

# Prophylactic Effect of Somatostatin in Preventing Post-ERCP Pancreatitis: An Updated Meta-Analysis

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## ABSTRACT

**Background/Aims:** Somatostatin is regarded as a prophylactic agent on post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP), but studies are still controversial. **Materials and Methods:** Electronic databases, including PubMed, EMBASE, the Cochrane library, and the Science Citation Index, were searched to retrieve relevant trials. In addition, meeting abstracts and the reference lists of retrieved articles were reviewed for further relevant studies. **Results:** Eleven randomized controlled trials (RCTs), enrolling a total of 2869 patients, were included in the meta-analysis. After data were pooled from somatostatin trials, PEP occurred in 8.36% of controls versus 5.62% of the treated group, with a slight significance [relative risk (RR) = 0.58, 95% confidence interval (CI) 0.35–0.98,  $P = 0.04$ ]. The funnel plot showed no asymmetry with a negative slope ( $P = 0.108$ ). The meta-analysis produced negative results for short-term infusion of somatostatin (RR = 1.40, 95% CI 0.93–2.12,  $P = 0.11$ ), whereas a bolus or long-term injection of the drug proved effective (RR = 0.25, 95% CI 0.13–0.47,  $P < 0.0001$ ; RR = 0.44, 95% CI 0.27–0.71,  $P = 0.0008$ ). Postprocedure hyperamylasemia and pain was also observed in the meta-analysis, the pooled RR was significant for reduced risk of postprocedure hyperamylasemia (RR = 0.72, 95% CI 0.63 to 0.81,  $P < 0.00001$ ), but not for the pain (RR = 0.67, 95% CI 0.42 to 1.08,  $P = 0.10$ ). **Conclusion:** The current meta-analysis on the prophylactic use of somatostatin in patients undergoing ERCP documents a lack of benefit when given as short-term infusion, but showed an advantage of a single bolus or long-term injection. The beneficial effect of somatostatin, in reducing the incidence of postprocedural hyperamylasemia seems of marginal clinical significance. However, more new confirmatory data are needed to settle residual doubts.

**Key Words:** Endoscopic retrograde cholangiopancreatography, pancreatitis, somatostatin

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Acute pancreatitis is a common complication of endoscopic retrograde cholangiopancreatography (ERCP), either diagnostic or therapeutic, with an incidence rate between 1% and 40% in published studies.<sup>[1-5]</sup> Over the past few years, several attempts had been made to learn how to lower associated risks and to render the procedure safer. Somatostatin (SS), octreotide, and gabexate are the three most widely investigated agents. However, controversies existed in previous studies about these drugs, especially in the prophylactic effects of somatostatin.

Somatostatin can be administrated as a continuous infusion or bolus intravenous injection before ERCP. A previous study demonstrated that somatostatin can reduce the incidence of post-ERCP by infusion started 30 min before and continued for 12 h after the procedure.<sup>[6]</sup> A meta-analysis of randomized controlled trials (RCTs) in 2007 indicated that short- (<6 h) or long-term (>12 h) infusion of somatostatin and gabexate proved ineffective in reducing post-ERCP and pain, whereas a bolus injection was effective. The study also found that somatostatin was more cost effective than gabexate from a pharmacoeconomic point of view.<sup>[7]</sup> Until now, the opinions on clinical benefits are still inconsistent. Somatostatin has not been routinely adopted in most endoscopic centers nor recommended by guidelines for prevention of post-ERCP pancreatitis (PEP). However, considering the cost-benefit ratio, somatostatin should be used only in patients with a high risk of PEP.

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The objective of the current study was to reassess the prophylactic effects of SS on postprocedural pancreatitis with a meta-analytic approach. Moreover, for positive results, sensitivity analyses were planned that would subgroup trials according to the schedule of drug administration to test the hypothesis that long infusion time would provide higher benefits than a shorter one or a bolus injection.

## MATERIALS AND METHODS

### Literature search

A search was conducted for clinical trials on the administration of SS in the prevention of PEP. First, electronic databases, including PubMed (1966 to July 2014), EMBASE (1974 to 2014), the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4 of July 4, 2014), and the Science Citation Index were searched. The search strategy was performed with the following search terms as both free-text terms and MeSH terms: somatostatin, pancreatitis, ERCP, and endoscopic retrograde cholangiopancreatography. Secondly, meeting abstracts and the reference lists of retrieved articles were reviewed for additional relevant studies. No language restriction was imposed.

### Study selection

RCTs comparing SS with placebo in prevention of PEP were included for analysis. Only the most recent study was included if more than one study was published using the same study population. Open, uncontrolled, observational studies and case reports were excluded from the meta-analysis.

### Data abstraction

All the data were tabulated with standard data abstraction sheets. For each study and each type of intervention, the following characteristics were extracted: Sample size; patients' characteristics; dose; timing; regimen of drug administration (bolus, short- or long-term continuous infusion); and the incidence of PEP, hyperamylasemia, and abdominal pain.

Two investigators (Xie Q, Feng S) independently extracted details of the study population, interventions, and outcomes. The paper was reviewed if either one of the two investigators thought an abstract was relevant. If there were any discrepancies about information given in the title and abstract, the full article was reviewed for clarification. Differences in opinion were resolved by discussing with the third author (Wen SL).

### Assessment of risk of bias in included studies

For the risk of bias assessment, two investigators independently used an assessment form recommended by the Cochrane Handbook. Any disagreements were resolved by a third

author until consensus was obtained. We considered the following criteria:

- Sequence generation: Was the allocation sequence adequately generated?
- Allocation concealment: Was the allocation adequately concealed?
- Blinding: Was knowledge of the allocated intervention adequately prevented during the study?
- Incomplete outcome data: Were incomplete outcome data adequately addressed?
- Selective outcome reporting: Were reports of the study free of suggestion of selective outcome reporting?
- Other sources of bias: Was the study apparently free of other problems that could put it at a high risk of bias?

Each domain was graded as yes (low risk of bias), no (high risk of bias), or unclear (uncertain risk of bias) according to the criteria.

For ranking the strength and quality of the evidence for a given comparison, the GRADE and Summary of Findings tables recommended by the Cochrane Collaboration were used.

### Assessment of reporting biases

For the assessment of publication bias, a funnel plot was conducted if sufficient data were available.

### Statistics

Meta-analyses were conducted for trials comparing SS with placebo, using the statistical tool Revman 5.2. Dichotomous data were expressed as relative risk (RR) or odds ratio (OR) and continuous outcomes as the weighted mean difference (WMD) with 95% confidence interval (CI). A fixed effects model was used for pooling of data when statistical heterogeneity was not present. If heterogeneity existed, a random effects model was performed.

Heterogeneity was quantified with Cochran's  $Q$  test and the  $I^2$  metric, and 95% CI for  $I^2$  were calculated.  $I^2$  was in a scale of 0–100%. If there was “considerable heterogeneity,” which is defined by the “Cochrane Hand-book for Systematic Reviews of Interventions” as an  $I^2$  value between 75% and 100%, the data were not pooled. When  $I^2 > 50\%$ , suggesting very large heterogeneity between studies, the random effects model was used and a sensitivity analysis was planned to evaluate heterogeneity among studies.

## RESULTS

### Evaluation of heterogeneity

When all the 11 clinical trials<sup>[6,8-17]</sup> on SS were evaluated, a significant heterogeneity was present among the individual

studies for the incidence of PEP, but not for the other two outcomes (postprocedural hyperamylasemia and pain [Table 1]. Heterogeneity appeared to be eliminated when subgroups according to the regimen of drug administration were considered.

The quality of the evidence for the outcomes for the included studies is shown in Table 2.

**Acute pancreatitis**

After data from the 11 homogeneous trials were pooled, PEP was documented in 115 of 1375 controls (8.36%) versus 84 of 1494 (5.62%) patients treated with SS. Seven of the 11 reports did not produce statistically significant results, and their pooled RR was slightly significant (RR = 0.58, 95% CI 0.35–0.98, P = 0.04) [Figure 1]. The funnel plot showed no asymmetry with a negative slope (a coefficient = 1.025, 95% CI 0.85–2.87, P = 0.108), suggesting no potential for publication bias or small study effects.

By subgrouping studies according to the schedule of SS administration, three trials that used a short-term infusion were found to be homogeneous (P = 0.11), whereas for the five and five trials on bolus injection or a long-term infusion, heterogeneity was detected (P < 0.0001 and P < 0.0008, respectively). In control subjects and patients, respective pancreatitis rates were 10.42% and 2.83% after a bolus

injection, 5.95% and 8.39% for short-term infusion, and 9.60% and 4.77% after a >12 h infusion. The meta-analysis produced negative results for short-term infusion of SS (RR = 1.40, 95% CI 0.93–2.12, P = 0.11) [Figure 2], whereas a bolus or long-term injection of the drug proved effective (RR = 0.25, 95% CI 0.13–0.47, P < 0.0001; RR = 0.44, 95% CI 0.27–0.71, P = 0.0008) [Figures 3 and 4].

**Hyperamylasemia and pain**

Eleven studies and five high-quality trials provided data on the other outcome, postprocedure hyperamylasemia was observed in 378 of 1375 control subjects (27.49%) versus 315 of 1494 SS-treated patients (21.08%) and post-ERCP pain in 104 of 857 control subjects (12.14%) versus 72 of 794 (9.07%) cases. The pooled RR was significant for reduced risk of postprocedure hyperamylasemia (RR = 0.72, 95% CI 0.63–0.81, P < 0.00001) [Figure 5], but not for the pain (RR = 0.67, 95% CI 0.42–1.08, P = 0.10). The funnel plot showed no asymmetry (P = 0.274).

**DISCUSSION**

Despite the technical improvements in recent years and the increased expertise of operations, the incidence of pancreatitis after ERCP has not decreased.<sup>[5]</sup> The search for ideal pharmacological agents for prevention of PEP is important. Somatostatin is a potent inhibitor of exocrine

**Table 1: The characteristics of included trials comparing somatostatin with placebo during ERCP**

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (grade)	Comments
	Assumed risk	Corresponding risk				
	Placebo	SS				
A.P.	Study population 84 per 1000 Moderate	49 per 1000 (29-82)	RR 0.58 (0.35-0.98)	2869 (11 studies)	⊕⊕⊕⊖ moderate	
A.P.(BOLUS)	Study population 104 per 1000 Moderate	29 per 1000 (16-54)	RR 0.28 (0.15-0.52)	792 (5 studies)	⊕⊕⊕⊕ high	
A.P.(short)	Study population 59 per 1000 Moderate	83 per 1000 (55-126)	RR 1.40 (0.93-2.12)	1182 (3 studies)	⊕⊕⊕⊖ moderate	
A.P.(long)	Study population 96 per 1000 Moderate	42 per 1000 (26-68)	RR 0.44 (0.27-0.71)	1066 (5 studies)	⊕⊕⊕⊖ moderate	
Hyperamylasemia	Study population 275 per 1000 Moderate	198 per 1000 (173-223)	RR 0.72 (0.63-0.81)	2869 (11 studies)	⊕⊕⊕⊖ moderate	
Pain	Study population 121 per 1000 Moderate	81 per 1000 (51-131)	RR 0.67 (0.42-1.08)	1651 (5 studies)	⊕⊕⊕⊖ moderate	

\*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio. GRADE Working Group grades of evidence: High quality = further research is very unlikely to change our confidence in the estimate of effect; moderate quality = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality = we are very uncertain about the estimate

Table 2: Summary of findings for the main comparison

Author	Year	Country	Publication		Placebo group				SS group						
			Type	Total patients	Study design	No. of patients	A.P. Hyperamylasemia	Pain	Doseage (µg)	Duration (h)	No. of patients	A.P. Hyperamylasemia	Pain		
Bordas JM	1988	Spain	F	33	R	17	2	16	11	4 mg/kg	Bolus	16	0	8	2
Persson B	1992	Sweden	F	54	R	28	5	14	NR	1040	4 h	26	4	9	NR
Bordas JM	1998	Spain	F	160	R	80	8	43	NR	4 µg/kg	Bolus	80	2	40	NR
Poon RT	1999	Hongkong	F	220	R	111	11	55	18	3000	12 h	109	3	42	8
Andriulli A	2002	Italy	F	382	R	199	13	29	27	750	2.5 h	183	21	28	28
Poon RT	2003	Hongkong	F	270	R	135	18	52	27	250	Bolus	135	6	35	16
Andriulli A	2004	Italy	F	746	R	395	19	53	21	750	6.5 h	351	22	32	18
Anvanitidis	2004	Greece	F	356	R	122	12	52	NR	240 vs 3000	Bolus or 12 h	234	2	90	NR
Lee KT	2008	Korea	F	391	R	198	19	25	NR	3000	12 h	193	7	15	NR
Chan HH	2008	Taiwan	F	133	R	49	2	20	NR	250 vs 3250	Bolus or 12 h	84	3	26	NR
Wang ZK	2013	China	F	124	R	41	6	19	NR	12000	24 h	83	11	17	NR

pancreatic secretion. In the last few years, several properly designed, well-executed, prospective randomized trials of SS have appeared with contradictory results, so opinions on their clinical benefit are still inconsistent. We conducted the most updated and comprehensive meta-analysis of RCTs involving PEP described in the English literature.

This meta-analysis included 11 RCTs published up to July 2014, including a total of 2869 participants who received SS or placebo during ERCP. Somatostatin showed decreased frequency of PEP as well as lowered risk of postprocedure hyperamylasemia, without affecting the incidence of pain. In the comparison of somatostatin and placebo, seven of 11 individual studies had not shown advantages in terms of the PEP incidence, but the pooled data slightly favored the treated group. A large number of participants reduced the sampling error, which influenced the significance of the difference of PEP rates and the result is meaningful in clinical practice since. Outcomes were also analyzed in three subgroups based on the administration of SS (bolus, short- or long- time infusion) to evaluate its preventive efficacy. By contrast, only bolus or long-time infusion can decline the occurrence of PEP; however, short-time infusion showed no difference between the two groups.

In 2000, Andriulli *et al.*<sup>[18]</sup> conducted a meta-analysis reviewing the prophylactic effects of somatostatin, octreotide, and gabexate mesylate on PEP and showed the preventive efficacy of SS or gabexate mesylate (OR 0.38, 95% CI 0.14–0.42 and OR 0.27, 95% CI 0.13–0.57, respectively). Seven years later, Andriulli *et al.*<sup>[7]</sup> updated their meta-analysis by including nine high-quality trials on somatostatin, reported that SS cannot reduce the incidence of PEP, whereas significant efficacy was obtained only in the subgroup of patients who received somatostatin as a bolus injection. Almost around the same period, Rudin *et al.*<sup>[19]</sup> also performed a meta-analysis of five somatostatin studies, demonstrated that SS can significantly decrease the PEP rate with an infusion for 12 h or more as well as for bolus infusion, with risk differences of 7.7, 95% CI 3.4–12 and 8.2, 95% CI 4.4–12, respectively. In 2010, Omata *et al.*<sup>[20]</sup> summarize 17 studies about the preventive efficacy of somatostatin, its long-acting analogue, and octreotide for PEP and suggested significant efficacy. They stated that somatostatin and high-dose octreotide may prevent PEP. That meta-analysis also reported that 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.

In our study, we found that somatostatin can prevent the occurrence of pancreatic injury after ERCP with the administration of bolus or long-term injection and reduce risk of postprocedure hyperamylasemia. Although not totally unexpected, the results of this updated meta-analysis

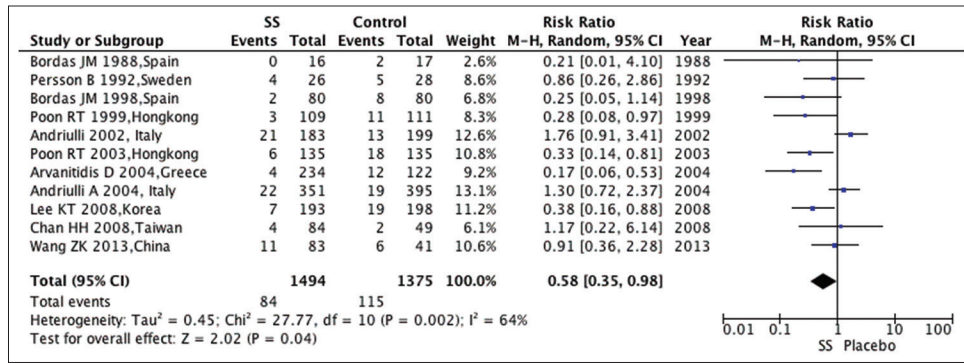


Figure 1: The effect of SS treatment on post-ERCP pancreatitis (PEP) comparing with placebo; relative risk (RR) with 95% confidence intervals (CI)

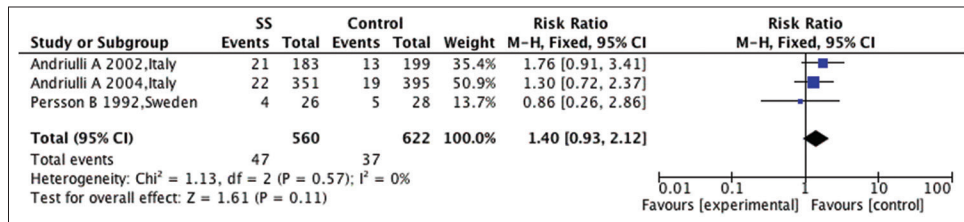


Figure 2: PEP rate: Subgroup analysis of trials comparing short-term infusion with placebo; relative risk (RR) with 95% confidence intervals (CI)

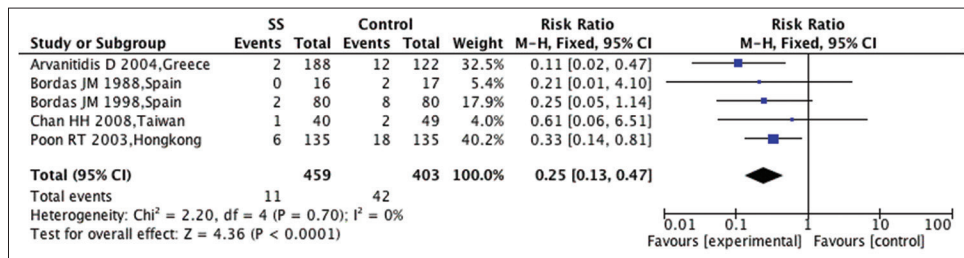


Figure 3: PEP rate: Subgroup analysis of trials comparing bolus injection with placebo; relative risk (RR) with 95% confidence intervals (CI)

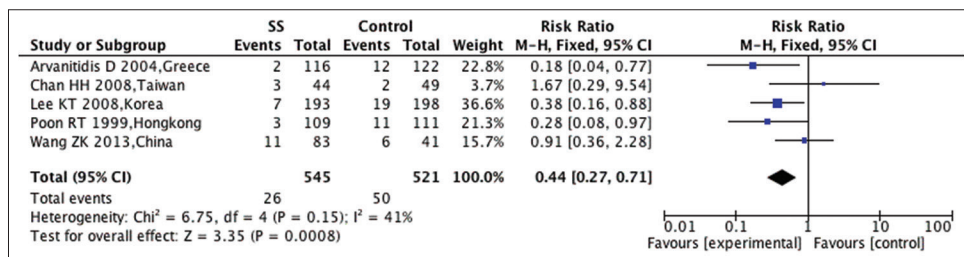


Figure 4: PEP rate: Subgroup analysis of trials comparing long-term infusion with placebo; relative risk (RR) with 95% confidence intervals (CI)

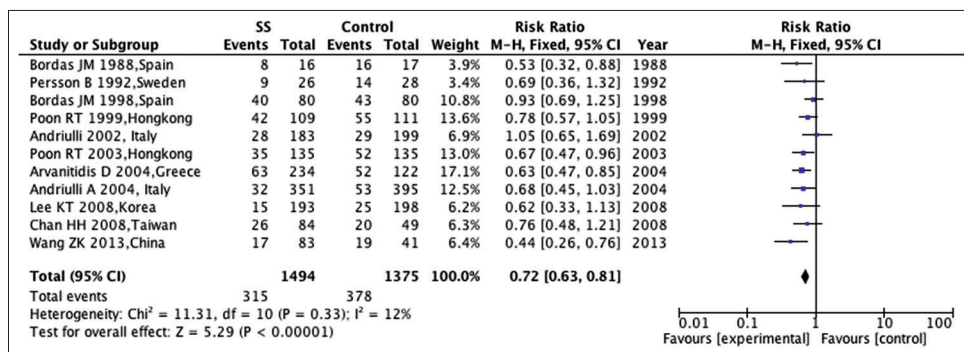


Figure 5: The rate of hyperamylasemia after ERCP with SS treatment and placebo; relative risk (RR) with 95% confidence intervals (CI)

contradict those previous studies. This may be explained by a number of factors. First, only six publications had an adequate sample size (>100 patients in each treatment arm); the other lower sample size studies tend to report larger treatment effects than do those of larger size. Second, 5 of the published before 2000, which are of poor quality, with most carrying a low (<2) precision rate (the inverse of the SE) and a high (>50%) relative error. Finally, the techniques of ERCP before are robust that could greatly increase the occurrence of postprocedure pancreatitis. The recent developments with the ERCP techniques and procedures may account for the different results produced in the current study.

In addition, from a pharmacoeconomic point of view, SS appears to be more cost-effective than other drugs and long-term infusion can achieve study endpoints. Our data showed a bolus injection reduces the postprocedure pancreatitis as well as long-term infusion, which is contradicted with the onset of pancreatitis after ERCP because of its half-life period. The explanation for this might be the heterogeneity of these conclusions. Therefore, despite the favorable evidence provided by the present meta-analysis, more information is needed before recommending the use of SS in every patient undergoing ERCP.

A major limitation of the current analysis is its inability to stratify patients by baseline risk features because data could not be retrieved as such from the selected trials. Consequently, the resulting outcomes of prophylaxis with somatostatin pertain only to average-risk patients. Moreover, all the considered trials were carried out in European or Far Eastern countries, where pancreatic stenting is not in current use, therefore the impact of this technical factor in modifying the risk of PEP could not be addressed.

## CONCLUSION

In conclusion, the current meta-analytic synthesis of data on the prophylactic use of somatostatin in patients undergoing ERCP documents a lack of benefit when given as short-term infusions. The beneficial effect of SS, in reducing the incidence of postprocedural hyperamylasemia seems of marginal clinical significance. Several large-scale, high-quality RCTs guarantee the robustness of previous conclusions. When given as a single bolus or long-term injection, somatostatin still maintains its role in this field, but new confirmatory data are needed to settle residual doubts.

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