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Int J Clin Oncol
DOI 10.1007/s10147-010-0060-y

SPECIAL ARTICLE

Quality of guideline development assessed by the Evaluation Committee of the Japan Society of Clinical Oncology

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Received: 5 January 2010

Abstract
Background The Japan Society of Clinical Oncology started implementing clinical practice guidelines for cancer in 2001. It created a Guideline Committee and has published cancer-related information in collaboration with individual subspecialty cancer societies. The society then established an Evaluation Committee to assess the quality of guidelines.

Methods The quality of development and general characteristics of guidelines were reviewed using the AGREE instrument. The six standardized domain scores and 23-item crude scores were described, and items with a low median score or a wide inter-quartile range were explored. Kappa statistics for inter-rater reproducibility were also described.

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Published online: 24 March 2010

Results Domains in which the median score was >50 points in 18 guidelines developed between March 2005 and May 2009 included "scope and purpose," "rigor of development," and "clarity and presentation." Domains with a median score < 50 points were "stakeholder involvement," "applicability," and "editorial independence." Scores in all domains except "stakeholder involvement" were higher during the second half of the period than during the first half of the period, although *P* values were 0.10–0.93. Crude scores remained low for items 5, 7, 19, 20, 22, and 23, and the inter-quartile ranges of items 2, 6, 10, and 22 were wide. Kappa statistics ranged from –0.02 to 0.64, and they were especially low for items 3, 5, 7, 18, and 23.

Conclusion Guideline quality has tended to improve during the 10 years since the society started this activity. However, issues remain to be improved through continuous revisions.

Keywords Clinical practice guideline · AGREE instrument · Cancer

Introduction

The Japan Society of Clinical Oncology started implementing clinical practice guidelines (CPGs) for cancer in 2001 in collaboration with allied subspecialty societies. The society has developed summary versions of CPGs and flowcharts, and it has published them on the Internet with structured abstracts of important articles. Around 20 guidelines have been developed by subspecialty societies by November 2009, and 13 of them are presented on the society's homepage (http://www.jsco-cpg.jp/) [1].

The society established a Guideline Committee (GC) for this activity, as well as an Evaluation Committee (EC) to evaluate and ensure the quality of published guidelines. The aims of the present study were to identify issues requiring resolution from a summary of the assessment results generated by the EC.

Methods

Process before publishing the guidelines

The activity of CPG publishing and implementation in the society proceeds as follows. A subcommittee of the GC for a specific cancer writes a draft summary, algorithm, and structured abstract in accordance with the specific subspecialty society, and submits them, or sometimes a complete CPG, to the board of the GC. The board of the GC reviews and sends them to the EC. The EC evaluates them and reports the result to the chair of the GC and the members of GC subcommittee. If there is no major flaw, a homepage is developed. These tools for implementation of the CPG are then released to the public after the final approval of the GC and the board of the society.

The review in the EC

The EC has ten members, including a chair and four members from outside the society. All members individually review drafts under evaluation before attending a meeting where all members reach a consensus-based final assessment.

The AGREE instrument [2] was used for reviews that focus on the process of CPG development and the general characteristics of the CPGs, but not on the validity of specific statements. The AGREE instrument is a comprehensive tool for evaluation whose validity and reproducibility have been investigated [3, 4]. The EC did not require revision of the content and format of the draft after review, but revisions were expected for a subsequent version. The EC previously presented the appropriate methods for developing evidence-based CPGs to the GC.

Method of review

The present study summarizes the results of the review of the CPGs by the EC.

The AGREE instrument consists of 23 items that assess six domains of the CPG development process: "scope and purpose" (items 1–3), "stakeholder involvement" (items 4–7), "rigor of development" (items 8–14), "clarity and presentation" (items 15–18), "applicability" (items 19–21), and "editorial independence" (items 22–23). For each item, a crude score of 1–4 is assigned based on the reviewers' certainty of fulfilling the requirements of the items and the quantity of information contained in the CPG. A standardized domain score is calculated for the 6 domains after summing and adjusting the crude scores into a scale from 0 to 100 points. A global assessment could be given, but such global assessments were not recorded for all CPGs. Global quality was described as an aggregated score determined from the summation of all domain scores, although AGREE does not suggest using this strategy for global assessment.

The distributions of the crude scores for the items were determined. Low-score items in which the medians were ≤ 2 and dispersed items, for which the inter-quartile range of the crude score was 1–4, were identified. The dispersed items contained CPGs with both low and high scores, which led to the supposition that they could be easily improved.

Kappa statistics were calculated for each item to determine inter-rater reproducibility [5, 6]. Low kappa values

indicate a trend toward the item scoring differently among raters. When calculating kappa, crude scores of 1 and 2, as well as those of 3 and 4, were combined into one level. The EC used only one representative score based on consensus for evaluation at meetings and did not use the individual crude scores from which the kappa values were derived.

When members thought that determining a score was difficult, the committee used its own criteria to standardize

Table 1 Guidelines that have been reviewed by the evaluating committee

Type of cancer	Title	Version
Stomach[a]	Japanese Gastric Cancer Association: guidelines for the diagnosis and treatment of carcinoma of the stomach, April 2004 edition	2
Liver[b]	The Japan Society of Hepatology:[c] "clinical practice guidelines for hepatocellular carcinoma:" evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan (the print/web version)	1
GIST[a]	Japanese Gastric Cancer Association, Japan Society of Clinical Oncology, Japanese Study Group on GIST: clinical practice guidelines for gastrointestinal stromal tumors (GIST) in Japan	1
Oral cancer	Japan Society for Oral Tumors: clinical practice guidelines for oral cancer	1
Uterine cervix	The Japan Society of Gynecologic Oncology: treatment guidelines for cervical cancer, 2007 edition	1
Uterine body	The Japan Society of Gynecologic Oncology: treatment guidelines for uterine body cancer, 2006 edition	1
Children's leukemia	The Japanese Society of Pediatric Hematology: guidelines for the treatment of childhood leukemia/lymphoma, 2007 edition	1
Esophagus[d]	The Japan Esophageal Society: guidelines for the diagnosis and treatment of esophageal cancer	2
Kidney[d]	The Japanese Urological Association: clinical practice guidelines for managing renal carcinoma and the digest edition (web version)	1
Pancreas[d]	Japan Pancreas Society: evidence-based clinical practice guidelines for pancreatic cancer	1
Colon[d]	Japanese Society for Cancer of the Colon and Rectum: guidelines for the treatment of colon cancer, 2005 edition	1
Biliary tract[d]	Japanese Society of Hepato-Biliary-Pancreatic Surgery: clinical practice guidelines for the management of biliary tract and ampullary carcinomas (the print and web digest version)	1
Head and neck	Japan Society for Head and Neck Cancer: clinical practice guidelines for head and neck cancer	1
Breast[a]	The Japanese Breast Cancer Society: evidence-based clinical practice guidelines of the Japanese Breast Cancer Society (5 volumes) and web version	1
	1. Systemic therapy	
	2. Surgery	
	3. Radiation therapy	
	4. Screening and diagnosis	
	5. Epidemiology and prevention	
Lung	The Japan Lung Cancer Society: clinical practice guidelines for lung cancer, revised edition	2
Skin[d]	The Japanese Skin Cancer Society: clinical practice guidelines for the management of cutaneous malignancies	1
Ovary[d]	The Japan Society of Gynecologic Oncology: ovarian cancer treatment guidelines, 2004 edition	1
Ovary	The Japan Society of Gynecologic Oncology: ovarian cancer treatment guidelines, 2007 edition	2

Order in table reflects the list in the homepage of the Japan Society of Clinical Oncology (order of Japanese 50 sounds)

[a] Presentation was partly funded by the Scientific Study for the Third Term Comprehensive Control Research for Cancer of the Ministry of Health, Labour, and Welfare in 2007

[b] Development was funded by the Scientific Study for Supporting Clinical Practice Guidelines of the Ministry of Health, Labour, and Welfare in 2002–2003

[c] On October 2009

[d] Development and presentation was partly funded by the Scientific Study for the Research on the Medical Safety and Health Technology Assessment of the Ministry of Health, Labour, and Welfare in 2005–2006

Table 2 Domain scores determined using the AGREE instrument for clinical practice guidelines

Domain	Total ($n = 18$)		The first half, March 2005–March 2007 ($n = 10$)		The second half, April 2007–May 2009 ($n = 8$)		P value[a]
	Median	IQR[b]	Median	IQR	Median	IQR	
Scope and purpose	72.2	66.7–100	66.7	55.5–100	83.3	66.7–100	0.38
Stakeholder involvement	41.7	16.7–50.0	43.1	25.0–58.3	41.7	29.2–50.0	0.93
Rigor of development	66.7	38.9–83.3	44.4	16.7–72.2	72.2	61.1–86.1	0.13
Clarity and presentation	75.0	58.3–91.7	70.8	33.3–91.7	83.3	70.8–100	0.18
Applicability	33.3	0–66.6	16.7	0–33.3	50.0	25.0–66.7	0.10
Editorial independence	0	0–50.0	0	0–0	33.3	0–50.0	0.12
Aggregated	56.3	36.5–69.8	48.6	28.6–58.7	65.9	54.8–71.4	0.11

[a] Comparison of scores between the first half of the period and the second half of the period was tested using the Wilcoxon rank-sum test

[b] Inter-quartile range

the score among its members. Item 13 indicates a requirement for an external review of the CPG. This item was not scored because review by the EC is compatible with this. Item 21 requires the CPG to present key review criteria for monitoring or audit. This item was also omitted from scoring because quality indicators for measuring adherence to CPGs have not been developed.

Results

The EC started reviewing CPGs in March 2005, and 18 of them had been reviewed by May 2009 (Table 1). Table 2 shows the standardized domain scores of these CPGs. The domains with median scores > 50 points during the entire period of review were "scope and purpose," "rigor of development," and "clarity and presentation." The median scores for "stakeholder involvement," "applicability," and "editorial independence" were <50 points. All domain scores except "stakeholder involvement" were higher during the second half of the period than during the first half of the period, although the P values were 0.10—0.93.

Figure 1 shows the distribution of crude scores for each item in all CPGs. Item numbers with median crude scores ≤ 2.0 were 5 (emphasizing patients' perspectives), 7 (pre-test before publication), 19 (discussion about potential organizational barriers), 20 (considering cost implications), 22 (editorial independence from funding body), and 23 (records of conflicts of interest). The item numbers with widely distributed crude scores were 2 (description of clinical questions), 6 (target users defined clearly), 10 (presentation of methods for formulating recommendations), and 22 (editorial independence from funding body).

Table 3 shows the inter-rater reproducibility for each item. The kappa statistics were –0.02 to 0.64, and the null hypothesis that the consistency of the results occurred by chance alone could not be rejected for items 3 (target patients described specifically), 5 (emphasizing patients' perspectives), 7 (pre-test before publication), 18 (tools for application), and 23 (records of conflicts of interest).

Discussion

The present report describes the results of continuous evaluation of CPGs assembled by the Japan Society of Clinical Oncology. Changes in standardized domain scores indicated that the methods and organization for developing CPGs have improved slightly, although the differences were not statistically significant and the number of CPGs assessed was small. The domains with median scores > 50 points were "scope and purpose" (items 1–3), "rigor of development" (items 8–14), and "clarity and presentation" (items 15–18). Domains with median scores < 50 points were "stakeholder involvement" (items 4–7), "applicability" (items 19–21), and "editorial independence" (items 22–23). Developers must consider these findings when developing new guidelines or revising those that have been already established. For individual items, low scores were observed in items 5, 7, 19, 20, 22, and 23.

Item 5 emphasizes patients' perspectives. The values of individual patients with cancer should be considered in clinical decision making. Several guidelines seemed to specifically recommend a single option without providing alternatives. Representatives of patients or paramedical staff should be involved in these processes.

Item 7 addresses the pilot use of the CPG before formal publication. When a pilot is not used to improve the quality of the CPG, early feedback about its validity, implementation, and impact on routine practice after publication should be obtained.

Item 19 addresses potential organizational barriers. Alternatives should be discussed when barriers interfere with CPG implementation.

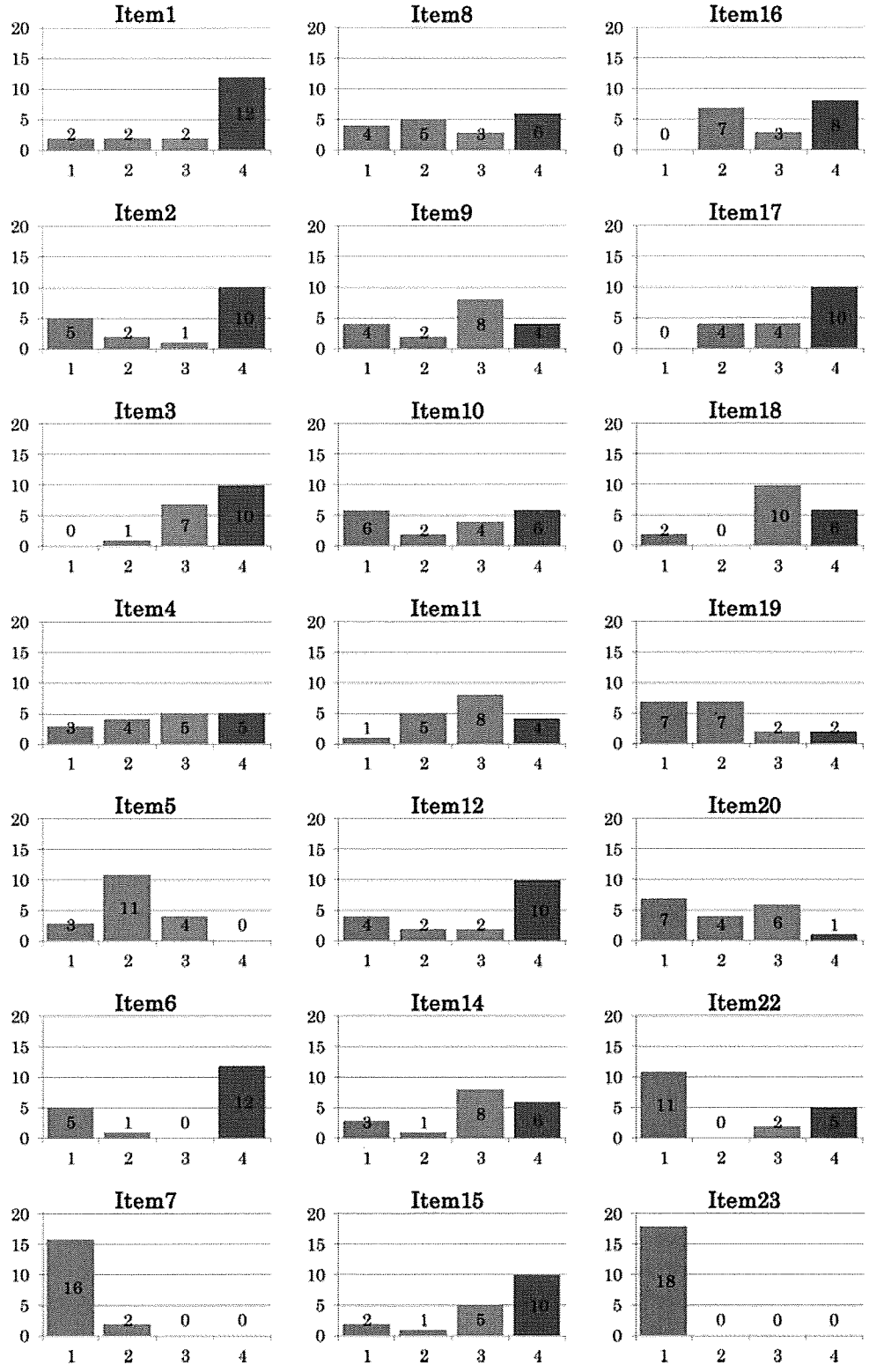

Fig. 1 Distribution of crude scores for each item. Crude scores of each item were reached by consensus after discussion in a committee meeting and are not simple means or medians of scores supplied by individual members of the Evaluation Committee

Item 20 refers to cost issues. The clinical practice of oncology must be individualized because it is based on patient status and value judgments. In general, the issue of cost is important, especially in preventive medicine and in the long-term management of prevalent chronic disorders such as hypertension or dyslipidemia. Cost is more urgent in preventive medicine than for oncologists whose patients have cancer.

Table 3 Inter-rater reproducibility of each item

Item	Kappa[a]	*P* value	Item	Kappa[a]	*P* value
1	0.23	<0.01	12	0.31	<0.01
2	0.64	<0.01	14	0.49	<0.01
3	0.00	0.49	15	0.15	<0.01
4	0.37	<0.01	16	0.20	<0.01
5	−0.02	0.61	17	0.15	<0.01
6	0.34	<0.01	18	0.05	0.18
7	0.04	0.23	19	0.19	<0.01
8	0.33	<0.01	20	0.28	<0.01
9	0.35	<0.01	22	0.14	0.01
10	0.33	<0.01	23	0.05	0.20
11	0.18	<0.01			

[a] Kappa statistics express agreement of several raters above the expected value

Item 22 requires editorial independence from funding bodies. The source of financial support should be documented. If pharmaceutical companies are the source, then the procedure for maintaining editorial independence should also be documented.

Item 23 asks about records of conflicts of interest. None of the CPGs described records for conflicts of interest, although the impact of CPGs on routine practice is substantial. Concern about conflicts of interest is increasing in Japan, where medical journals have not managed this issue as foreign journals have. The Japan Society of Clinical Oncology and the Japan Society of Medical Oncology have developed the "Clinical Oncology Research Conflict of Interest Policy (ver. 1)" [7, 8]. According to this policy, all members of the society must report their status regarding conflict of interest when they report and publish in the society, and these reports are centrally reviewed. This procedure must be followed when CPGs are developed, and records about conflicts of interest should be explicit.

The distribution of crude scores was wide for items 2, 6, 10, and 22, for which the same item scored low and high in several CPGs. Improving these points might not be difficult, although guideline-specific conditions might be involved. The involvement of experts specialized in the field of guidelines will be useful. Item 2 requires clear descriptions of clinical questions. When "Clinical Question" is first described for each CPG topic, it may help focus readers to understand the content more easily. This format of clinical question is preferable. Item 6 asks for a clear definition of the target users. It is important to define that clearly when developing and using CPGs. Item 10 addresses an explicit document that describes the methods of formulating recommendations; however, many CPGs did not provide this information. The impact of an assessment of benefits and harms after a systematic review on formulating a recommendation should be addressed. If disagreement about a recommendation arises, the methods used to reach consensus should be described.

Although the EC has reviewed a dozen CPGs, this report has some challenging issues as limitations. First, the inter-rater reproducibility of several items of the AGREE instrument was poor. Previous studies have identified good validity and reproducibility [3, 4], but we found that reproducibility was not easily achieved in our setting. Although AGREE is a good method of evaluation, the scoring remains subjective. We did not directly use the crude scores of individual members to reach the final assessment. Nevertheless, low reproducibility means that judgment by a member using the AGREE items is not a simple matter. Among low-score items, the score of items 5, 7, and 23 might be influenced by a difficult evaluation. Consensus will be achieved if the committee has criteria for scoring that maintain the original concept of the AGREE items.

Second, common scoring methods are not applicable to all CPGs, because solid evidence is not available in some fields of cancer. Although all CPGs of the society are related to cancer, each type of cancer has specific characteristics. AGREE itself does not recommend establishing a threshold to differentiate CPGs of "good" or "bad" quality.

The activity of CPG development is continuous, and CPGs of the subspecialty societies and the published material of the society (http://www.jsco-cpg.jp/) will be revised sequentially. These guidelines have also been published on the homepages of the subspecialty societies and of the Medical Information Network Distribution Service (MINDS), thus bringing the CPGs closer not only to medical professionals but also to patients. The activities of publishing and implementing CPGs within the society over the first decade seem to have begun well. Efforts to improve quality must be maintained, and users, including patients, should be able to easily understand the contents.

Acknowledgments The authors thank Ms. Misao Oda, who manages the affairs of the Evaluation Committee and maintains detailed records. We also acknowledge the assistance of Ms. Kaoruko Nakazawa, who helped with drafting the manuscript. This report was partly funded by the "Study for Development and Revision of Clinical Practice Guidelines for Cancer and Maintenance of Publishing," which is supported by the Ministry of Health, Labour, and Welfare, and by the fund for Scientific Studies for Cancer Clinical Research.

Conflict of interest statement M. Toi received honoraria from GlaxoSmithKline. The other authors have no conflict of interest.

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J Gastroenterol
DOI 10.1007/s00535-010-0234-4

ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Meta-analysis: somatostatin or its long-acting analogue, octreotide, for prophylaxis against post-ERCP pancreatitis

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Received: 18 December 2009 / Accepted: 3 March 2010

Abstract
Background Acute pancreatitis is a most serious complication following endoscopic retrograde cholangiopancreatography (ERCP). Previous meta-analyses and randomized controlled trials have shown conflicting results regarding the preventive efficacy of somatostatin or octreotide for this complication. The aim of this study was to resolve these conflicts.
Methods A standardized comprehensive literature search was performed through September 2009. Depending on heterogeneity of outcomes, either random-effects model (REM) or fixed-effects model (FEM) was applied to calculate pooled estimates of drug efficacy.
Results Seventeen studies, including 3818 participants, met the inclusion criteria. Analysis of somatostatin and octreotide trials showed that these drugs prevented post-ERCP pancreatitis (pooled risk ratio [95% confidence interval; CI], 0.63 [0.42–0.96] in REM. Pooled risk ratios [95% CI] of each subgroup were: 0.52 [0.30–0.90] for somatostatin in REM; 0.30 [0.17–0.53] for high-dose somatostatin infused over 12 h in FEM; 0.27 [0.13–0.52] for bolus somatostatin in FEM; 0.35 [0.15–0.82] for pancreatic duct (PD) injection with somatostatin in FEM; 0.33 [0.16–0.70] for biliary sphincterotomy (BS) with somatostatin in FEM; 0.53 [0.24–1.17] for intention-to-treat (ITT) analysis with somatostatin in REM; 0.42 [0.20–0.90] for high-dose octreotide in FEM; 0.61 [0.27–1.35] for PD injection with octreotide in FEM; 0.64 [0.32–1.29] for BS with octreotide in FEM; and 0.83 [0.34–2.03] for ITT analysis with octreotide in REM.
Conclusions Somatostatin and high-dose octreotide may prevent post-ERCP pancreatitis. The preventive efficacy of somatostatin is more prominent in cases of PD injection, or BS, or high-dose administration over 12 h, or bolus injection.

Keywords Somatostatin · Octreotide · Post-ERCP pancreatitis

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Introduction

Acute pancreatitis is a serious complication that can result from either diagnostic or therapeutic endoscopic retrograde cholangiopancreatography (ERCP). The causal mechanisms of post-ERCP pancreatitis are not clear but are likely to be multifactorial, including patient-related risk factors (young age, female gender, sphincter of Oddi dysfunction, prior post-ERCP pancreatitis) and procedure-related factors [pancreatic duct (PD) injection, pancreatic sphincterotomy,

Published online: 07 April 2010

balloon dilation of the intact biliary sphincter, difficult or failed cannulation, precut sphincterotomy], as well as an interactive effect between the two [1].

Previous studies have evaluated several drugs for the prevention of post-ERCP pancreatitis, including somatostatin [2–10], octreotide [11], gabexate mesylate [12], and corticosteroids [13–16]. Although several of these have shown benefit, there have been no definitive studies showing that any of these drugs prevent post-ERCP pancreatitis. Somatostatin and its long-acting cyclic octapeptide, octreotide, have a wide spectrum of biologic activities. Most of them are inhibitory [17–20]. In addition, both agents have an effect on the contractility of the sphincter of Oddi [11]. Due to these properties, these agents have undergone much study for the prevention of post-ERCP pancreatitis. Despite this, the efficacy of somatostatin and octreotide remains controversial.

A comprehensive literature review revealed several randomized controlled trials (RCTs) investigating the preventive efficacy of somatostatin or octreotide for post-ERCP pancreatitis [3–11, 15, 21–27] employing a variety methods of administration in various populations with different risks of developing post-ERCP pancreatitis. Additionally, procedures during ERCP, such as PD injection and sphincterotomy (biliary or pancreatic) varied from study to study. The results of these different studies were not consistent.

Two previous meta-analyses found no overall preventive efficacy of somatostatin [28, 29]. Another meta-analysis suggested possible efficacy of high-dose (total dosage $\geq$0.5 mg) octreotide [30]. Stratified meta-analyses of procedure-related factors and intention-to-treat (ITT) analyses have not been reported.

Methods

Data sources and searches

We conducted a literature search using MEDLINE (January 1966 to September 2009), EMBASE (January 1974 to September 2009), and the Cochrane Central Register of Controlled Trials (January 1970 to September 2009) to identify all potential clinical trials using somatostatin or octreotide for the prevention of post-ERCP pancreatitis. We performed the literature search using the following search term: [pancreatitis AND (ERCP OR endoscopic retrograde cholangiopancreatography)] AND (somatostatin OR octreotide). Additionally, we searched review articles in the Cochrane Database of Systematic Reviews, and checked the references of these articles to ensure that we identified all relevant RCTs. The bibliographies of all relevant meta-analyses were also reviewed.

Study selection

Using the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement as a conceptual framework for this meta-analysis [31], we included only double-blinded RCTs that analyzed the efficacy of somatostatin or octreotide for the prevention of post-ERCP pancreatitis and had a primary outcome measure of acute pancreatitis following ERCP. To be as comprehensive as possible, we included all reports that met these criteria, even if they did not adequately describe the allocation sequence or concealment of allocation. Studies with hyperamylasemia as the primary outcome measure or those that were not double-blinded were excluded to avoid systematic error such as information bias. Studies involving co-administration of gabexate mesylate were not included. We restricted study eligibility to full reports in English to allow proper scrutiny of the quality of the trial.

Data extraction and quality assessment

For this study, we chose acute pancreatitis following diagnostic or therapeutic ERCP as the primary outcome measure. The definition of acute pancreatitis varied among studies, but in each case was clearly differentiated from hyperamylasemia. We independently reviewed the identified RCTs without the information on the journal, institution, or authors' names, using a standardized data abstraction form. We extracted the number of outcomes in both treatment and control groups. We also evaluated each of the studies based on the following criteria: (1) treatment details including drug, dosage, and duration; (2) details of procedures during ERCP; (3) allocation sequence; (4) concealment of allocation; and (5) ITT analysis. When the extracted data differed among our investigators, discussion was used to reach consensus.

Data synthesis and analysis

Three investigators independently extracted the number of events (pancreatitis) and total number of patients in the treatment and control groups for each study. We identified the number of events in each study arm in a standard contingency table for each study. We calculated the P value for the heterogeneity test (HT) as well as the I^2 statistic, which represents the percentage of total variation across trials that is attributable to heterogeneity rather than chance [32]. We applied a random-effects model (REM) if the I^2 was 25% or more. Otherwise, a fixed-effects model (FEM) was applied. Pooled risk ratios of FEM and REM were calculated using the Mantel–Haenszel method and DerSimonian and Laird method, respectively. Dichotomous effect measures, such as post-ERCP pancreatitis,

were expressed as a risk ratio with 95% confidence intervals (CIs) with risk ratios of less than 1.0 indicating a comparatively reduced risk of post-ERCP pancreatitis for participants in the treatment group.

We also performed stratified meta-analyses by drug type (somatostatin or octreotide), duration of administration (>12 h or not), drug dosage, and other possible risk factors such as PD injection and common therapeutic procedures such as biliary sphincterotomy (BS). Regarding the quality of the RCTs, we performed subgroup analysis only in terms of ITT analysis because sequence and concealment of allocation were not described in many studies.

We assumed that differences in the treatment regimen; differences of risk for developing acute pancreatitis, such as PD injection or BS; and differences in analytic measures, such as ITT analysis, would explain study heterogeneity. Regarding our quality analysis, we classified allocation sequences as 'adequate' for four trials that described the process as based on random number generation (computer or otherwise). We classified allocation concealment as 'adequate' for eight trials with the description of "opaque sealed envelope" or "envelope draw" [33].

We performed Egger's test to investigate funnel-plot asymmetry for small study effects including publication bias [34]. All analyses were performed using Stata Statistical Software: Release 10.0 (Stata, College Station, TX, USA).

Results

We identified 127 articles in MEDLINE, 332 in EMBASE, and 48 in the Cochrane Central Register of Controlled Trials, for a total of 507 abstracts; 399 articles remained after 108 duplicates were removed. Two investigators started with 399 articles and independently chose only papers which satisfied the prespecified inclusion criteria. Thirty-one abstracts passed the initial screening. We subsequently synthesized data from a final 17 double blinded RCTs [3–11, 15, 21–27] following the PRISMA flow diagram (Fig. 1; Table 1).

When all extracted data were pooled, 3818 subjects were considered for our analysis. 280 patients out of the 3818 were diagnosed with post-ERCP pancreatitis. In 16 of the 17 studies, acute pancreatitis was defined by clinical features including abdominal pain, nausea, or vomiting associated with elevated serum amylase more than 3 times the upper limit of normal. In one study [5], it was unclear whether nine patients diagnosed with pancreatitis had elevated serum amylase in addition to clinical symptoms. Ten of the 17 reports involved somatostatin [3–10, 21, 22] and 7 of the 17 used octreotide [11, 15, 23–27] (Table 2).

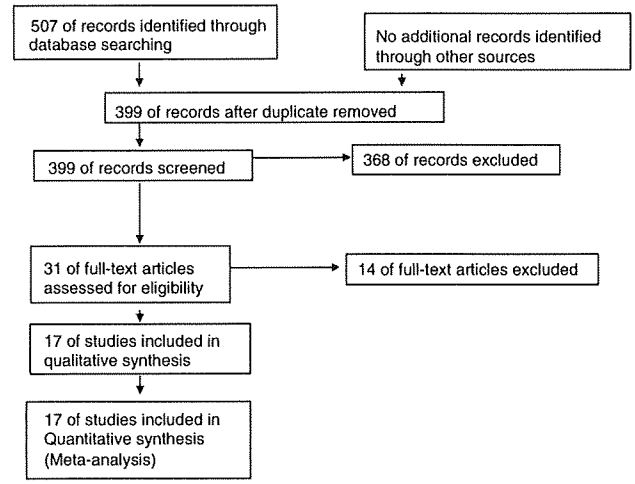


Fig. 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (*PRISMA*) flow diagram. Starting with 507 records identified in the database, 17 studies were finally selected for meta-analysis

In the study by Arvanitidis et al. [9], participants were randomized into three arms (somatostatin 3000 μg/12 h, bolus somatostatin 4 μg/kg, or placebo). We used the sample size numbers of the two respective intervention arms for subgroup analysis in terms of the dose of somatostatin and the duration of administration.

Any discrepancy in the identified literature was resolved by discussion. Discrepancies in the identified literature included the following: we excluded a paper by Bordas et al. [2] published in 1988 because all subjects in this study were included in the literature by the same author [6] published in 1998. Similarly, two reports by Duvnjak et al. [25, 35] were regarded as being based on one RCT, as both the recruitment period and the participants' basic characteristics were identical. We extracted the data from the first report and disregarded the second paper, as the primary outcome of only the former was acute pancreatitis. We excluded one paper [36] because no pancreatitis developed in either study arm, and another [37] because the measured outcome was not objectively pancreatitis.

The risk ratios of post-ERCP pancreatitis among all 17 studies ranged from 0.17 to 3.08. The overall risk ratio [95% CI] calculated using REM (HT $P < 0.001$, $I^2 = 62\%$) was 0.63 [0.42–0.96] (Fig. 2). Because the 95% CI did not include 1.0, the pooled risk ratio of all studies together with either somatostatin or octreotide was found to be statistically significant.

In the subgroup of subjects in whom somatostatin was administered, the risk ratio ranged from 0.17 to 1.76. The pooled risk ratio [95% CI] using REM (HT $P = 0.001$, $I^2 = 67\%$) was 0.52 [0.30-0.90] (Fig. 3). Somatostatin significantly reduced the risk of post-ERCP pancreatitis. Pooled risk ratios [95% CI] in terms of diagnostic and therapeutic procedures with somatostatin use were as

Table 1 Baseline characteristics of patients and somatostatin or octreotide regimen in double-blind randomized controlled trials

Publication year	References	Patients (*n*)	Mean age years (SD)		Treatment regimen	Starting time of therapy	Duration of therapy	Total dose (μg)	Rate of PD injection (%)	Rate of BS (%)
			Treatment group	Control group						
Trials of somatostatin in the order of publication year										
1988	Saari et al. [3]	47	48	50	250 μg i.v. followed by 250 μg/h) vs. NS	During procedure	3 h	1000	100	0
1991	Guelrud et al. [4]	16	NR	NR	250 μg/h i.v. vs. NS	1 h prior to dilation	12 h	3000	100	100
1992	Persson et al. [5]	54	62 (14)	61 (16)	300 μg/h i.v. for 3 h reduced to 140 μg/h for 1 h	30 min before ERCP	4 h	1040	61	NR
1998	Bordas et al. [6]	160	61 (15)	58 (18)	4 μg/kg i.v. vs. NS	On identification of papilla	Single bolus	240	100	34
1999	Poon et al. [8]	220	63 (15)	63 (16)	250 μg/h i.v. vs. NS	30 min before ERCP	12 h	3000	43	51
2002	Andriulli et al. [7]	382	59 (18)	58 (17)	300 μg/h i.v. vs. NS	30 min before ERCP	2.5 h	750	88	NR
2003	Poon et al. [21]	270	69	67	250 μg i.v. vs. NS	Immediately after diagnostic ERCP but before therapeutic ERCP	Single bolus	250	29	100
2004	Andriulli et al. [10]	746	66 (15)	66 (16)	750 μg/6.5 h i.v. vs. NS	30 min before ERCP	6.5 h	750	NR	NR
2004	Arvanitidis et al. [9]	356	65 (13), 63 (13)	61 (12)	4 μg/kg i.v. or 3000 μg/12 h i.v. vs. NS	1 h before ERCP	Single bolus or 12 h	240 vs 3000	40	89
2008	Lee et al. [22]	391	63 (14)	62 (14)	250 μg/h i.v. vs NS	30 min before ERCP	12 h	3000	40	54
Trials of octreotide in the order of publication year										
1992	Sternlieb et al. [23]	84	59	59	100 μg i.v. followed by 100 μg s.c. vs. NS	At the beginning of ERCP and 45 min later	Bolus and s.c.	200	NR	56
1992	Binmoeller et al. [11]	245	58	61	100 μg i.v. followed by 100 μg s.c. vs. NS	5 min before and immediately after ERCP	Bolus and s.c.	200	81	16
1994	Arcidiacono et al. [24]	151	61	63	100 μg s.c. X3 vs. NS	120 min, 30 min before and 4 h after ERCP	3 times	300	100	100
1999	Duvnjak et al. [25]	209	56	54	500 μg s.c. vs. NS	1 h before ERCP	Single s.c.	500	100	100
2000	Hardt et al. [26]	59	60	58	200 μg s.c. X5	10 p.m. (day −1), 6 a.m., 2 p.m., 10 p.m. (day 0), 6 a.m. (day 1)	5 times s.c.	1000	NR	100
2002	Manolakopoulos et al. [15]	227	62	64	100 μg s.c. vs. NS	30 min before ERCP	Single s.c.	100	71	35
2006	Thomopoulos et al. [27]	201	70 (14)	70 (15)	500 μg s.c. X6 vs. NS	8 a.m., 4 p.m., 12 p.m. (day −1), 8 a.m., 4 p.m. (day 0)	5 times s.c.	3000	59	81

SD Standard deviation, *PD* pancreatic duct, *S* somatostatin, *NR* not reported, *i.v.* intravenously, *s.c.* subcutaneously, *NS* normal saline, *BS* biliary sphincterotomy, *ERCP* endoscopic retrograde cholangiopancreatography

Table 2 Methodological quality characteristics of included articles

Publication year	References	Allocation sequence[a]	Concealment of allocation[b]	Intention-to-treat[c]	% (patients analyzed/randomization)
Trials of somatostatin in the order of publication year					
1988	Saari et al. [3]	NR	NR	No	84 (47/56)
1991	Guelrud et al. [4]	Adequate	NR	Yes	100
1992	Persson et al. [5]	NR	NR	No	90 (54/60)
1998	Bordas et al. [6]	NR	Adequate	No	83 (160/192)
1999	Poon et al. [8]	Adequate	Adequate	Yes	96 (220/230)
2002	Andriulli et al. [7]	Adequate	NR	Yes	91 (382/420)
2003	Poon et al. [21]	Adequate	Adequate	Yes	100
2004	Andriulli et al. [10]	Adequate	NR	Yes	100
2004	Arvanitidis et al. [9]	NR	Adequate	Yes	96 (356/372)
2008	Lee et al. [22]	NR	Adequate	No	98 (391/400)
Trials of octreotide in the order of publication year					
1992	Sternlieb et al. [23]	NR	NR	Yes	100
1992	Binmoeller et al. [11]	NR	NR	Yes	100
1994	Arcidiacono et al. [24]	NR	Adequate	No	66 (151/229)
1999	Duvnjak et al. [25]	NR	NR	Yes	100
2000	Hardt et al. [26]	NR	NR	No	63 (59/94)
2002	Manolakopoulos et al. [15]	NR	Adequate	Yes	NR
2006	Thomopoulos et al. [27]	NR	Adequate	Yes	99 (201/202)

NR Not reported

[a] Description of allocation sequence was considered adequate if the study used computer-generated random number or number system by chance

[b] Concealment of allocation was considered adequate if the study used opaque sealed envelopes or envelope draw

[c] The analysis including all participants who underwent ERCP was considered as intention-to-treat analysis even if there were some dropout cases caused by failure of duodenal intubation, or drug allergy, or inability to undergo ERCP

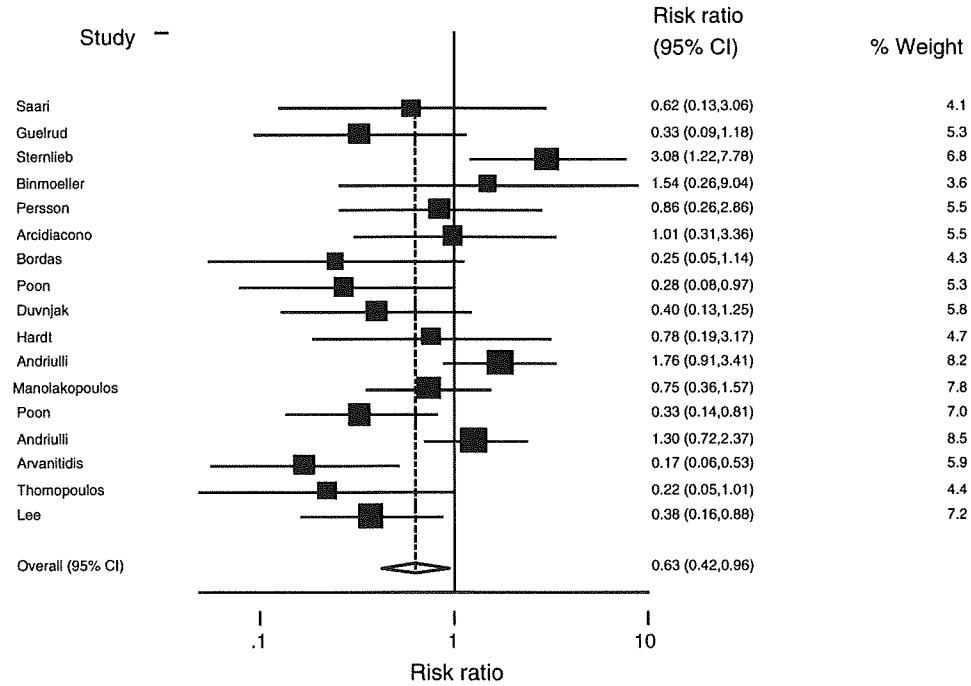
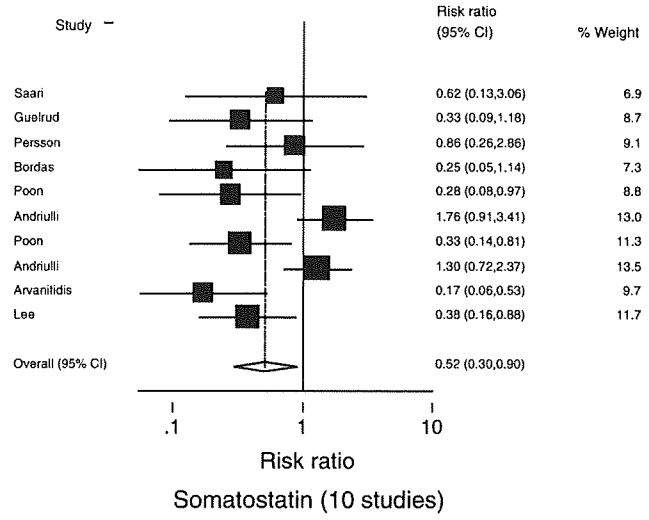


Fig. 2 Forest plot (somatostatin and octreotide). The pooled risk ratio of 17 studies was calculated by random-effects model. The pooled risk ratio including both somatostatin and octreotide was significant. Egger's test ($P = 0.023$) suggested small study effects including publication bias. *CI* Confidence interval



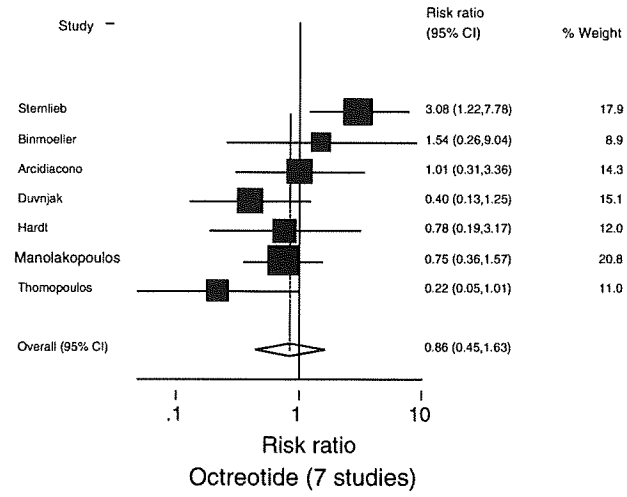
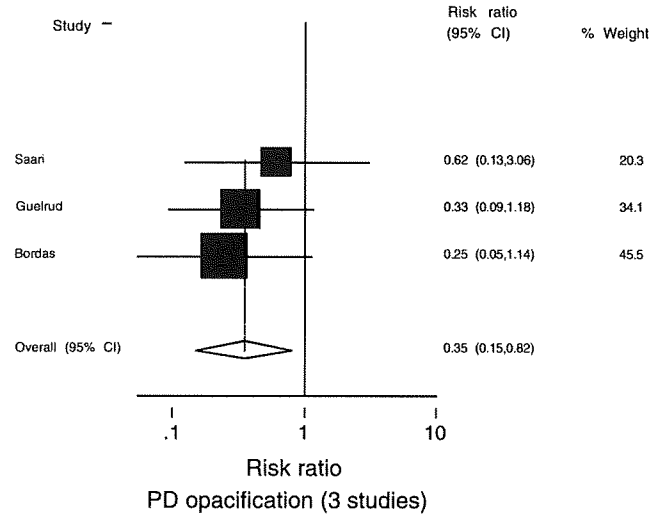


Fig. 3 Forest plot of subgroups by drug; ten studies of somatostatin and seven studies of octreotide. The pooled risk ratio of somatostatin was significant by random-effects model. In contrast, the pooled risk ratio of octreotide was not significant by random-effects model. Egger's test ($P = 0.01$) suggested small study effects including publication bias in the meta-analysis of somatostatin, while Egger's test ($P = 0.86$) was not significant in the meta-analysis of octreotide



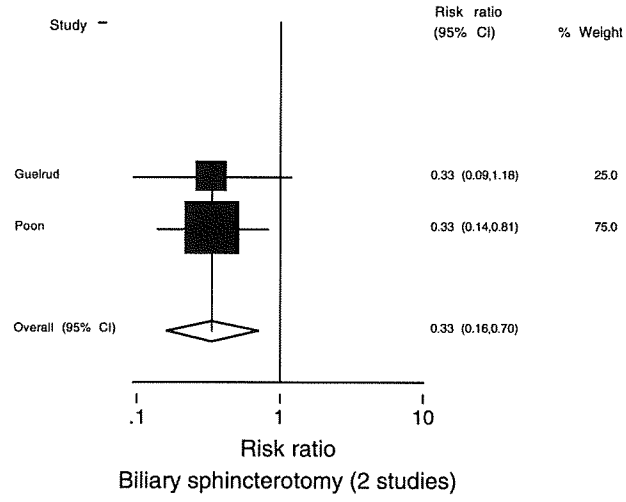


Fig. 4 Forest plot of subgroups by procedure with somatostatin use. The pooled risk ratios of three studies for pancreatic duct (*PD*) injection and two studies for biliary sphincterotomy were significant by fixed-effects model. Egger's test ($P = 0.76$) of the former meta-analysis was not significant

follows: 0.35 [0.15–0.82] for PD injection using FEM (HT $P = 0.711$, $I^2 = 0\%$) and 0.33 [0.16–0.70] for BS using FEM (HT $P = 1$, $I^2 = 0\%$) (Fig. 4). The preventive efficacy of somatostatin was prominent in some particular cases: using FEM, the pooled risk ratios [95% CI] were 0.30 [0.17–0.53] for high-dose somatostatin (3 mg administered over 12 h) (HT $P = 0.84$, $I^2 = 0\%$), and 0.27 [0.13–0.52] for bolus injection (HT $P = 0.75$, $I^2 = 0\%$) (Fig. 5).

The pooled risk ratio [95% CI] of six ITT studies with somatostatin use was 0.53 [0.24–1.17] using REM (HT $P < 0.001$, $I^2 = 78\%$) (Fig. 8). The pooled risk ratios [95% CI] of additional subgroup analysis restricted by ITT-based studies were 0.25 [0.11–0.54] for high-dose somatostatin using FEM (HT $P = 0.796$, $I^2 = 0\%$) and 0.27 [0.13–0.58] for bolus somatostatin using FEM (HT $P = 0.45$, $I^2 = 0\%$). The pooled risk ratio [95% CI] for ITT BS studies was exactly the same as that with somatostatin BS studies, 0.33 [0.16–0.70], because there were no non-ITT BS studies. The result of one ITT study [4] for PD injection was not significant.

In the subgroup of patients receiving octreotide, the risk ratio ranged from 0.22 to 3.08. The pooled risk ratio [95% CI] was 0.86 [0.45–1.63] using REM (HT $P = 0.049$,

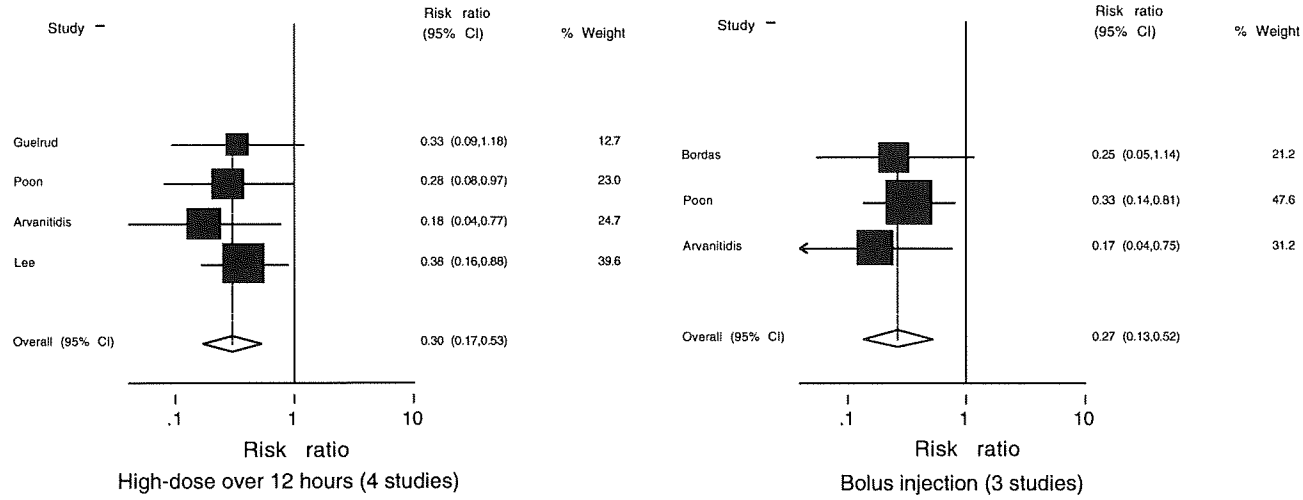


Fig. 5 Forest plot of subgroups by somatostatin use. The pooled risk ratios of high-dose somatostatin given over 12 h and by bolus injection were statistically significant by fixed-effects model. Egger's tests ($P = 0.13$ for high-dose somatostatin, $P = 0.28$ for bolus) were not significant

$I^2 = 53\%$) (Fig. 3). However, high-dose octreotide appeared to be effective, with a pooled risk ratio [95% CI] of 0.42 [0.2–0.9] using FEM (HT $P = 0.49$, $I^2 = 0\%$) (Fig. 6). Pooled risk ratios [95% CI] in terms of diagnostic and therapeutic procedures using octreotide were 0.61 [0.27–1.35] for PD injection using FEM (HT $P = 0.27$, $I^2 = 17\%$) and 0.64 [0.32–1.29] for BS using FEM (HT $P = 0.53$, $I^2 = 0$) (Fig. 7).

The pooled risk ratio [95% CI] of five octreotide studies with ITT analysis was 0.83 [0.34–2.03] using REM (HT $P = 0.013$, $I^2 = 68\%$) (Fig. 8). However, additional subgroup analysis of two studies [25, 27] using high-dose octreotide on an ITT basis was 0.32 [0.13–0.78] using FEM (HT $P = 0.54$, $I^2 = 0\%$).

Egger's test was significant in some meta-analyses: $P = 0.023$ for 17 studies of somatostatin or octreotide, $P = 0.01$ for ten studies of somatostatin, and $P = 0.024$ for six studies of somatostatin on an ITT basis. Adverse events related to somatostatin or octreotide were reported in one study [27], in which one patient in the octreotide group developed an allergic reaction and was excluded from the analysis.

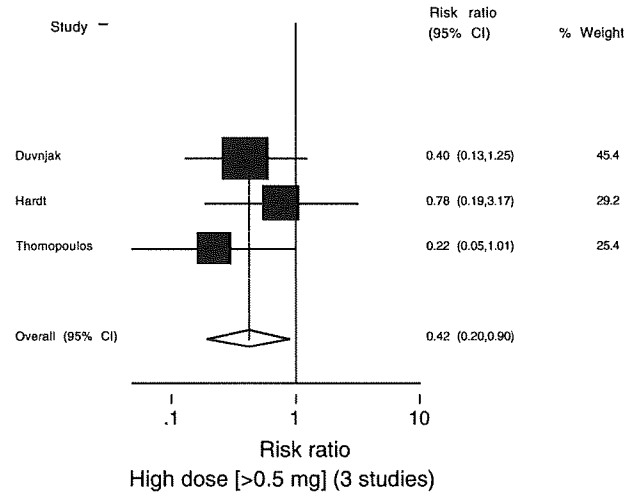


Fig. 6 Forest plot of subgroups by high-dose octreotide use. High-dose octreotide showed preventive efficacy for post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis by a fixed-effects model. Egger's test ($P = 0.97$) was not significant

Discussion

Our study is the most updated and comprehensive meta-analysis of RCTs involving post-ERCP pancreatitis described in the English-language literature. Our study suggests that somatostatin is effective and its preventive efficacy becomes even more prominent when it is either administered in high doses infused over 12 h, bolused, or used in patients undergoing PD injection or BS. Our study also showed that high-dose octreotide (more than 0.5 mg) may be effective for preventing post-ERCP pancreatitis.

In 2000, Andriulli et al. [38] conducted a meta-analysis reviewing the preventive efficacy of somatostatin, octreotide, and gabexate mesylate on post-ERCP pancreatitis. That analysis concluded that pancreatic injury after ERCP could be prevented with the administration of either somatostatin or gabexate mesylate, with an odds ratio of 0.38 (95% CI [0.14–0.42]) and 0.27 (95% CI [0.13–0.57]), respectively. In contrast, the odds ratio for octreotide was 1.43 (95% CI [0.87–2.49]). In comparing Andriulli's meta-analysis with ours, they included five studies on somatostatin [2, 39–42], which we ultimately excluded. We

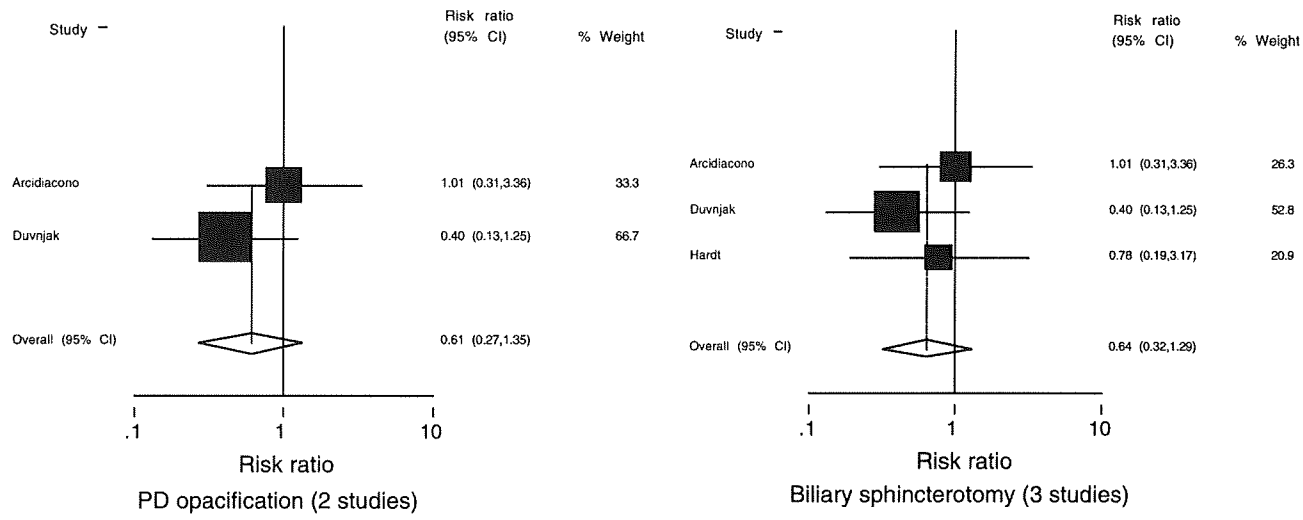


Fig. 7 Forest plot of subgroups by procedure with octreotide use. Subgroup analysis by procedure did not show preventive effectiveness of octreotide by fixed-effects model. Egger's test ($P = 0.65$) for PD injection was not significant

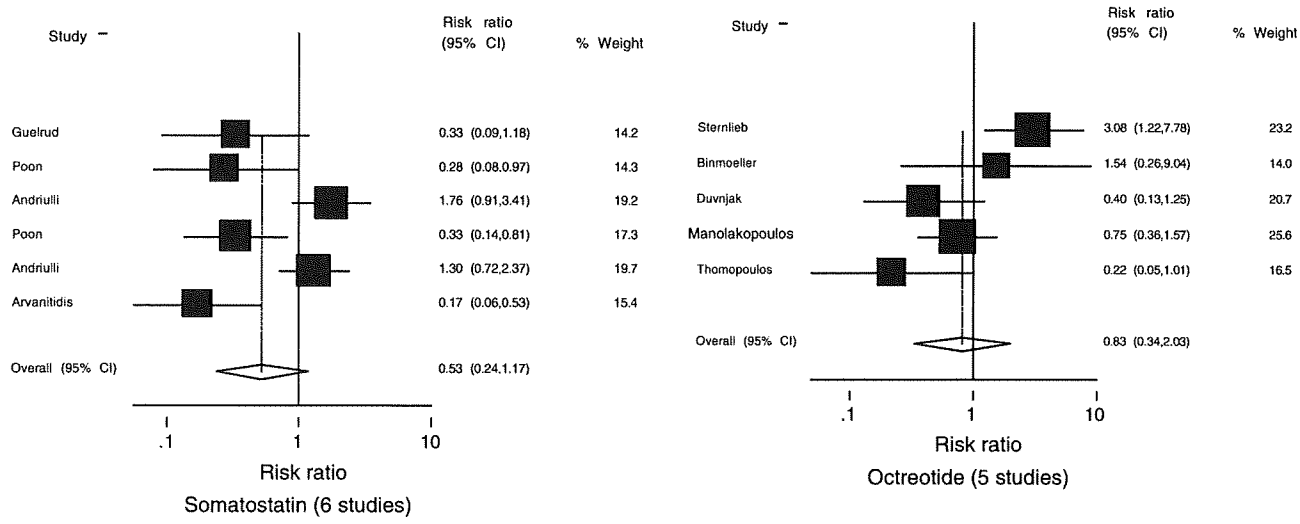


Fig. 8 Subgroup analysis of intention-to-treat studies by drugs. The pooled risk ratios of somatostatin and octreotide became less significant if restricted by intention-to-treat-based studies, using random-effects model. Egger's test ($P = 0.024$) was significant for somatostatin, while it was not significant ($P = 0.90$) for octreotide

excluded two [39, 41] because they were non-English language, one [40] for no description of double-blindedness, and one [2] which included subjects duplicated in another study. In addition, we included five studies [7, 9, 10, 21, 22] published after 2000, which were not available to them. Regarding studies of octreotide, Andriulli et al. [38] included five trials [43–47] that we excluded. We excluded two [43, 45] for non-English language and three [44, 46, 47] for no information on double-blindedness. We included an additional four studies [15, 25–27] published after 1999.

Andriulli et al. [28] updated their meta-analysis in 2007 to include nine high-quality trials on somatostatin and reported that there was no significant preventive effectiveness of somatostatin for post-ERCP pancreatitis. Significant efficacy was obtained only in the subgroup of patients who received somatostatin as a bolus injection. Their meta-analysis included the abstract by Benvenuti et al. [48], which we excluded because it was not a full article, precluding thorough evaluation. They excluded one report for an unknown reason [4] that we included in our meta-analysis. These differences in inclusion and exclusion of studies, in addition to one recently published RCT [22], resulted in a significantly different pooled risk ratio for somatostatin between our respective studies.

In 2007, Rudin et al. [29] also performed a meta-analysis of five somatostatin studies, stratifying somatostatin administration into three groups: an infusion for 12 h or

more, an infusion for less than 12 h, and bolus infusion. They reported significant efficacy of somatostatin with an infusion for 12 h or more as well as for bolus infusion, with risk differences [95% CI] of 7.7% [3.4–12] and 8.2% [4.4–12], respectively [29]. They did not include three studies [3–5] that we included. Additionally, they double-counted the control group of one study [9] when calculating the overall risk ratio of somatostatin. Despite these differences, our results also suggested significant efficacy of bolus infusion of somatostatin and high-dose somatostatin, defined as more than 3000 μg infused over 12 h.

In 2009, Zhang et al. [30] conducted a meta-analysis including six studies [25, 27, 46, 49–51] about the preventive efficacy of octreotide for post-ERCP pancreatitis and suggested possible significant efficacy of high-dose octreotide over 0.5 mg. Their meta-analysis included three non-double-blinded RCTs [46, 50, 51] and one abstract [49], all of which we excluded from our meta-analysis. They excluded one study [26] in which 1000 μg of octreotide was given in five divided doses. Our stratified meta-analysis, involving three double-blinded RCTs, also showed significant efficacy of high-dose octreotide.

By using ITT analysis, results of RCTs can be analyzed more conservatively, thereby avoiding bias induced by loss to follow-up. Eleven RCTs were identified that used ITT analysis, six studies [4, 8–10, 21, 22] involving somatostatin and five [11, 15, 23, 25, 27] using octreotide. Although the pooled estimate of the somatostatin studies became less significant if restricted to ITT analysis, the pooled estimates of high-dose somatostatin, bolus somatostatin, and somatostatin for BS, as well as the pooled estimates for high-dose octreotide, suggested significant preventive efficacy of both drugs.

Sofuni et al. [52] reported the effectiveness of pancreatic stent (polyethylene 5F diameter, 3-cm long, unflanged on the pancreatic ductal side, with 2 flanges on the duodenal side) placement for the prevention of post-ERCP pancreatitis. They showed a significant reduction of post-ERCP pancreatitis with the administration of gabexate mesylate (100 mg dissolved in 500 ml solution for 12 h) in both stent and control groups. We may also speculate on the additive preventive effectiveness of combining a pancreatic stent and drugs such as somatostatin or octreotide.

Our study has some limitations. First, we disregarded non-English-language literature, though these studies were few. This might be one of the reasons for publication bias in some meta-analyses, as suggested by Egger's test. We also included studies that did not describe the allocation sequence or concealment of allocation. Finally, in the subgroup analyses, the pooled estimates may have become significant by chance, and further studies with these subgroups are warranted [53].

In conclusion, somatostatin may have significant preventive efficacy against post-ERCP pancreatitis, especially when used in appropriate diagnostic or therapeutic procedures or with high-dose administration as a 12-h infusion or a bolus. High-dose octreotide may also prevent post-ERCP pancreatitis. The efficacy of both drugs in these contexts is expected to be confirmed by large high-quality RCTs in future.

Acknowledgments The authors thank Jose M. Bordas, MD, for his comments on his two reports and Yoshinori Noguchi, MD, for his comments. The authors also thank Kayo Ichikawa for secretarial assistance, and Fujiko Kawai and Harumi Oikawa for excellent library support.

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