCP (Fig. 1).

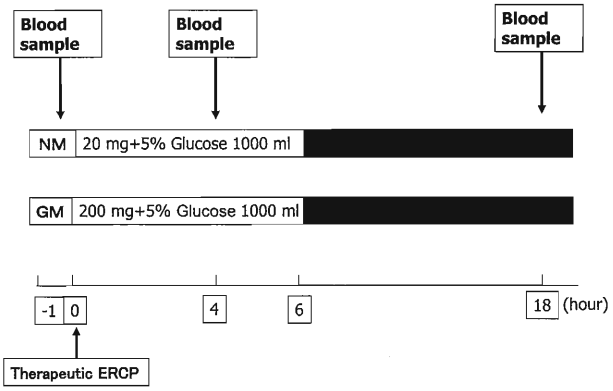

Fig. 1 ERCP protocol
NM or GM was administered one hour before the start of ERCP. Patients in the NM group received a 1,000-ml infusion of 5% glucose solution containing 20 mg NM over a 6-hour period. Similarly, patients in the GM group received a 1,000-ml infusion of 5% glucose solution containing 200 mg GM over a 6-hour period.
Blood sample was measured before and 4, 18 hours after ERCP.
NM: nafamostat mesilate, GM: gabexate mesilate, ERCP: Endoscopic retrograde cholangiopancreatography.

To compare the efficacy of NM and GM in preventing PEP associated with therapeutic ERCP, the endpoints examined were incidence of PEP and changes in serum amylase and lipase levels at 4 hours and at 18 hours after ERCP. We also examined the frequency of hyperamylasemia and hyperlipasemia in the EPBD and EST subgroups at 4 hours and at 18 hours after ERCP.

Results were evaluated by using the Chi-square and Mann-Whitney U tests with significance defined as $p<0.05$.

Definitions

The definition of PEP was derived from the Japan Ministry of Health, Labour, and Welfare (MHLW) standard for acute pancreatitis[10]. For a patient with either ① an increase in pancreatic enzymes in blood or urine and/or ② abnormal appearance of the pancreas on abdominal ultrasound, CT, or magnetic resonance imaging accompanied by ③ acute pain and/or pressure in the upper abdomen, a diagnosis of pancreatitis was made. CT was carried out in patients presenting with abdominal pain and high levels of pancreatic enzymes the day after ERCP. The severity of pancreatitis was defined by using the 2008 MHLW severity criteria; cases with three or more prognostic factors or a CT result of

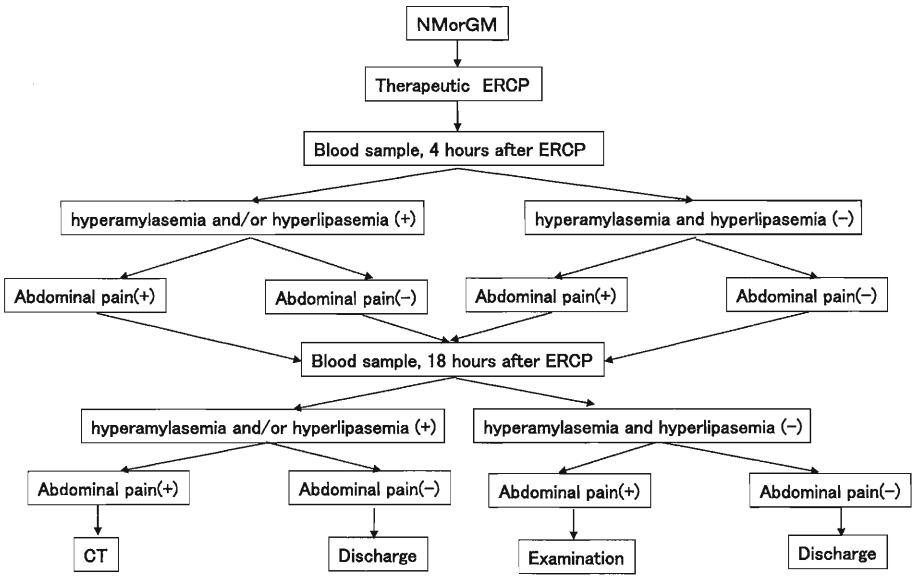

Fig. 2 Flow chart
NM: nafamostat mesilate, GM: gabexate mesilate, ERCP: Endoscopic retrograde cholangiopancreatography, CT: computed tomography.

Table 2 Percentage of post-ERCP pancreatitis cases

	PEP (EST + EPBD)		PEP (EPBD)		PEP (EST)	
NM	5/86 (5.8%) Severe cases = 0	p = 0.906	1/28 (3.6%)	p = 0.509	4/58 (6.9%)	p = 0.770
GM	5/80 (6.3%) Severe cases = 0		2/26 (7.7%)		3/54 (5.6%)	

NM: nafamostat mesilate, GM: gabexate mesilate, ERCP: Endoscopic retrograde cholangiopancreatography, PEP: post-ERCP pancreatitis, EST: endoscopic sphincterotomy, EPBD: endoscopic papillary balloon dilatation.

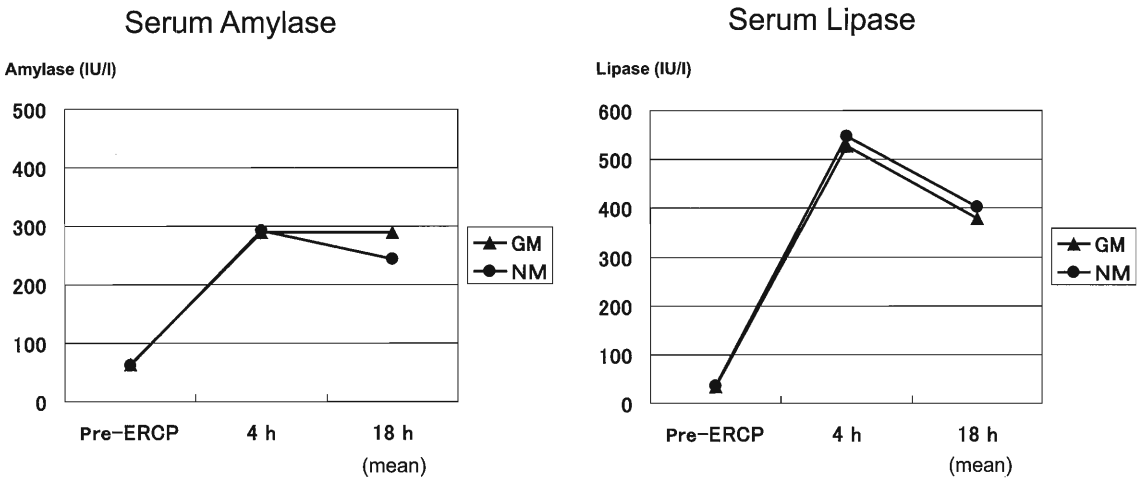

Fig. 3 Changes in serum amylase and lipase levels
Serum amylase levels (IU/*l*, mean) taken before ERCP, at 4 hours after ERCP, and at 18 hours after ERCP in the NM and GM groups. None of the levels were significantly different between the two groups. Serum lipase levels (IU/*l*, mean) taken before ERCP, at 4 hours after ERCP, and at 18 hours after ERCP in the NM and GM groups. None of the levels were significantly different between the two groups. There were no significant differences in serum lipase levels between the groups.
NM: nafamostat mesilate, GM: gabexate mesilate, ERCP: Endoscopic retrograde cholangiopancreatography.

grade 2 or more were considered severe (Fig. 2). Hyperamylasemia and hyperlipasemia were defined as a level of serum amylase or serum lipase at 4 hours or at 18 hours after ERCP that was three times the regarded norm[5)11)].

Results

There were no significant differences between the NM and GM groups with respect to patient characteristics, and there were no occurrences of vasculitis or other adverse events that resulted in termination of drug administration. Of the 86 patients in the NM group, 5 (5.8%) experienced PEP; similarly, of the 80 patients in the GM group, 5 (6.3%) experienced PEP. There were no serious cases in either group and the difference in the incidence of PEP between the two groups was not significant (p = 0.906) (Table 2).

Serum amylase levels (IU/*l*, mean ± SD) taken before ERCP, at 4 hours after ERCP, and at 18 hours after ERCP in the NM and GM groups were 64 ± 27 vs 62 ± 25 (p = 0.863), 289 ± 490 vs 293 ± 604 (p = 0.629), and 289 ± 455 vs 244 ± 431 (p = 0.585), respectively. None of the levels were significantly different between the two groups (Fig. 3). Serum lipase levels (IU/*l*, mean ± SD) taken before ERCP, at 4 hours after ERCP, and at 18 hours after ERCP in the NM and GM groups were 34 ± 15 vs 36 ± 18 (p = 0.649), 527 ± 1,148 vs 547 ± 1,318 (p = 0.511), and 378 ± 680 vs 402 ± 1,510 (p = 0.483), respectively. None of the levels were significantly different between the two groups (Fig. 3).

There were no significant differences in the inci-

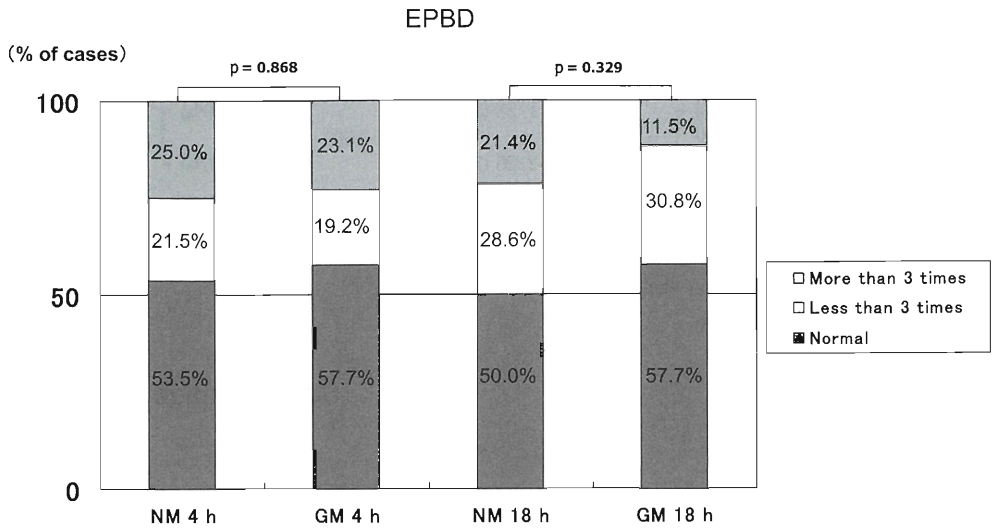

Fig. 4 Incidence of hyperamylasemia of EPBD

There were no significant differences in the incidence of hyperamylasemia between the NM and GM groups at 4 hours or at 18 hours after EPBD.

NM: nafamostat mesilate, GM: gabexate mesilate, EPBD: endoscopic papillary balloon dilatation.

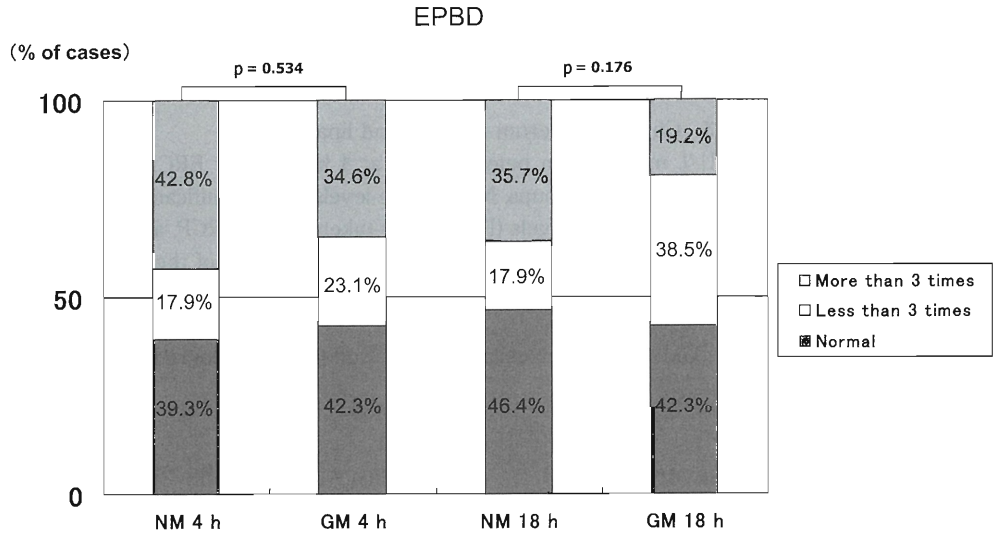

Fig. 5 Incidence of Hyperlipasemia of EPBD

There were no significant differences in the incidence of hyperlipasemia between the NM and GM groups at 4 hours after EPBD or at 18 hours after EPBD.

NM: nafamostat mesilate, GM: gabexate mesilate, EPBD: endoscopic papillary balloon dilatation.

dence of hyperamylasemia between the NM and GM groups at 4 hours (25.0% vs 23.1%; p = 0.868) or at 18 hours after EPBD (21.4% vs 11.5%; p = 0.329) (Fig. 4). There were no significant differences in the incidence of hyperlipasemia between the NM and GM groups at 4 hours after EPBD (42.8% vs 34.6%; p = 0.534) or at 18 hours after EPBD (35.7% vs 19.2%; p = 0.176) (Fig. 5).

There were no significant differences in the incidence of hyperamylasemia between the NM and GM groups at 4 hours (10.3% vs 12.9%; p = 0.665) or at 18 hours after EST (13.8% vs 12.9%; p = 0.897) (Fig. 6). There were no significant differences in the incidence of hyperlipasemia between the NM and GM groups at 4 hours (29.3% vs 27.8%; p = 0.857) or at 18 hours after EST (20.7% vs 20.4%; p = 0.966) (Fig. 7).

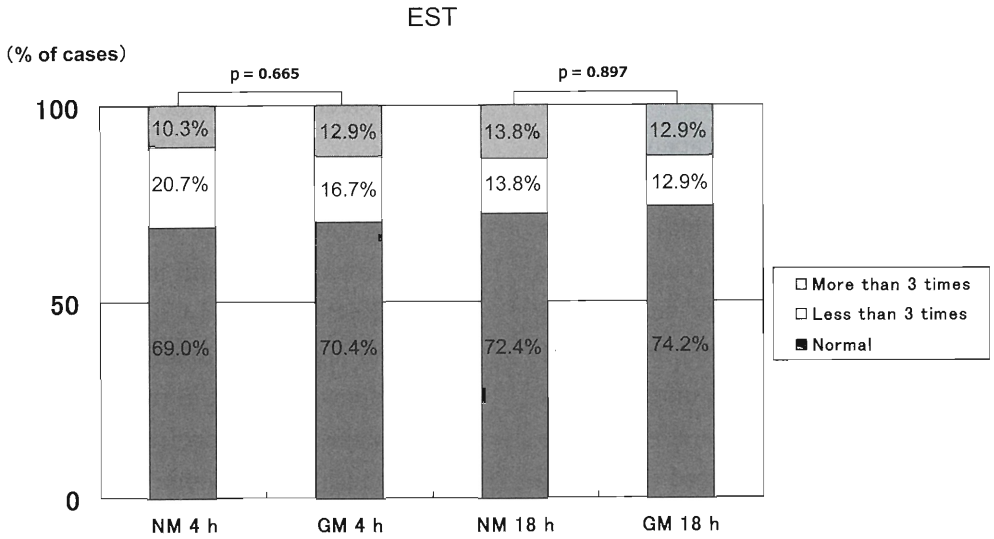

Fig. 6 Incidence of hyperamylasemia of EST
There were no significant differences in the incidence of hyperamylasemia between the NM and GM groups at 4 hours or at 18 hours after EST.
NM: nafamostat mesilate, GM: gabexate mesilate, EST: endoscopic sphincterotomy.

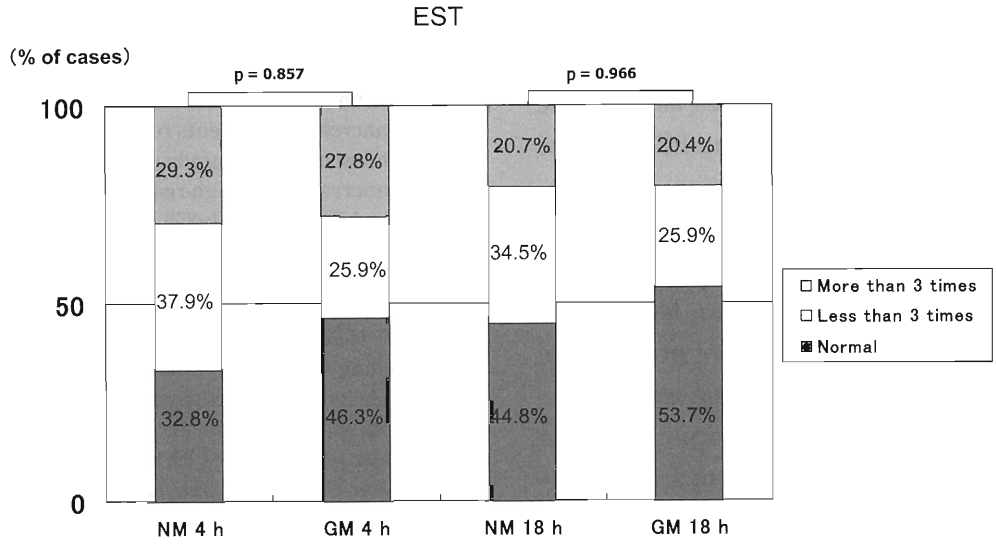

Fig. 7 Incidence of hyperlipasemia of EST
There were no significant differences in the incidence of hyperlipasemia between the NM and GM groups at 4 hours or at 18 hours after EST.
NM: nafamostat mesilate, GM: gabexate mesilate, EST: endoscopic sphincterotomy.

Discussion

There are three outcomes from the present study: ① There was no significant difference in the efficacy of NM and GM in preventing PEP following therapeutic ERCP. There was also no significant difference between the frequency of PEP among the EST and EPBD subgroups. ② No significant differences were found in the levels of pancreatic enzymes in the NM and GM groups at 4 hours or at 18 hours after therapeutic ERCP. ③ There were no significant differences in the frequency of hyperamylasemia or hyperlipasemia in the NM and GM groups at 4 hours and 18 hours after EPBD or EST; however, the frequencies of hyperamylasemia and hyperlipasemia were slightly higher in subjects who underwent EPBD than in those who under-

went EST.

PEP remains the most common complication of ERCP with occurrence rates of 0.4-1.5%[12][13] for diagnostic ERCP and 1.6-5.4%[14][15] for therapeutic ERCP. Complication rates for therapeutic ERCP are higher than those for diagnostic ERCP, and although rare, there have been incidences of severe complications and even death[15]. It has been reported that 300 mg GM administered over 5 hours[4], 1,000 mg GM administered over 24 hours[1], or 150,000 units ulinastatin administered over 10 minutes are effective preventing PEP[16]. It has also been reported that 20 mg NM administered over 24 hours[5] or 50 mg NM administered over 6 hours[11] are also effective preventing PEP.

In the present study, we compared the efficacy of NM and GM in EPBD and EST subgroups. PEP occurred at rates of 3.6% in the NM group and 7.7% in the GM group after EPBD and at rates of 6.9% in the NM group and 5.6% in the GM group after EST. There were no significant differences between the efficacy of NM and GM in preventing PEP in these subgroups.

Pancreatic enzyme levels that are three times the norm directly after ERCP are predictive of the occurrence of PEP[7]. High serum lipase levels, especially at 4 hours after ERCP, are more predictive of the occurrence of PEP than are serum amylase levels[8]. In the present study, we found no significant differences in serum lipase and serum amylase levels between the NM and GM groups at 4 hours or at 18 hours after therapeutic ERCP, indicating that NM and GM have a similar efficacy in preventing elevated levels of pancreatic enzymes. Until now there have been no studies of hyperamylasemia and hyperlipasemia conducted in separate groups of patients undergoing EPBD or EST. Therefore this study is the first to clarify the rates of hyperamylasemia and hyperlipasemia in these separate subgroups.

With regards to safety, there were no significant drug-related adverse events in either the NM or GM group, although vasculitis occurred in 1.5% of patients in the GM group (data not shown). Limitations of this study include the fact that there was no comparison with a placebo group and that it was a prospective, double-blind, randomized, control trial that involved only a single center.

Conclusion

Here we studied the effectiveness of low-dose NM and low-dose GM, which are covered by the Japanese national health insurance, for the prevention of PEP associated with therapeutic ERCP. We found no significant differences between low-dose NM and low-dose GM in frequency of PEP, pancreatic enzyme levels, or frequency of hyperamylasemia and hyperlipasemia after therapeutic ERCP. Therefore, low-dose NM and low-dose GM are equally effective for the prevention of pancreatitis.

The authors declare no conflicts of interest.

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治療的内視鏡的逆行性胆道膵管造影後膵炎予防におけるナファモスタットメシル酸塩とガベキサートメシル酸塩の比較検討—前向き，二重盲検，無作為化試験—

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ERCP後膵炎（post ERCP pancreatitis：PEP）の予防，治療目的で蛋白分解酵素阻害剤が投与されている．しかし，それら薬剤の低用量でのPEP予防効果については不明な点が少なくない．今回PEP頻度の高い治療的ERCPを対象とし，ナファモスタットメシル酸塩（NM）の保険収載内の用量でのPEP予防効果を明らかにする目的で，ガベキサートメシル酸塩（GM）と対比し，前向き，二重盲検，無作為化試験で検討した．

2007年1月～2010年12月に治療的ERCPを施行した166例を対象とした．

NM群は86例でEST 58例，EPBD 28例であった．GM群は80例でEST 54例，EPBD 26例であった．ERCP開始1時間前より5%ブドウ糖液1,000 mlにNM 20 mgを溶解し6時間かけて投与した．GM群は同じ投与方法，溶解液でGM 200 mgを投与した．

NM群とGM群のPEP発症率，血清アミラーゼ値，血清リパーゼ値の経時的変化および高膵酵素血症の発現率をEST，EPBDにわけて検討した．

PEPの発症率は，NM群5.8%，GM群6.3%で，いずれにも重症例はなく，PEP発症率に差は認められなかった．血清アミラーゼ値，リパーゼ値の経時的変化でもERCP後4時間，18時間で両群間に差は認められなかった．

さらにEST，EPBDにわけた検討では，ERCP後4時間，18時間での高膵酵素血症の発現率に両群間とも差は認められなかった．

以上より治療的ERCPを対象とした低用量のNMとGMの投与はPEPの発症率および膵酵素値の経時的変化，高膵酵素血症の発現率において差がないことが明らかになった．それゆえ保険診療内用量のNMはGMと同程度の膵炎発症予防効果がある．