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Post-ERCP pancreatitis

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Abstract Pancreatitis remains the most common severe complication of endoscopic retrograde cholangiopancreatography (ERCP). Detailed information about the findings of previous studies concerning post-ERCP pancreatitis has not been utilized sufficiently. The purpose of the present article was to present guidelines for the diagnostic criteria of post-ERCP pancreatitis, and its incidence, risk factors, and prophylactic procedures that are supported by evidence. To achieve this purpose, a critical examination was made of the articles on post-ERCP pancreatitis, based on the data obtained by research studies published up to 2009. At present, there are no standardized diagnostic criteria for post-ERCP pancreatitis. It is appropriate that post-ERCP pancreatitis is defined as acute pancreatitis that has

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developed following ERCP, and its diagnosis and severity assessment should be made according to the diagnostic criteria and severity assessment of the Japanese Ministry of Health, Labour and Welfare. The incidence of acute pancreatitis associated with diagnostic and therapeutic ERCP is 0.4–1.5 and 1.6–5.4%, respectively. Endoscopic papillary balloon dilation is associated with a high risk of acute pancreatitis compared with endoscopic sphincterotomy. It was made clear that important risk factors include dysfunction of the Oddi sphincter, being of the female sex, past history of post-ERCP pancreatitis, and performance of pancreaticography. Temporary prophylactic placement of pancreatic stents in the high-risk group is useful for the prevention of post-ERCP pancreatitis [odds ratio (OR) 3.2, 95% confidence interval (CI) 1.6–6.4, number needed to treat (NNT) 10]. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with a reduction in the development of post-ERCP pancreatitis (OR 0.46, 95% CI 0.32–0.65). Single rectal administration of NSAIDs is useful for the prevention of post-ERCP pancreatitis [relative risk (RR) 0.36, 95% CI 0.22–0.60, NNT 15] and decreases the development of pancreatitis in both the low-risk group (RR 0.29, 95% CI 0.12–0.71) and the high-risk group (RR 0.40, 95% CI 0.23–0.72) of post-ERCP pancreatitis. As for somatostatin, a bolus injection may be most useful compared with short- or long-term infusion (OR 0.271, 95% CI 0.138–0.536, risk difference 8.2%, 95% CI 4.4–12.0%). The usefulness of gabexate mesilate was not apparent in any of the following conditions: acute pancreatitis (control 5.7 vs. 4.8% for gabexate mesilate), hyperamylasemia (40.6 vs. 36.9%), and abdominal pain (1.7 vs. 8.9%). Formulation of diagnostic criteria for post-ERCP pancreatitis is needed. Temporary prophylactic placement of pancreatic stents in the high-risk group offers the most promise as a means of preventing post-ERCP pancreatitis. As for pharmacological attempts, there are high expectations concerning NSAIDs because they are excellent in terms of cost-effectiveness, ease of use, and safety. There was no evidence of effective prophylaxis with the use of protease inhibitors, especially gabexate mesilate.

Keywords Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis · Pancreatitis · Guidelines · ERCP · Complications

Introduction

The first edition of the Guidelines for the Management of Acute Pancreatitis that was based on evidence was published in 2003 with the cooperation of the Japanese Society of Abdominal Emergency Medicine, the Japan Pancreas Society, and a Research Group of the Ministry of Health, Labour and Welfare of Japan. An English-language version of the Guidelines was published in 2006 [1]. A revised second edition was published in 2007 on the basis of a detailed examination mainly of new related studies that had been reported since 2003. In 2008, a revision was made of the Japanese diagnostic criteria and the criteria for severity assessment. Accordingly, a third Japanese edition that included the latest evidence was prepared [2].

Pancreatitis remains the most common severe complication of endoscopic retrograde cholangiopancreatography (ERCP) and there are many studies that report on its incidence, risk factors, and prophylactic procedures. However, detailed information about previous reports has not been utilized sufficiently in Japan. There is a possibility that diagnostic examinations will be insufficient or that adequate prophylactic treatment may not be delivered to high-risk patients. A chapter on the management of post-ERCP pancreatitis was included de novo in the third edition of the Guidelines for the Management of Acute Pancreatitis [2].

In the present article, we present the results of a search for references, mainly of studies published until January 2009, through PubMed and the internet edition of the Japana Centra Revuo Medicina; we collected and included references concerning the diagnostic criteria, incidence, risk factors, and prevention of post-ERCP pancreatitis. Further search for references was conducted in a manual fashion as needed. Critical appraisals of references obtained through these procedures were made. Evidence obtained was put in order and recommended management procedures were formulated taking into account the opinions of specialists and actual medical circumstances. The evidence obtained from each item was evaluated in accordance with the scientific classification method used at the Cochrane Library (Level and Recommendation) [3]. The recommendation grades were classified in A, B, C1, C2, D [4].

Diagnosis of post-ERCP pancreatitis

CQ1: Are there any diagnostic criteria for post-ERCP pancreatitis ?

There are no standardized diagnostic criteria.

Post-ERCP pancreatitis refers to a condition that presents with clinical signs of acute pancreatitis following ERCP and is accompanied by elevated levels of pancreatic enzymes, although, according to present knowledge, there are no standardized criteria for the timing of blood collection and the cutoff values of pancreatic enzymes. As for the diagnostic criteria, the severity classification by Cotton et al. [5] (Table 1; Level 5) is generally used, although there are problems associated with promptness in diagnosis and inability of severity assessment to be made in the early phase of the disease.

Table 1 Severity classification of post-ERCP pancreatitis by Cotton et al.

Mild	Moderate	Severe
Clinical pancreatitis, amylase at least 3 times normal at more than 24 h after the procedure, requiring admission or prolongation of planned admission to 2–3 days	Pancreatitis requiring hospitalization of 4–10 days	Hospitalization for more than 10 days, or hemorrhagic pancreatitis, necrosis, or pseudocyst, or intervention (percutaneous drainage or surgery)

From Ref. [5] with some modification

ERCP Endoscopic retrograde cholangiopancreatography

According to present knowledge, post-ERCP pancreatitis is defined as acute pancreatitis that has occurred de novo following ERCP. The diagnosis and severity assessment of post-ERCP pancreatitis in Japan should be made according to the diagnostic criteria for acute pancreatitis and the criteria for severity assessment of the Japanese Ministry of Health, Labour and Welfare. Prior endoscopic procedures that induce pancreatitis include endoscopic sphincterotomy (ES) and endoscopic papillary balloon dilation (EPBD).

Incidence of post-ERCP pancreatitis

There are several reports on the incidence of complications associated with diagnostic ERCP and therapeutic ERCP in which ES or EPBD is undertaken simultaneously. The incidence of acute pancreatitis associated with the use of diagnostic ERCP is reported to be 0.4–1.5% (Level 2b) [6–8]. The incidence of acute pancreatitis induced by therapeutic ERCP is high compared with that induced by diagnostic ERCP (Level 1b–2b) [9, 10] at 1.6–5.4% (Level 1b–2b) [6, 7, 9–11] and that of severe acute pancreatitis induced by diagnostic ERCP is 0.4–0.7% (Level 2b–4) [8, 12]. The risk of acute pancreatitis associated with EPBD is high compared with that associated with ES [relative risk (RR) 1.98, 95% confidence interval (CI) 1.35–2.90] (Level 1a) [13].

According to studies of 21 medical facilities in Japan, acute pancreatitis occurred in 166 (1.1%) of 14,947 cases in which diagnostic and/or therapeutic ERCP was performed during the 4 years, 1995–1998. The incidence of acute pancreatitis was 0.8% with diagnostic ERCP and 1.9% with therapeutic ERCP. On the other hand, the incidence of severe acute pancreatitis was 0.07% with diagnostic ERCP and 0.1% with therapeutic ERCP. There was 1 case of death with therapeutic ERCP and the overall mortality rate was 0.007%. The mortality rate was 0.02% when the cases involved were limited to therapeutic ERCP (Level 4) [14]. The incidence of acute pancreatitis was reported to be 5–20% in cases in which EPBD was undertaken in operations for common bile duct stones (Level 4) [15].

Risk factors of post-ERCP pancreatitis

A meta-analysis of 15 prospective cohort studies and 52 retrospective cohort studies that examined the risk factors of post-ERCP pancreatitis found that the risk factors for acute pancreatitis associated with ERCP included dysfunction of the Oddi sphincter (RR 4.09, 95% CI 3.37–4.96), being of the female sex (RR 2.23, 95% CI 1.75–2.84), and a past history of pancreatitis (RR 2.46, 95% CI 1.93–3.12; Level 2a) [16]. It was also reported that the absence of bile duct dilation (Level 2b) [6], bile duct diameter of <1 cm (Level 2b) [11, 17–19], Younger age (Level 2b) [6, 20], difficult cannulation (Level 1b–2b) [11, 21, 22], and performance of pancreatography (Level 1b–4) [6, 18, 23–25] were risk factors for acute pancreatitis.

Prevention of post-ERCP pancreatitis

CQ2. Are there any preventive procedures for post-ERCP pancreatitis ?

Prophylactic pancreatic stent placement is useful in the high-risk group* of post-ERCP pancreatitis. (Recommendation B)

As for pharmacological prophylaxis, there is a possibility that nonsteroidal anti-inflammatory drugs (NSAIDs) will be useful. (Recommendation C1)

There is insufficient evidence supporting the usefulness of combined use of pancreatic stent placement and NSAIDs.

There is a possibility that bolus injection of somatostatin will be useful.**

*Cases with a definitive diagnosis of dysfunction of the Oddi sphincter or suspected cases, cases in which cannulation is difficult, cases with EPBD, and cases with precut sphincterotomy (refer to the following text and Tables 1, 2).

**Note: In Japan, somatostatin is not on the market, but octreotide (Sandostatin®, Novartis, East Hanover, NJ, USA), an analogue of somatostatin, is on the market. For details, refer to the following text.

Prophylactic endoscopic procedures

Prophylactic temporary placement of pancreatic stents

As far as prophylactic temporary placement of pancreatic stents in the high-risk group of post-ERCP pancreatitis is

Table 2 Effects of prophylactic pancreatic stent placement in post-ERCP pancreatitis

Reference	Number of cases	Age (years; SEM)	Proportion of females (%)	Reasons for indicated stent placement				Cases of occurrence of pancreatitis		OR (95% CI)	*P* value
				SOD suspected	Difficult cases of cannulation	Precut	EBD	Placement group	No-placement group		
Smithline et al. [27]	93	47	38	+	+	+	−	6/43	9/50	0.73 (0.25, 2.27)	0.60
Sherman et al. [28]	104			+	+	+	−	1/46	8/58	0.13 (0.017, 1.15)	0.03
Tarnasky et al. [29]	80	45.7 ± 2.2	73	+	+	−	−	3/41	10/39	0.07 (0.01, 0.59)	0.003
Aizawa and Ueno [30]	130	68.21 ± 4	43	−	−	−	+	0/38	6/92	0.17 (0.009, 3.14)	0.18
Fazel et al. [31]	74	44.6 ± 2.2	86	+	+	−	−	2/38	10/36	0.14 (0.02, 0.71)	0.009

From Ref. [26] with some modification

SOD Sphincter of Oddi dysfunction, *EBD* endoscopic balloon dilatation

concerned, there is a meta-analysis of 5 prospective studies including 4 randomized controlled trials (RCTs; 481 cases; Level 1a) [26] (Table 2) [27–31] (Level 1a–2b). Included in the high risk group in the 5 studies were cases with a definitive diagnosis of dysfunction of the sphincter of Oddi or suspected cases, those in which cannulation was difficult, those with EPBD, and those with precut sphincterotomy. The incidence of post-ERCP pancreatitis was 5.8% in the group in which stents were placed and 15.5% in the group in which no stent was placed, showing that pancreatic stent placement was useful [odds ratio (OR) 3.2, 95% CI 1.6–6.4]. As for the incidence of post-ERCP pancreatitis according to severity, the incidence of mild to moderate post-ERCP pancreatitis was lower in the stent group (12/206 vs. 36/275) and no significant difference was observed between the 2 groups, although there were no severe cases in the stent placement group (0/206 vs. 7/275). The ARR (absolute risk reduction) was 0.1 and the number needed to treat (NNT) was 10, which means that 10 cases of pancreatic stent placement are required to prevent 1 case of post-ERCP pancreatitis.

A review (Level 5) [32] concerning the reports published between January 1966 and January 2004 expressed almost the same opinions as those in the above-quoted meta-analysis. Cost-effectiveness, risks, and clinical benefits should be taken into account when pancreatic stents are placed.

An RCT (Level 1b) [33] published in 2007 reported on 201 cases in which spontaneous stent dislodgement occurred found that the incidence of post-ERCP pancreatitis was 3.2% in the group in which stents were placed and 13.6% in the group in which no stent was placed ($P = 0.019$), and that there was also a significant reduction in the development of hyperamylasemia. An RCT conducted in Japan in 2007 asserted that there was a tendency similar to that reported in the previous studies, but failed to show a significant difference between stented and unstented groups because the number of cases (64 cases) was small (Level 1b) [34].

Table 3 Indications for pancreatic stent placement to reduce risk of post-ERCP pancreatitis

Generally recommended indications
SOD (suspected or documented)
Previous post-ERCP pancreatitis
Difficult cannulation involving pancreatic instrumentation or injection
Precut sphincterotomy starting at orifice (after pancreatic instrumentation)
Pancreatic sphincterotomy (major or minor papilla)
Aggressive instrumentation of pancreatic duct (such as brush cytology)
Balloon dilatation of intact sphincter
Endoscopic ampullectomy
Not generally recommended indications
Low-risk patients (older, obstructive jaundice, obstructed pancreatic duct)
Needle-knife precut or fistulotomy starting above orifice, in absence of other risks
Pancreatic duct not injected with contrast, and limited pancreatic guidewire manipulation in otherwise low-risk patient
Doubtful feasibility of successful pancreatic wire access and stent placement

From Ref. [35] with some alterations

SOD Sphincter of Oddi dysfunction

In 2007, Freeman [35] asserted the usefulness of prophylactic pancreatic stent placement on the basis of a detailed examination of the previous reports, and summarized its indications (Table 3) (Level 5).

Other endoscopic procedures

There are reports of several RCTs concerning endoscopic procedures other than prophylactic pancreatic stent placement. According to studies of conventional cannulation using contrast medium and cannulation using a guidewire, there was no significant difference between the 2 methods in terms of the development of post-ERCP pancreatitis (Level 1b) [36, 37]. Some RCTs (Level 1b) [38, 39] have asserted the usefulness of a procedure that uses a needle knife.

The evidence is weak that supports the recommendation of the use of a single procedure, so a safe procedure should be selected by taking into account the equipment at facilities and the skills of the operators.

Pharmacological prophylaxis

There are many studies of pharmacological prophylaxis of post-ERCP pancreatitis. According to a detailed examination of the above review [32] reported in 2004 (Level 5), most of the studies failed to show clearly the usefulness of prophylactic use of drugs (Table 4). Important factors responsible for this result are pointed out, including the lack of a high-risk group in patient selection, the case mix, and/or the variety of criteria used to define post-ERCP pancreatitis. Even with the 2 most promising agents for the prevention of post-ERCP at that time, gabexate mesilate and somatostatin, problems were pointed out, such as the long time required for administration and the cost-effectiveness (the NNT is 35 for gabexate mesilate), especially in outpatients.

Discussion follows concerning the results of examinations of individual drugs based mainly on the data in meta-analyses and RCTs that were reported recently.

NSAIDs

According to a meta-analysis of 6 RCTs concerning the administration of NSAIDs in a total of 1,300 patients, post-ERCP pancreatitis was significantly lower in the group in which NSAIDs were administered (652 cases, including 271 cases in which diclofenac was used and 381 cases in which indomethacin was used; 8.9 vs. 16.8%; OR 0.46, 95% CI 0.32–0.65, $P < 0.0001$; Level 1a) [40]. There were no side effects associated with the use of NSAIDs. Of these 6 RCTs, a meta-analysis of 4 RCTs evaluating a rectally administered drug involving a total of 912 patients (456 patients received a placebo, 160 patients received diclofenac 100 mg, and 296 received indomethacin 100 mg) reported that the single use of NSAIDs just before or after ERCP was useful in preventing post-ERCP pancreatitis (4.4 vs. 12.5%; RR 0.36, 95% CI 0.22–0.60, NNT 15; Level 1a) [41]. A subgroup analysis of the same 4 RCTs reported that, in the group in which NSAIDs were administered, there was a significant decrease in post-ERCP pancreatitis in both the low-risk group (RR 0.29, 95% CI 0.12–0.71, $P = 0.006$) and the high-risk group (RR 0.40, 95% CI 0.23–0.72, $P = 0.002$; Level 1a) [42]. Of the 4 RCTs, 2 studies referred to pancreatic stent placement. In one study, prophylactic pancreatic stents were not placed in either group; in the other study, stents were placed in 13 patients in the drug administration group and in 12 patients in the placebo group, although subgroup analysis was not conducted. The reason that stent placement was indicated was not mentioned.

Table 4 Pharmacological attempts to reduce risk of post-ERCP pancreatitis

Medication	Assessment	Results of meta-analyses since 2007	Results of recent RCTs
Calcium inhibitors	Ineffective		
Lidocaine (local administration)	Ineffective		
Nitroglycerin	Possibly effective		
Antibiotics	Possibly effective		
Nonionic contrast medium	Ineffective		
Steroid	Ineffective	Ineffective	
PAF inhibitors	Ineffective		
IL-10	Ineffective		
Heparin	Ineffective		
NSAID	Possibly effective	Effective	
Gabexate mesilate			
Short-term infusion	Ineffective	Ineffective	Effective
Long-term infusion	Effective	Ineffective	
Octreotide	Ineffective	Ineffective	
Somatostatin			
Short-term infusion	Ineffective	Ineffective	
Long-term infusion	Possibly effective	Possibly effective	
Bolus injection		Effective	
Allopurinol	Ineffective	Ineffective	
N-acetylcysteine			Ineffective
Ulinastatin			Possibly ineffective
Semapimod			Possibly effective

From Ref. [32] with alterations

RCT Randomized controlled trial, *PAF* Platelet activating factor, *IL* interleukin, *NSAID* nonsteroidal anti-inflammatory drug

In Western countries, a 100-mg suppository and a 100-mg tablet of both diclofenac and indomethacin are on the market and the maximum dosage per administration is 100 mg. In Japan, only medication with a maximum dose of 50 mg is on the market and the ordinary dosage is 25–50 mg per administration. At present, the prophylactic effect of the use of 50 mg of such medication against post-ERCP pancreatitis is not known. According to the sales data of a company concerning the use of Voltaren®, Novartis, East Hanover, NJ, USA (diclofenac) suppositories, the incidence of side effects caused by the administration of 25–50 mg/was 1.76% (301/17,094) and the incidence of side effects caused by the administration of 50–100 mg was 0.52% (1/191). However, side effects of other types of NSAIDs (phenylbutazone and oxyphenbutazone) were reported in many countries in 1984, so the dosage was re-examined and the upper dosage/administration limit was reduced in 1985 in Japan. Consideration of the dosage for prophylactic use is needed in Japan.

Gabexate mesilate

A meta-analysis of 4 RCTs on gabexate mesilate concluded that gabexate mesilate was ineffective in the prevention of post-ERCP pancreatitis, (OR 0.67, 95% CI 0.31–1.47) and it failed to show usefulness in the prevention of severe pancreatitis, death, hyperamylasemia, and abdominal pain (Level 1a) [43]. According to a meta-analysis that took note of the administration schedule (Level 1a) [44], the incidence of post-ERCP pancreatitis after long-term infusion (12 h) was decreased by 5.2% (95% CI 1.1–9.4%, $P = 0.01$), but a significant difference was not observed in the development of hyperamylasemia. An examination of short-term infusion (within 12 h) failed to show usefulness both in post-ERCP pancreatitis (difference in the incidence −1.1%, 95% CI −3.8 to 1.6%) and in hyperamylasemia.

A third meta-analysis (Level 1a) [45] of the 5 RCTs including all of the RCTs examined by two meta-analyses mentioned already (Level 1a) [43, 44] found that the incidence of post-ERCP pancreatitis was 5.7% in the control group vs. 4.8% in the administration group and concluded that gabexate mesilate was not useful in the prevention of post-ERCP pancreatitis and also in reducing hyperamylasemia (40.6% vs. 36.9%) and abdominal pain (1.7% vs. 8.9%). A meta-analysis of long-term infusion of gabexate mesilate conducted by 2 RCTs also failed to show its usefulness in the prevention of post-ERCP pancreatitis. According to a recent report (Level 1b) [46], the incidence of post-ERCP pancreatitis was 3.9% (8/203) in the group in which 500 mg/6 h of gabexate mesilate was administered prior to ERCP (preoperative group), 3.4% (7/203) in the group in which 500 mg/6 h of gabexate mesilate was administered after ERCP (post-operative group), and 9.4% (19/202) in the control group, showing that a significant decrease was observed in the group (3.7%; 15/406) in which gabexate mesilate was administered compared with the control group ($P < 0.01$). There was no significant difference between the preoperative group and the post-operative group, so gabexate mesilate administration is recommended post-operatively only in patients with a high risk.

Somatostatin and octreotide

According to a meta-analysis (Level 1a) [44] that paid attention to the administration schedule of somatostatin, long-term infusion (12 h) was associated with a decrease of post-ERCP pancreatitis by 7.7% (95% CI 3.4–12.0%, $P < 0.0001$), and somatostatin was also found to be useful in hyperamylasemia ($P = 0.017$). Short-term infusion (within 12 h) failed to show usefulness either in post-ERCP pancreatitis (difference in the incidence −2.3%, 95% CI −5.2 to 0.5%) or in hyperamylasemia. The examination of 670 cases in which bolus injection was conducted (4 μg/kg or 250 μg just before catheter insertion or just after diagnostic ERCP; 337 vs. 333) found that bolus injection reduced post-ERCP pancreatitis by 8.2% (95% CI 4.4–12.0%, $P < 0.0001$) and that it was also useful in hyperamylasemia ($P = 0.001$). The study asserted that bolus injection was most likely to be useful in consideration of its practical utility in clinical settings. According to a meta-analysis (Level 1a) [45] of 9 RCTs that included all RCTs contained in the meta-analysis mentioned above [44], the incidence of acute pancreatitis was 7.3% (96/1,309) in the control group and 5.3% (72/1,349) in the treatment group (OR 0.73, 95% CI 0.54–1.006, RR 0.734, 95% CI 0.535–1.006), showing that there was no significant difference between the 2 groups. An examination of 4 RCTs of short-term infusion and 3 RCTs of long-term infusion found that the incidence of post-ERCP pancreatitis in the control group vs. the treatment group was 6.4 vs. 11.8% and 6.4 vs. 2.9%, respectively, showing that there was no significant difference. Similar to the meta-analyses mentioned already, a study of the bolus injection group in 3 RCTs showed that the bolus injection was useful in the prevention of post-ERCP pancreatitis (OR 0.271, 95% CI 0.138–0.536, difference in incidence 8.2%, 95% CI 4.4–12.0, NNT 12, 95% CI 8–23) and hyperamylasemia. Another RCT was also conducted in 2008 (Level 1b) [47]. A study of 391 cases in which therapeutic ERCP was undertaken showed that the incidence of post-ERCP pancreatitis was significantly lower in the group in which somatostatin administration continued for 12 h starting from 30 min before ERCP (3.6% in the treatment group vs. 9.6% in the placebo group, $P = 0.02$). As far as octreotide is concerned, there is a meta-analysis of 15 RCTs. The overall examination of a total of 2,621 cases failed to show the usefulness of

octreotide in the prevention of post-ERCP pancreatitis (OR 0.78, 95% CI 0.57–1.08; Level 1a) [48]. However, when the analysis was limited to a total of 1,714 cases including cases in 5 RCTs that studied more than 200 cases, it was found that post-ERCP pancreatitis was decreased significantly by octreotide (OR 0.50, 95% CI 0.32–0.79, $P = 0.003$, NNT 31).

Allopurinol

An examination concerning allopurinol was conducted in a total of 1,554 cases; 783 cases in the treatment group and 771 cases in the control group, based on 6 RCTs but the study failed to show treatment effects on any of the following conditions: post-ERCP pancreatitis (OR 0.74, 95% CI 0.37–1.48, $P = 0.40$), severe post-ERCP pancreatitis (OR 0.87, 95% CI 0.33–2.28, $P = 0.78$), or hyperamylasemia (OR 0.88, 95% CI 0.37–2.11, $P = 0.78$), or death (OR 0.19, 95% CI 0.01–3.91, $P = 0.28$; Level 1a) [49]. Furthermore, an examination of 4 RCTs, including an RCT reported in 2008, also failed to show a significant difference in the incidence of post-ERCP pancreatitis between allopurinol-treated and allopurinol-untreated groups (8.9 vs. 9.7%, $P = 0.68$, RR 0.86, 95% CI 0.42–1.77; Level 1a) [50].

Steroids

There is a meta-analysis of 7 RCTs concerning steroid use, which concluded that steroid use had no effect on post-ERCP pancreatitis (OR 1.13, 95% CI 0.89–1.44, $P = 0.32$), severe acute pancreatitis (OR 1.61, 95% CI 0.74–3.52, $P = 0.23$), or hyperamylasemia (OR 0.92, 95% CI 0.57–1.48, $P = 0.73$), and that prophylactic use of steroid cannot be recommended (Level 1a) [51].

N-acetylcysteine

According to 2 RCTs, the use of *N*-acetylcysteine, which was expected to act as a free radical scavenger, was found to be ineffective in preventing post-ERCP pancreatitis (Level 1b) [52, 53].

Ulinastatin

A report from Japan on a multicenter RCT concerning ulinastatin found a significantly lower incidence of post-ERCP pancreatitis in the treatment group compared with the control group [2.9% (6/204) vs. 7.4% (15/202), $P = 0.041$; Level 1b] [54]. The report defined post-ERCP pancreatitis as a condition that is accompanied by abdominal pain continuing for more than 24 h following ERCP, or elevated levels of pancreatic enzymes (amylase or lipase) of more than 3 times the upper limit of normal at 18 h after ERCP, but a significant difference was not observed in the incidence of abdominal pain [8.8% (18/204) vs. 14.4% (29/202)]. An RCT reported in 2006 compared a group with a high dosage of ulinastatin (450,000 units), a group with low dosage (150,000 units), and a group treated with gabexate mesilate (900 mg) and found that the incidence of post-ERCP pancreatitis was 3/46 (6.5%), 4/47 (8.5%), and 2/46 (4.3%), respectively, showing that a difference was not observed among the groups (Level 1b) [55]. Furthermore, an RCT was reported in 2007 comparing a group with ulinastatin administration (150,000 units) and a group with gabexate mesilate administration (600 mg); that study found that the incidence of post-ERCP pancreatitis was similar in both groups [2.9% (1/34); Level 1b] [56]. Neither the 2006 report [55] nor the 2007 report [56] found any superiority of gabexate mesilate over ulinastatin, and the effectiveness of gabexate mesilate is being denied according to present knowledge. According to an RCT of 227 cases limited to a high-risk group by considering cost-effectiveness, post-ERCP pancreatitis occurred in 6.7% of patients in the treatment group (100,000 units of ulinastatin) and in 5.6% in the placebo group. Accordingly, the RCT concluded that ulinastatin was not useful in the prevention of post-ERCP pancreatitis (Level 1b) [57].

Mitogen-activated protein kinase inhibitor

An RCT of 242 patients treated with semapimod, a synthetic guanylhydrazone that inhibits the phosphorylation of p38 mitogen-activated protein kinase, found a significant reduction of post-ERCP hyperamylasemia in the group that underwent a single use of semapimod (29.8% in the placebo group vs. 18.4% in the treatment group, $P = 0.031$), but failed to detect a significant difference in the incidence of post-ERCP pancreatitis (14.9% in the placebo group vs. 9.1% in the treatment group, $P = 0.117$). There were no serious side effects associated with the use of semapimod (Level 1b) [58].

Conclusion

The formulation of reliable and standardized diagnostic criteria for post-ERCP pancreatitis is needed (Level 5) [59]. As far as the prevention of post-ERCP pancreatitis is concerned, placement of pancreatic stents in the high-risk group would be useful according to present knowledge. Concerning pharmacological prophylaxis, NSAIDs are most strongly recommended in terms of cost-effectiveness, ease of use, and safety. Because studies that have been carried out to date concern only a small number of cases,

further studies are required. Bolus injection of somatostatin is expected to be useful, although the number of cases that have been studied is also small. The usefulness of protease inhibitors, which are used widely in Japan, gabexate mesilate in particular, is equivocal. So it is thought that the cost-effectiveness would be low, unless such agents are used only in limited cases.

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