



Role of Somatostatin in Preventing Post-endoscopic Retrograde Cholangiopancreatography (ERCP) Pancreatitis: An Update Meta-analysis

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Hu J, Li P-L, Zhang T, Chen J-P, Hu Y-J, Yu Z, Wang J-P, Zhu D and Tong X-F (2016) Role of Somatostatin in Preventing Post-endoscopic Retrograde Cholangiopancreatography (ERCP) Pancreatitis: An Update Meta-analysis. Front. Pharmacol. 7:489. doi: 10.3389/fphar.2016.00489 **Background:** Acute pancreatitis is the most common serious complication of endoscopic retrograde cholangiopancreatography (ERCP). Although, somatostatin (SOM) has been used in the prevention of post-ERCP pancreatitis (PEP), the efficacy of SOM remains inconsistent.

Methods: Electronic databases, including PubMed/MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), and the Science Citation Index were searched to retrieve relevant studies. Details of the study population, including patients' characteristics, sample size, regimen of drug administration and incidence of PEP, hyperamylasemia and abdominal pain were extracted by two investigators. Data were analyzed with Review Manager 5.3 software.

Results: Eleven randomized controlled trials, enrolling a total of 4192 patients, were included in the meta-analysis. After data were pooled, we observed decreased incidence of ERCP-induced outcomes, such as PEP (RR = 0.63, 95% CI: 0.40, 0.98; P = 0.04) and hyperamylasemia (RR = 0.75, 95% CI: 0.66, 0.84; P < 0.001) in patients treated with SOM than those with placebo. Subgroup analysis by ethnicity found decreased incidence of PEP and hyperamylasemia in Asia only. Subgroup analysis by treatment schedule and dosage revealed decreased incidence of PEP and hyperamylasemia when SOM were treated with a single bolus or long-term infusion, or at dose above 3000 μ g. We did not observed efficacy of SOM on abdominal pain in pooled or subgroup analysis.

Conclusion: This meta-analysis of patients undergoing ERCP showed reduced incidence of PEP and hyperamylasemia when SOM was administrated with single bolus, long-term infusion, or high dosage. More data are needed to confirm our findings.

Keywords: somatostatin, endoscopic retrograde cholangiopancreatography, pancreatitis, hyperamylasemia, meta-analysis

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INTRODUCTION

Acute pancreatitis is the most common serious complication of endoscopic retrograde cholangiopancreatography (ERCP) that has been associated with high morbidity and mortality (Freeman and Guda, 2004). It occurs in 2-9% general population and 15% in high-risk patients (Cheng et al., 2006). Although, mild post-ERCP pancreatitis (PEP) generally has few complications with optimal outcome, severe PEP can lead to serious complications, such as systemic inflammatory response, pseudocysts or pancreatic necrosis and even death in a significant portion of patients. In the last three decades, extensive studies were made to investigate the solutions of reducing associated risk and increasing the safety (Choudhary et al., 2011; Dumonceau et al., 2014; Luo et al., 2016). It has demonstrated that the major therapy for PEP is pharmaco-prevention with different agents, such as somatostatin (SOM), non-steroidal anti-inflammatory drugs (NSAIDs), and indomethacin (Kubiliun et al., 2015).

Somatostatin, a potent inhibitor of pancreatic exocrine function, has been found to prevent or mitigate the processes of pancreatic inflammation. However, the efficacy is not consistent when SOM was used at different doses and duration schedules. Rudin et al. (2007) found that SOM administered as a bolus could reduce the incidence of ERCP-induced complications, such as PEP and hyperamylasemia. Consistently, a meta-analysis reported decreased risk of PEP in patients receiving high-dose SOM over 12 h (Omata et al., 2010). A recent meta-analysis further demonstrated decreased incidence of PEP at a single bolus or long-term injection, but no decreased incidence when given as short-term infusion, but (Qin et al., 2015). Therefore, further investigation is required to uncover appropriate methods of administration of SOM to prevent PEP.

In this study, we aim to reassess the effects of SOM on ERCP-induced complications, including PEP, hyperamylasemia and abdominal pain using a meta-analytic approach. We also performed subgroup analyses according to ethnicity, treatment schedule, and dosage to investigate the rational application of SOM for improved benefits.

MATERIALS AND METHODS

Literature Search

Literature search was conducted according to the PRISMA statement developed specifically for meta-analyses to improve the reporting of reviews (Moher et al., 2009). The following databases were searched from their inception through July 2016: PubMed/MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), and the Science Citation Index. Search strategy was performed with both free-text terms and MeSH terms, including "pancreatitis," "ERCP," and "somatostatin." There is no requirement on publication date or type of studies.

Study Selection

Two investigators (Pei-Lin Li, Tao Zhang) independently reviewed titles and abstracts for relevance. All articles assessed

as relevant were included for full-text review. The criteria for inclusion were: (1) randomized controlled trials (RCTs), (2) reporting at least two outcomes, (3) only the most recent study was included if more than one study was published using the same study population. Open or uncontrolled clinical trials, observational studies and case reports were excluded from the meta-analysis.

Data Extraction and Quality Assessment

Two investigators (Tao Zhang, Jin-Ping Chen) independently extracted details of the study population, including patients' characteristics, sample size, regimen of drug administration and incidence of PEP, hyperamylasemia and abdominal pain. The Jadad score is used to assess the methodological quality of selected studies (Jadad et al., 1996). Assessment discrepancies were resolved by discussion with by Dr. Jing Hu until consensus was reached.

Data Analysis

Meta-analyses were conducted using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK). Dichotomous data, such as incidence of PEP, hyperamylasemia and abdominal pain, were expressed as relative risk (RR) with 95% confidence interval (CI). Heterogeneity was quantified with Cochran's Q test. When there was considerable heterogeneity ($P \ge 0.10$ and $I^2 \le 50\%$), the data were analyzed in a fixed-effects model. When there was low heterogeneity ($I^2 > 50\%$ or P < 0.10), the data were analyzed in a fixed-effects mode. When there was low heterogeneity ($I^2 > 50\%$ or P < 0.10), the data were analyzed in a fixed-effects mode. A funnel plot was used to assess potential publication bias.

RESULTS

Identification of Eligible Studies

As shown in **Figure 1**, a total of 543 articles were identified and 146 were remained after removal of duplications. 119 articles were excluded: 87 articles due to non-relevance, 18 non-RCT articles, and 14 articles unable to retrieve. In total, 27 articles were reviewed in detail, of which 16 were excluded due to non-relevance. Finally, 11 eligible studies satisfied the criteria for our meta-analysis.

Characteristics of Included Studies

The baseline characteristics of the 11 studies published between 1998 to 2015 are presented in Supplementary Table S1 (Bordas et al., 1998; Poon et al., 1999; Andriulli et al., 2002, 2004; Poon et al., 2003; Arvanitidis et al., 2004; Chan et al., 2008; Lee et al., 2008; Wang et al., 2013; Concepción-Martín et al., 2014; Bai et al., 2015). Totally, 4192 patients undergo ERCP procedures above average age of 58 years were analyzed. The Jaded score for 11 RCTs were \geq 4, suggesting their high quality. **Table 1** lists the intervention of SOM and post-ERCP complications.

Incidence of PEP

PEP occurred in 117 (5.44%) out of 2,152 patients treated with SOM, and 159 (7.79%) out of 2,040 patients treated with



TABLE 1 | Intervention in 11 RCTs.

Study (years)	Treatment style of SOM	Dosage	Starting time of therapy	Duration	Outcome measures
Bordas et al., 1998	Intravenous injection	4 μg/kg	On identification of papilla	Bolus	IPEP
Poon et al., 1999	Intravenous injection	3000 µg	30 min before ERCP	12 h	IPEP, H, AP
Andriulli et al., 2002	Intravenous injection	750 µg	30 min before ERCP	2.5 h	IPEP, H, AP
Poon et al., 2003	Intravenous injection	250 µg	Immediately after diagnostic ERCP	Bolus	IPEP, H, AP
Andriulli et al., 2004	Intravenous injection	750 µg	30 min before ERCP	6.5 h	IPEP, H, AP
Arvanitidis et al., 2004	Intravenous injection	4 μg/kg	1 h before ERCP	Bolus	IPEP, H
		3000 µg		12 h	
Chan et al., 2008	Intravenous injection	250 μg/h	Before ERCP	Bolus plus 12 h	IPEP, H
		250 µg		Bolus	
Lee et al., 2008	Intravenous injection	3000 µg	30 min before ERCP	12 h	IPEP, H
Wang et al., 2013	Intravenous injection	250 μg/h	1 h before ERCP	24 h	IPEP, H
		250 μg/h	1 h after ERCP		
Concepción-Martín et al., 2014	Intravenous injection	1250 µg	Before cannulation of papilla	Bolus plus 4 h	IPEP, H, AP
Bai et al., 2015	Intravenous injection	3000 µg	Before ERCP	Bolus plus 11 h	IPEP, H

SOM, somatostatin; ERCP, endoscopic retrograde cholangiopancreatography; IPEP, incidence of post-ERCP pancreatitis; H, hyperamylasemia; AP, abdominal pain.

placebo (Supplementary Figure S1). The random-effect model demonstrated significantly decreased PEP risk in patients treated with SOM (RR = 0.63, 95% CI: 0.40, 0.98; P = 0.04).

We then performed subgroup analysis according to area, treatment schedule and dosage. In five RCTS in Europe, PEP incidence is comparable in patients treated with SOM (6.16%) and placebo (6.56%) (RR = 0.77, 95% CI: 0.37, 1.61; P = 0.49) (**Figure 2A**). In six RCTs in Asia, we found significantly decreased risk of PEP incidence when patients were treated

with SOM (RR = 0.48, 95% CI: 0.34, 0.69; P < 0.001) (Figure 2B).

Figure 3 shows RR in subgroup analysis according to doses and duration schedules of SOM. PEP risk is decreased in patients receiving SOM with a single bolus than placebo (2.95% vs. 10.36%) (RR = 0.28, 95% CI: 0.15, 0.54; P < 0.001) (**Figure 3A**). When SOM was administrated as short-term infusion, the incidence of PEP showed marginal decrease than placebo (8.05% vs. 5.39%) (R = 1.49, 95% CI: 0.96, 2.32; P = 0.08) (**Figure 3B**).

	Somato	statin	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI Ye	ear M-H, Random, 95% Cl
Bordas 1998	2	80	8	80	12.8%	0.25 [0.05, 1.14] 19	998
Andriulli 2002	21	183	13	199	22.9%	1.76 [0.91, 3.41] 20	002
Arvanitidis 2004	4	234	12	122	17.1%	0.17 [0.06, 0.53] 20	004
Andriulli 2004	22	351	19	395	23.8%	1.30 [0.72, 2.37] 20	004
Concepción-Martín 2014	19	255	17	255	23.3%	1.12 [0.59, 2.10] 20)14
otal (95% CI)		1103		1051	100.0%	0.77 [0.37, 1.61]	-
otal events	68		69				
leterogeneity: Tau ² = 0.5	0; Chi ² = 16	6.51, df =	= 4 (P = 0.	002); l ^a	² = 76%		
est for overall effect: Z =	0.69 (P = 0).49)					Eavours [Somatostatin] Eavours [Placebo]
	Somatost	atin	Placeb	•		Risk Ratio	Risk Ratio
Study or Subaroup	Somatosta Events	atin Total I	Placeb Events	o Total	Weight	Risk Ratio M-H. Fixed. 95% CI Yea	Risk Ratio r M-H. Fixed, 95% Cl
Study or Subgroup	Somatosta Events 3	atin <u>Total</u> 109	Placeb Events 11	o <u>Total</u> 111	<u>Weight</u> 11.9%	Risk Ratio <u>M-H, Fixed, 95% CI Yea</u> 0.28 [0.08, 0.97] 1999	Risk Ratio r M-H. Fixed, 95% Cl
Study or Subgroup Poon 1999 Poon 2003	Somatosta Events 3 6	atin <u>Total</u> 109 135	Placeb Events 11 18	o <u>Total</u> 111 135	<u>Weight</u> 11.9% 19.6%	Risk Ratio <u>M-H. Fixed, 95% CI Yea</u> 0.28 [0.08, 0.97] 1999 0.33 [0.14, 0.81] 2003	Risk Ratio r M-H. Fixed, 95% CI 0
Study or Subgroup Poon 1999 Poon 2003 Lee 2008	Somatosta Events 3 6 7	atin Total 109 135 193	Placeb Events 11 18 19	o <u>Total</u> 111 135 198	Weight 11.9% 19.6% 20.4%	Risk Ratio <u>M-H. Fixed, 95% Cl Yea</u> 0.28 [0.08, 0.97] 1999 0.33 [0.14, 0.81] 2000 0.38 [0.16, 0.88] 2000	Risk Ratio r M-H. Fixed, 95% Cl
Study or Subgroup Poon 1999 Poon 2003 Lee 2008 Chan 2008	Somatosta Events 3 6 7 4	atin <u>Total</u> 109 135 193 84	Placeb Events 11 18 19 2	o Total 111 135 198 49	Weight 11.9% 19.6% 20.4% 2.8%	Risk Ratio <u>M-H, Fixed, 95% Cl Yea</u> 0.28 [0.08, 0.97] 1999 0.33 [0.14, 0.81] 2000 0.38 [0.16, 0.88] 2000 1.17 [0.22, 6.14] 2000	Risk Ratio
Study or Subgroup Poon 1999 Poon 2003 Lee 2008 Chan 2008 Nang 2013	Somatosta Events 3 6 7 4 11	atin Total 109 135 193 84 83	Placeb Events 11 18 19 2 6	o Total 111 135 198 49 41	Weight 11.9% 19.6% 20.4% 2.8% 8.7%	Risk Ratio <u>M-H. Fixed, 95% Cl Yea</u> 0.28 [0.08, 0.97] 1999 0.33 [0.14, 0.81] 2000 0.38 [0.16, 0.88] 2000 1.17 [0.22, 6.14] 2000 0.91 [0.36, 2.28] 2013	Risk Ratio rH, Fixed, 95% Cl 9 3 3 3 3 3 3
Study or Subgroup Poon 1999 Poon 2003 Lee 2008 Chan 2008 Wang 2013 Bai 2015	Somatosta <u>Events</u> 3 6 7 4 11 18	atin Total 109 135 193 84 83 445	Placeb Events 11 18 19 2 6 34	o Total 111 135 198 49 41 455	Weight 11.9% 19.6% 20.4% 2.8% 8.7% 36.6%	Risk Ratio M-H, Fixed, 95% Cl Yea 0.28 [0.08, 0.97] 199 0.33 [0.14, 0.81] 200 0.38 [0.16, 0.88] 1.17 [0.22, 6.14] 0.91 [0.36, 2.28] 0.54 [0.31, 0.94]	Risk Ratio r M-H, Fixed, 95% Cl
Study or Subgroup Poon 1999 Poon 2003 .ee 2008 Chan 2008 Wang 2013 Bai 2015 Fotal (95% CI)	Somatosta Events 3 6 7 4 11 18	atin Total 109 135 193 84 83 445 1049	Placeb Events 11 18 19 2 6 34	o Total 111 135 198 49 41 455 989	Weight 11.9% 19.6% 20.4% 2.8% 8.7% 36.6% 100.0%	Risk Ratio M-H. Fixed, 95% CI Yea 0.28 [0.08, 0.97] 1999 0.33 [0.14, 0.81] 2000 0.38 [0.16, 0.88] 2000 1.17 [0.22, 6.14] 2000 0.91 [0.36, 2.28] 2013 0.54 [0.31, 0.94] 2013 0.48 [0.34, 0.69] 2014	Risk Ratio
Study or Subgroup Poon 1999 Poon 2003 .ee 2008 Chan 2008 Nang 2013 Bai 2015 Fotal (95% CI) Fotal events	Somatost: <u>Events</u> 3 6 7 4 11 18 49	atin Total 109 135 193 84 83 445 1049	Placeb Events 11 18 19 2 6 34 90	o Total 111 135 198 49 41 455 989	Weight 11.9% 19.6% 20.4% 2.8% 8.7% 36.6% 100.0%	Risk Ratio M-H, Fixed, 95% Cl Yea 0.28 [0.08, 0.97] 199 0.33 [0.14, 0.81] 200 0.38 [0.16, 0.88] 200 1.17 [0.22, 6.14] 200 0.91 [0.36, 2.28] 2013 0.54 [0.31, 0.94] 2013 0.48 [0.34, 0.69] 1000	Risk Ratio r M-H. Fixed, 95% Cl
Study or Subgroup Poon 1999 Poon 2003 .ee 2008 Chan 2008 Nang 2013 Bai 2015 Fotal (95% CI) Fotal events Heterogeneity: Chi² = 4.3	Somatosta <u>Events</u> 3 6 7 4 11 18 49 77, df = 5 (atin Total 109 135 193 84 83 445 1049 P = 0.45	Placeb <u>Events</u> 11 18 19 2 6 34 90 5); I ² = 0%	o Total 111 135 198 49 41 455 989	Weight 11.9% 19.6% 20.4% 2.8% 8.7% 36.6% 100.0%	Risk Ratio M-H. Fixed, 95% Cl Yea 0.28 [0.08, 0.97] 199 0.33 [0.14, 0.81] 200 0.38 [0.16, 0.88] 200 1.17 [0.22, 6.14] 200 0.91 [0.36, 2.28] 2013 0.54 [0.31, 0.94] 2013 0.48 [0.34, 0.69] 100	Risk Ratio r M-H, Fixed, 95% Cl
Study or Subgroup Poon 1999 Poon 2003 .ee 2008 Chan 2008 Wang 2013 Bai 2015 Fotal (95% CI) Fotal events Heterogeneity: Chi ² = 4 Fest for overall effect: Z	Somatosta <u>Events</u> 3 6 7 4 11 18 49 77, df = 5 (= 4.09 (P <	atin <u>Total</u> 109 135 193 84 83 445 1049 P = 0.45 < 0.0001	Placeb Events 11 18 19 2 6 34 90 5); I ² = 0%)	o Total 111 135 198 49 41 455 989	Weight 11.9% 19.6% 20.4% 2.8% 8.7% 36.6% 100.0%	Risk Ratio M-H. Fixed, 95% Cl Yea 0.28 [0.08, 0.97] 1999 0.33 [0.14, 0.81] 2000 0.38 [0.16, 0.88] 2000 1.17 [0.22, 6.14] 2000 0.91 [0.36, 2.28] 2013 0.54 [0.31, 0.94] 2013 0.48 [0.34, 0.69] 2014	Risk Ratio r M-H. Fixed, 95% Cl

We observed significantly decreased PEP risk when SOM was administrated as long-term infusion (RR = 0.39, 95% CI: 0.24, 0.65; P < 0.001) (**Figure 3C**). However, when SOM was treated as bolus plus continuous infusion, the incidence was comparable between SOM and placebo (5.38% vs. 6.98%) (RR = 0.77, 95% CI: 0.52, 1.14; P = 0.20) (**Figure 3D**).

Subgroup analysis according to dose shows decreased incidence of PEP in patients treated with SOM at \geq 3000 µg (4.44% vs. 8.61%) (RR = 0.48, 95% CI: 0.33, 0.69; *P* < 0.0001) (**Figure 4A**). However, when SOM dose decreased to less than 3000 µg, there is no significant difference in PEP risk (RR = 0.71, 95% CI: 0.38, 1.33; *P* = 0.28) (**Figure 4B**).

Hyperamylasemia

Hyperamylasemia was analyzed in 10 studies and in a total of 4,032 patients. Hyperamylasemia occurred in 346 (16.7%) out of 2,072 patients treated with SOM, and 388 (19.80%) out of 1,960 patients treated with placebo (Supplementary Figure S2). The fixed-effect model demonstrated significantly decreased risk of hyperamylasemia (RR = 0.75, 95% CI: 0.66, 0.84; P < 0.001).

Subgroup analysis according to ethnicity shows no difference in hyperamylasemia incidence in SOM and placebo-treated patients (17.99% vs. 17.61%) (RR = 0.89, 95% CI: 0.64, 1.23; P = 0.48) in Europe (**Figure 5A**). The incidence of hyperamylasemia was decreased in SOM patients (15.44% vs. 20.73%) (RR = 0.48, 95% CI: 0.34, 0.69; P < 0.001) in Asia (**Figure 5B**).

Subgroup analysis according to schedules showed decreased incidence of hyperamylasemia with a single bolus treatment of

SOM compared with placebo (RR = 0.70, 95% CI: 0.57, 0.86; P < 0.001) (**Figure 6A**). When SOM was administrated as shortterm infusion, the risk of hyperamylasemia incidence was not decreased compared with placebo (RR = 0.86, 95% CI: 0.53, 1.41; P = 0.56) (**Figure 6B**). We observed significantly decreased hyperamylasemia risk when SOM was administrated as longterm infusion (RR = 0.69, 95% CI: 0.57, 0.83; P < 0.0001) (**Figure 6C**), but no difference when SOM was treated as bolus plus continuous infusion (RR = 0.84, 95% CI: 0.50, 1.40; P = 0.51) (**Figure 6D**).

Subgroup analysis according to dose shows decreased incidence of hyperamylasemia in patients treated with SOM at \geq 3000 µg (16.16% vs. 23.67%) (RR = 0.67, 95% CI: 0.57, 0.79; *P* < 0.001) (**Figure 7A**). When SOM dose decreased to less than 3000 µg, we found significantly decreased risk of hyperamylasemia (RR = 0.81, 95% CI: 0.69, 0.96; *P* = 0.01) (**Figure 7B**).

Abdominal Pain

Post-ERCP abdominal pain was reported in 163 (15.78%) out of 1,033 patients treated with SOM, and 168 (15.34%) out of 1,095 patients treated with placebo (Supplementary Figure S3). There is no significant difference in the risk of abdominal pain (RR = 0.89, 95% CI: 0.62, 1.27; P = 0.52).

Publication Bias

A funnel plot was used to express the publication bias. There were 11 trials included in the funnel plot of incidence of PEP. A little asymmetry was observed in this funnel plot (**Figure 8A**). The



funnel plot of hyperamylasemia was also applied. Publication bias was found in the outcome of hyperamylasemia (**Figure 8B**).

DISCUSSION

Despite medical condition enormously improved over the several decades, little progress has been made toward the goal of founding appropriate agents for preventing PEP (Kubiliun et al., 2015). SOM was firstly found potential for PEP in 1980s. However, the efficacy of SOM on PEP seems to be along with contradictory results based on several properly designed, well-executed, prospective randomized trials. Therefore, the opinion on its clinical benefit remains far from consistent. In recent years, there were mainly six meta-analyses focusing on the efficacy of SOM. Andriulli reported a meta-analysis of the preventive efficacy of somatostatin and its analog on PEP in Andriulli et al. (2000). The analysis concluded that pancreatic

	Somatost	atin	Placeb	0		Risk Ratio				R	isk R	atio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year			М-Н,	Fixed	, 95% (CI		
Poon 1999	3	109	11	111	12.8%	0.28 [0.08, 0.97]	1999			•	_				
Arvanitidis 2004	2	116	12	122	13.8%	0.18 [0.04, 0.77]	2004	-		-	-				
Chan 2008	3	44	2	49	2.2%	1.67 [0.29, 9.54]	2008				-	•			
Lee 2008	7	193	19	198	22.1%	0.38 [0.16, 0.88]	2008				-				
Wang 2013	11	83	6	41	9.5%	0.91 [0.36, 2.28]	2013				-				
Bai 2015	18	445	34	455	39.6%	0.54 [0.31, 0.94]	2015			_					
Total (95% CI)		990		976	100.0%	0.48 [0.33, 0.69]				•					
Total events	44		84												
Heterogeneity: $Chi^2 = 6$.	80 df = 5	D = 0.2	1) 12 0-				H				_				
······································	.00, ui – 5 i	P - 0.24	4); I² = 2 <i>i</i>	7%				0.04	0 1		4		10		100
Test for overall effect: Z	= 3.96 (P	< 0.000	4); I ² = 27 1)	7%			C	0.01 Favou	0.1 ırs [Son	natostat	in] F	avours	10 s [Place	ebo]	100
Test for overall effect: Z	Somato	< 0.000 ⁻	4); I² = 27 1) Place	'%		Risk Ratio	(0.01 Favou	0.1 ırs [Son	natostat	in] F Risk F	avours	10 EPlace	ebo]	100
Test for overall effect: Z	Somato	 < 0.000² < 0.000² statin Total 	4); I ² = 27 1) Place <u>Events</u>	bo Total	Weight	Risk Ratio M-H. Random. 95% 0	(CI Year	0.01 Favou	0.1 Irs [Son	natostat M-H,	in] F Risk F Rande	avours Ratio 2000, 95%	10 5 [Place 6 Cl	ebo]	100
Test for overall effect: Z 3 Study or Subgroup Bordas 1998	Somato Events	 < 0.000' < statin Total 80 	4); I ² = 2 <i>1</i> 1) Place <u>Events</u>	'% bo <u>Total</u> 80	Weight 9.9%	Risk Ratio <u>M-H. Random. 95% (</u> 0.25 [0.05, 1.14]	(<u>)</u> () () ()	0.01 Favou	0.1 Irs [Son	M-H,	1 in] F Risk F Rando	avours Ratio	10 5 [Place 6 Cl	ebo]	100
Test for overall effect: Z Study or Subgroup Bordas 1998 Andriulli 2002	Somato Events 2 21	 c = 0.24 c = 0.000² statin <u>Total</u> 80 183 	4); ² = 27 1) Place Events 8 13	bo <u>Total</u> 80 199	<u>Weight</u> 9.9% 19.0%	Risk Ratio <u>M-H. Random, 95% (</u> 0.25 [0.05, 1.14] 1.76 [0.91, 3.41]	(<u>Cl Year</u>] 1998] 2002	0.01 Favou	0.1 Irs [Son	M-H,	1 in] F Risk F Rando	avours	10 5 [Place	ebo]	100
Test for overall effect: Z <u>Study or Subgroup</u> Bordas 1998 Andriulli 2002 Poon 2003	Somato Events 2 21 6	 < 0.000' statin Total 80 183 135 	4); ² = 27 1) Place Events 8 13 18	bo Total 80 199 135	Weight 9.9% 19.0% 16.2%	Risk Ratio <u>M-H. Random. 95% (</u> 0.25 [0.05, 1.14] 1.76 [0.91, 3.41] 0.33 [0.14, 0.81]	CI Year] 1998] 2002] 2003	0.01 Favou	0.1 Irs [Son	M-H.	in] F Risk F Rando	Ratio	10 5 [Place 6 Cl	ebo]	100
Test for overall effect: Z Study or Subgroup Bordas 1998 Andriulli 2002 Poon 2003 Andriulli 2004	Somato Events 2 21 6 22	 statin Total 80 183 135 351 	4); ² = 27 1) Place Events 8 13 18 19	*% bo Total 80 199 135 395	Weight 9.9% 19.0% 16.2% 19.8%	Risk Ratio <u>M-H. Random, 95% (</u> 0.25 [0.05, 1.14] 1.76 [0.91, 3.41] 0.33 [0.14, 0.81] 1.30 [0.72, 2.37]	Cl Year] 1998] 2002] 2003] 2004	0.01 Favou	0.1 Irs [Son	M-H.	in] F Risk F Rando	Ratio	10 5 [Place 6 Cl	ebo]	100
Test for overall effect: Z Study or Subgroup Bordas 1998 Andriulli 2002 Poon 2003 Andriulli 2004 Arvanitidis 2004	Somato Events 2 21 6 22 2	 statin Total 80 183 135 351 118 	4); 2 = 27 1) Place Events 8 13 18 19 12	7% bo Total 80 199 135 395 122	Weight 9.9% 19.0% 16.2% 19.8% 10.3%	Risk Ratio <u>M-H. Random, 95% (</u> 0.25 [0.05, 1.14] 1.76 [0.91, 3.41] 0.33 [0.14, 0.81] 1.30 [0.72, 2.37] 0.17 [0.04, 0.75]	Cl Year] 1998] 2002] 2003] 2004] 2004	0.01 Favοι	0.1 Irs [Son	M-H.	in] F Risk F Rando	Tavours	10 5 [Place 6 Cl	ebo]	100
Test for overall effect: Z Study or Subgroup Bordas 1998 Andriulli 2002 Poon 2003 Andriulli 2004 Arvanitidis 2004 Chan 2008	Somato Somato Events 2 2 1 6 22 2 1	 c = 0.24 c = 0.000⁻¹ statin Total 80 183 135 351 118 40 	4); 2 = 27 1) Place Events 8 13 18 19 12 2 2	7% Total 80 199 135 395 122 49	Weight 9.9% 19.0% 16.2% 19.8% 10.3% 5.4%	Risk Ratio 0.25 [0.05, 1.14] 1.76 [0.91, 3.41] 0.33 [0.14, 0.81] 1.30 [0.72, 2.37] 0.17 [0.04, 0.75] 0.61 [0.06, 6.51]	Cl Year] 1998] 2002] 2003] 2004] 2004] 2008	0.01 Favou	0.1 Irs [Son	M-H.	1 Risk F Rando	Ratio	10 5 [Place 6 Cl	ebo]	100
Test for overall effect: Z Study or Subgroup Bordas 1998 Andriulli 2002 Poon 2003 Andriulli 2004 Arvanitidis 2004 Chan 2008 Concepción-Martín 2014	Somatc <u>Events</u> 2 21 6 22 2 1 19	F = 0.24 \$ 0.000 ⁻¹ \$ statin Total 80 183 135 351 118 40 255	4); 2 = 27 1) Place Events 8 13 18 19 12 2 17	*% bo Total 80 199 135 395 122 49 255	Weight 9.9% 19.0% 16.2% 19.8% 10.3% 5.4% 19.4%	Risk Ratio 0.25 [0.05, 1.14] 1.76 [0.91, 3.41] 0.33 [0.14, 0.81] 1.30 [0.72, 2.37] 0.17 [0.04, 0.75] 0.61 [0.06, 6.51] 1.12 [0.59, 2.10]	Cl Year] 1998] 2002] 2003] 2004] 2004] 2008] 2014	0.01 Favou	0.1 Irs [Son	M-H,	1 in] F Risk F Rando	avours	10 5 [Place 6 CI	ebo]	100
Test for overall effect: Z Study or Subgroup Bordas 1998 Andriulli 2002 Poon 2003 Andriulli 2004 Arvanitidis 2004 Chan 2008 Concepción-Martín 2014 Total (95% CI)	Somatic <u>Somatic</u> <u>Events</u> 2 21 6 22 2 1 19	statin Total 80 183 135 351 118 40 255 1162	4); 2 = 27 1) Place Events 8 13 13 13 14 19 12 2 17	*bo Total 80 199 135 395 122 49 255 1235	Weight 9.9% 19.0% 16.2% 19.8% 10.3% 5.4% 19.4% 100.0%	Risk Ratio 0.25 [0.05, 1.14] 1.76 [0.91, 3.41] 0.33 [0.14, 0.81] 1.30 [0.72, 2.37] 0.17 [0.04, 0.75] 0.61 [0.06, 6.51] 1.12 [0.59, 2.10] 0.71 [0.38, 1.33]	Cl Year] 1998] 2002] 2003] 2004] 2004] 2004] 2008] 2014	0.01 Favou	0.1 Irs [Son	M-H.	Risk F Rando	Ratio	10 ₅ [Place 6 Cl	ebo]	100
Test for overall effect: Z Study or Subgroup Bordas 1998 Andriulli 2002 Poon 2003 Andriulli 2004 Arvanitidis 2004 Chan 2008 Concepción-Martín 2014 Total (95% CI) Total events	Somatc <u>Events</u> 2 21 6 22 2 1 19 73	statin Total 80 183 135 351 118 40 255 1162	4); 2 = 27 1) Place Events 8 13 18 19 12 2 17 89	bo <u>Total</u> 80 199 135 395 122 49 255 1235	Weight 9.9% 19.0% 16.2% 19.8% 10.3% 5.4% 19.4% 100.0%	Risk Ratio <u>M-H. Random, 95% 0</u> 0.25 [0.05, 1.14] 1.76 [0.91, 3.41] 0.33 [0.14, 0.81] 1.30 [0.72, 2.37] 0.17 [0.04, 0.75] 0.61 [0.06, 6.51] 1.12 [0.59, 2.10] 0.71 [0.38, 1.33]	Cl Year] 1998] 2002] 2003] 2004] 2004] 2008] 2014	.01 Favou	0.1 Irs [Son	M-H.	1 Risk F Rando	Ratio om. 95%	6 CI	ebo]	100
Test for overall effect: Z S Study or Subgroup Bordas 1998 Andriulli 2002 Poon 2003 Andriulli 2004 Arvanitidis 2004 Chan 2008 Concepción-Martín 2014 Total (95% CI) Total events Heterogeneity: Tau ² = 0.4	Somato <u>Somato</u> <u>Events</u> 2 21 6 222 2 1 19 73 12; Chi ² = 1:	statin Total 80 183 351 118 40 255 1162 3.46, df =	Place Place Events 13 18 19 12 22 17 89 = 6 (P = 0	*% Total 80 199 135 395 122 49 255 1235 .005); I	Weight 9.9% 19.0% 16.2% 19.8% 10.3% 5.4% 19.4% 100.0% ² = 68%	Risk Ratio <u>M-H. Random. 95% (</u> 0.25 [0.05, 1.14] 1.76 [0.91, 3.41] 0.33 [0.14, 0.81] 1.30 [0.72, 2.37] 0.17 [0.04, 0.75] 0.61 [0.06, 6.51] 1.12 [0.59, 2.10] 0.71 [0.38, 1.33]	Cl Year] 1998] 2002] 2003] 2004] 2004] 2008] 2014	0.01 Favou	0.1 Irs [Son	M-H,	1 in] F Risk F Rando	Ratio	 [Place	ebo]	100

FIG heterogeneity test, ♦ pooled risk ratio, -■- risk ratio and 95% Cl.

	Somato	statin	Place	bo		Risk Ratio			Risk	Ratio		
tudy or Subgroup	Events	Tota	I Events	Total	Weight	M-H, Random, 95% CI	Year		M-H, Rand	<u>dom, 95%</u>	6 CI	
Andriulli 2002	29	183	8 28	199	21.5%	1.13 [0.70, 1.82]	2002					
Arvanitidis 2004	90	234	66	122	33.5%	0.71 [0.56, 0.89] 2	2004					
Andriulli 2004	32	351	53	395	24.3%	0.68 [0.45, 1.03] 2	2004		-	†		
Concepción-Martín 2014	33	255	5 24	255	20.8%	1.38 [0.84, 2.26]	2014		_	-	_	
Fotal (95% CI)		1023		971	100.0%	0.89 [0.64, 1.23]						
rotal events	184		171									
	· · · ·	,						Favours [Sor	natostatinj	Favours	s [Placebo]	
1	Somatost	atin	Placeb	0		Risk Ratio			Risk	Ratio		
study or Subgroup	Somatost Events	atin Total	Placeb Events	o Total	Weight	Risk Ratio <u>M-H. Fixed. 95% CI Ye</u>	ar		Risk I <u>M-H, Fix</u> ę	Ratio d. 95% C		
Study or Subgroup	Somatost Events 42	atin <u>Total</u> 109	Placeb Events 55	o <u>Total</u> 111	<u>Weight</u> 25.3%	Risk Ratio <u>M-H. Fixed. 95% Cl Ye</u> 0.78 [0.57, 1.05] 199	<u>ar</u>		Risk M-H, Fixe	Ratio <u>d. 95% C</u>	21	
<u>\$tudy or Subgroup</u> ⊃oon 1999 ⊃oon 2003	Somatost Events 42 35	atin <u>Total</u> 109 135	Placeb Events 55 52	o <u>Total</u> 111 135	<u>Weight</u> 25.3% 24.1%	Risk Ratio <u>M-H. Fixed. 95% Cl Ye</u> 0.78 [0.57, 1.05] 199 0.67 [0.47, 0.96] 200	<u>ar</u> 99 03		Risk M-H, Fixe	Ratio <u>d, 95% C</u>	21	
<mark>}tudy or Subgroup</mark> ⊃oon 1999 ⊃oon 2003 .ee 2008	Somatost Events 42 35 15	atin <u>Total</u> 109 135 193	Placeb Events 55 52 25	o <u>Total</u> 111 135 198	<u>Weight</u> 25.3% 24.1% 11.5%	Risk Ratio <u>M-H. Fixed. 95% CI Ye</u> 0.78 [0.57, 1.05] 199 0.67 [0.47, 0.96] 200 0.62 [0.33, 1.13] 200	ar 99 03 08		Risk	Ratio <u>d. 95% C</u> -	0	
Study or Subgroup Poon 1999 Poon 2003 Lee 2008 Chan 2008	Somatost Events 42 35 15 26	atin Total 109 135 193 84	Placeb <u>Events</u> 55 52 25 20	o Total 111 135 198 49	<u>Weight</u> 25.3% 24.1% 11.5% 11.7%	Risk Ratio M-H. Fixed, 95% Cl Ye 0.78 [0.57, 1.05] 199 0.67 [0.47, 0.96] 200 0.62 [0.33, 1.13] 200 0.76 [0.48, 1.21] 200	<u>ar</u> 99 03 08 08		Risk	Ratio <u>d, 95% C</u> -	CI	
Study or Subgroup Poon 1999 Poon 2003 Lee 2008 Chan 2008 Nang 2013	Somatost Events 42 35 15 26 17	atin Total 109 135 193 84 83	Placeb <u>Events</u> 55 52 25 20 19	o Total 111 135 198 49 41	Weight 25.3% 24.1% 11.5% 11.7% 11.8%	Risk Ratio <u>M-H. Fixed. 95% CI Ye</u> 0.78 [0.57, 1.05] 199 0.67 [0.47, 0.96] 200 0.62 [0.33, 1.13] 200 0.76 [0.48, 1.21] 201 0.44 [0.26, 0.76] 201	ar 99 03 08 08 13		Risk	Ratio <u>d, 95% C</u> - -		
Study or Subgroup Poon 1999 Poon 2003 Lee 2008 Chan 2008 Wang 2013 Bai 2015	Somatost Events 42 35 15 26 17 27	atin Total 109 135 193 84 83 445	Placeb <u>Events</u> 55 52 25 20 19 34	o 111 135 198 49 41 455	Weight 25.3% 24.1% 11.5% 11.7% 11.8% 15.6%	Risk Ratio <u>M-H. Fixed. 95% CI Ye</u> 0.78 [0.57, 1.05] 199 0.67 [0.47, 0.96] 200 0.62 [0.33, 1.13] 200 0.76 [0.48, 1.21] 200 0.44 [0.26, 0.76] 200 0.81 [0.50, 1.32] 200	ar 99 03 08 08 13 15		Risk M-H. Fixe	Ratio <u>d. 95% C</u> 	21	
Study or Subgroup Poon 1999 Poon 2003 Lee 2008 Chan 2008 Wang 2013 Bai 2015 Fotal (95% CI)	Somatost Events 42 35 15 26 17 27	atin Total 109 135 193 84 83 445 1049	Placeb Events 55 52 25 20 19 34	o Total 111 135 198 49 41 455 989	Weight 25.3% 24.1% 11.5% 11.7% 11.8% 15.6% 100.0%	Risk Ratio <u>M-H. Fixed. 95% Cl Ye</u> 0.78 [0.57, 1.05] 199 0.67 [0.47, 0.96] 200 0.62 [0.33, 11.3] 200 0.76 [0.48, 1.21] 200 0.44 [0.26, 0.76] 200 0.41 [0.50, 1.32] 200 0.70 [0.59, 0.83]	ar 99 03 08 08 13 15		Risk	Ratio <u>d, 95% C</u> 	<u>ci</u>	
Study or Subgroup Poon 1999 Poon 2003 Lee 2008 Chan 2008 Wang 2013 Bai 2015 Fotal (95% CI) Fotal events	Somatost Events 42 35 15 26 17 27 162	atin Total 109 135 193 84 83 445 1049	Placeb Events 55 52 25 20 19 34 205	o Total 111 135 198 49 41 455 989	Weight 25.3% 24.1% 11.5% 11.7% 11.8% 15.6% 100.0%	Risk Ratio <u>M-H. Fixed. 95% Cl Ye</u> 0.78 [0.57, 1.05] 199 0.67 [0.47, 0.96] 200 0.62 [0.33, 11.3] 200 0.76 [0.48, 1.21] 200 0.44 [0.26, 0.76] 200 0.44 [0.26, 0.1.32] 200 0.81 [0.50, 1.32] 200 0.70 [0.59, 0.83]	ar 99 03 08 08 13 15		Risk	Ratio d. 95% C - 	CI	
Study or Subgroup Poon 1999 Poon 2003 Lee 2008 Chan 2008 Nang 2013 Bai 2015 Fotal (95% CI) Fotal events Heterogeneity: Chi ² = 3.	Somatost Events 42 35 15 26 17 27 162 97, df = 5 (atin Total 109 135 193 84 83 445 1049 (P = 0.5	Placeb <u>Events</u> 55 52 25 20 19 34 205 5); I ² = 0%	o Total 111 135 198 49 41 455 989	Weight 25.3% 24.1% 11.5% 11.7% 11.8% 15.6% 100.0%	Risk Ratio <u>M-H. Fixed. 95% CI Ye</u> 0.78 [0.57, 1.05] 199 0.67 [0.47, 0.96] 200 0.62 [0.33, 1.13] 200 0.76 [0.48, 1.21] 200 0.44 [0.26, 0.76] 200 0.81 [0.50, 1.32] 200 0.70 [0.59, 0.83]	ar 99 03 08 08 13 15		Risk	Ratio d. <u>95% C</u> - 	21	+

FIGURE 5 | Forest plot of RR of ERCP-induced hyperamylasemia in Europe (A) and Asia (B). I² and P is the criterion of heterogeneity test, \blacklozenge pooled risk ratio, —■— risk ratio and 95% CI.

Α	0		Discol				
or 1 o 1	Somatosta	atin	Placeb	0		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI Ye	ear M-H, Fixed, 95% Cl
Poon 2003	35	135	52	135	38.6%	0.67 [0.47, 0.96] 20	003
Arvanitidis 2004	44	118	66	122	48.1%	0.69 [0.52, 0.92] 20	004
Chan 2008	13	40	20	49	13.3%	0.80 [0.46, 1.39] 20	8008
Total (95% CI)		293	100	306	100.0%	0.70 [0.57, 0.86]	◆
Total events	92		138				
Heterogeneity: Chi ² = 0. Test for overall effect: Z	.26, df = 2 (l ∷ = 3.40 (P =	P = 0.88 = 0.0007	8); I² = 0% 7)	6			0.1 0.2 0.5 1 2 5 10 Favours [Somatostatin] Favours [Placebo]
В							
	Somatosta	tin	Placebo			Risk Ratio	Risk Ratio
Study or Subaroup	Events 1	Fotal E	Events T	otal	Weight	M-H. Random, 95% CI	Year M-H. Random, 95% Cl
Andriulli 2002	29	183	28	199	47 1%	1 13 [0 70 1 82] 2	2002
Andriulli 2004	32	351	53	395	52.9%	0.68 [0.45, 1.03] 2	2004
Total (95% CI)		534		594	100.0%	0.86 [0.53, 1.41]	
Total events	61		81				
Heterogeneity: Tau ² = 0.	.08; Chi ² = 2	2.45, df =	= 1 (P = 0).12); I	² = 59%		0.1 0.2 0.5 1 2 5 10
l'est for overall effect: 2	= 0.59 (P =	0.56)					Favours [Somatostatin] Favours [Placebo]
с							
	Somatosta	atin	Placeb	0		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI Ye	ear M-H, Fixed, 95% Cl
Poon 1999	42	109	55	111	32.3%	0.78 [0.57, 1.05] 19	999
Arvanitidis 2004	46	116	66	122	38.1%	0.73 [0.56, 0.97] 20	D04
Lee 2008	15	193	25	198	14.6%	0.62 [0.33, 1.13] 20	008
Wang 2013	17	83	19	41	15.1%	0.44 [0.26, 0.76] 20	013
Total (95% CI)		501		472	100.0%	0.69 [0.57, 0.83]	•
Total events	120		165				
Heterogeneity: Chi ² = 3. Test for overall effect: Z	.58, df = 3 (l : = 4.00 (P <	P = 0.3 ² < 0.0001	1); l² = 16 1)	%			0.1 0.2 0.5 1 2 5 10 Favours [Somatostatin] Favours [Placebo]
D							
Study or Subaroup	Somatos Events	statin Total	Place Events	bo Tota	l Weight	Risk Ratio M-H. Random, 95% CI	Risk Ratio Year M-H. Random, 95% Cl
Chap 2008	13	44	20	40	30.8%	0 72 [0 41 1 28]	2008
Concepción-Martín 2014	33	255	20	255	33.8%	1 38 [0 84 2 26]	2014
Bai 2015	27	445	46	455	35.5%	0.60 [0.38, 0.95]	2015
Total (95% CI)		744		759	100.0%	0.84 [0.50, 1.40]	
Total events	73		90				
Heterogeneity: Tau ² = 0.1 Test for overall effect: Z =	14; Chi² = 6. = 0.66 (P = 0	13, df =).51)	2 (P = 0.0	95); I² =	= 67%		0.1 0.2 0.5 1 2 5 10 Favours [Somatostatin] Favours [Placebo]
FIGURE 6 Forest plot of nfusion (C), and bolus plus	RR of ERC continuous	P-indu infusior	iced hyp n (D) . /² a	eramy nd <i>P</i> is	/lasemia s the criter	in patients treated with ion of heterogeneity test,	SOM as single bolus (A) , short-term infusion (B) , long-term ♦ pooled risk ratio, -■- risk ratio and 95% Cl.

injury after ERCP could be prevented with the administration of SOM with an OR of 0.38 (95% CI: 0.22, 0.65; P < 0.001). Moreover, SOM was also able to reduce hyperamylasemia and abdominal pain (OR = 0.65, 95% CI: 0.48, 0.90; P = 0.008 and OR = 0.24, 95% CI: 0.14, 0.42; P < 0.001). After 7 years, Andriulli and Rudin respectively updated the meta-analyses by including several high-quality trials on SOM. The result from Andriulli' research reported that SOM was ineffective in

reducing PEP and pain. Meanwhile, there was limited efficacy on hyperamylasemia. The significant efficacy of SOM on PEP was obtained only in the subgroup of patients receiving with bolus injection (Andriulli et al., 2007). The research from Rudin also confirmed that SOM can significantly decrease the incidence of PEP with only long-term infusion or bolus. However, there was no difference between control and SOM arms with shortterm infusion (Rudin et al., 2007). Further research performed

	Somatos	atin	Placeb	0		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year		M-H, Fixe	ed, 95% Cl		
Poon 1999	42	109	55	111	23.4%	0.78 [0.57, 1.05]	1999			-		
Arvanitidis 2004	46	116	66	122	27.6%	0.73 [0.56, 0.97]	2004					
Lee 2008	15	193	25	198	10.6%	0.62 [0.33, 1.13]	2008	-	-	-		
Chan 2008	13	44	20	49	8.1%	0.72 [0.41, 1.28]	2008		-			
Wang 2013	17	83	19	41	10.9%	0.44 [0.26, 0.76]	2013		•			
Bai 2015	27	445	46	455	19.5%	0.60 [0.38, 0.95]	2015					
Total (95% CI)		990		976	100.0%	0.67 [0.57, 0.79]			•			
Total events	160		231									
Heterogeneity: Chi ² = 3.9	99, df = 5	(P = 0.5	5); $I^2 = 0$	6							<u> </u>	- 10
• •		·						0.1 0.2	0.5	1 2	5	10
Test for overall effect: Z	= 4.68 (P	< 0.000	01)					Favours [Sc	omatostatin]	Favours [Pla	ICEDO	
Test for overall effect: Z	= 4.68 (P	< 0.000	01)					Favours [So	omatostatin]	Favours [Pla	icebo]	
Test for overall effect: Z	= 4.68 (P	< 0.000	01)					Favours [Sc	omatostatin]	Favours [Pla	icebo]	
Test for overall effect: Z	= 4.68 (P Somat	< 0.000	U1) Plac	ebo		Risk Ratio		Favours [So	omatostatin] Risk	Favours [Pla Ratio	iceboj	
Test for overall effect: Z	= 4.68 (P Somat Events	< 0.000 ostatin	01) Plac al Event	ebo <u>s Tota</u>	I Weight	Risk Ratio M-H. Fixed, 95% C	l Year	Favours [So	omatostatin] Risk <u>M-H. Fix</u>	Favours [Pla Ratio ed. 95% Cl	icebo]	
Test for overall effect: Z Study or Subgroup Andriulli 2002	= 4.68 (P Somat <u>Events</u> 29	< 0.000 ostatin <u>s Tota</u>) 18	Plac al Event 3 2	ebo <u>s Tota</u> 8 199	<u>I Weight</u> ∋ 11.4%	Risk Ratio <u>M-H. Fixed, 95% C</u> 1.13 [0.70, 1.82]	<u>I Year</u> 2002	Favours [Sc	omatostatin] Risk <u>M-H, Fix</u> ——	Favours [Pla Ratio ed. 95% Cl	icebo]	
Test for overall effect: Z Study or Subgroup Andriulli 2002 Poon 2003	= 4.68 (P Somat <u>Events</u> 29 35	< 0.000 ostatin <u>s Tota</u> 5 18 5 13	01) Plac a <u>l Event</u> 3 2 5 5	ebo <u>s Tota</u> 8 199 2 135	<u>I Weight</u>) 11.4% 5 22.1%	Risk Ratio <u>M-H. Fixed, 95% C</u> 1.13 [0.70, 1.82] 0.67 [0.47, 0.96]	<u>I Year</u> 2002 2003	Favours [Sc	Risk M-H, Fix	Ratio ed. 95% Cl	icebo]	
Test for overall effect: Z Study or Subgroup Andriulli 2002 Poon 2003 Arvanitidis 2004	= 4.68 (P Somat <u>Events</u> 29 35 44	 < 0.000 ostatin Tota 18 13 11 	Plac al Event 3 2 5 5 8 6	ebo <u>s Tota</u> 8 199 2 135 6 122	<u>I Weight</u> 9 11.4% 5 22.1% 2 27.5%	Risk Ratio <u>M-H. Fixed, 95% C</u> 1.13 [0.70, 1.82] 0.67 [0.47, 0.96] 0.69 [0.52, 0.92]	I Year 2002 2003 2004	Favours [Sc	Risk M-H, Fix	Ratio ed. 95% Cl	icebo]	
Test for overall effect: Z Study or Subgroup Andriulli 2002 Poon 2003 Arvanitidis 2004 Andriulli 2004	= 4.68 (P Somat Events 29 35 44 32	 < 0.000 ostatin <u>s</u> Tota 18 13 11 35 	Plac al Event 3 2 5 5 8 6 1 5	ebo <u>s Tota</u> 8 199 2 135 6 122 3 395	I Weight 9 11.4% 5 22.1% 2 27.5% 5 21.2%	Risk Ratio <u>M-H. Fixed, 95% C</u> 1.13 [0.70, 1.82] 0.67 [0.47, 0.96] 0.69 [0.52, 0.92] 0.68 [0.45, 1.03]	I Year 2002 2003 2004 2004	Favours [Sc	Risk M-H, Fix	Ratio ed. 95% Cl	icebo]	
Test for overall effect: Z Study or Subgroup Andriulli 2002 Poon 2003 Arvanitidis 2004 Andriulli 2004 Chan 2008	= 4.68 (P Somat <u>Events</u> 29 35 44 32 13	 < 0.000 ostatin s Tot;) 18 5 13 4 11 2 35 3 4 	01) Plac al Event 3 2 5 5 5 5 8 6 1 5 0 2	ebo <u>s Tota</u> 8 199 2 135 6 122 3 395 0 49	I Weight 0 11.4% 5 22.1% 2 27.5% 5 21.2% 0 7.6%	Risk Ratio M-H. Fixed. 95% C 1.13 [0.70, 1.82] 0.67 [0.47, 0.96] 0.69 [0.52, 0.92] 0.68 [0.45, 1.03] 0.80 [0.46, 1.39]	l Year 2002 2003 2004 2004 2008	Favours [Sc	Risk M-H. Fix	Ratio ed, 95% Cl	icebo]	
Test for overall effect: Z Study or Subgroup Andriulli 2002 Poon 2003 Arvanitidis 2004 Andriulli 2004 Chan 2008 Concepción-Martín 2014	= 4.68 (P Somat Events 29 35 44 32 13 33	 < 0.000 ostatin 5 Tota 18 5 13 5 13 4 11 2 35 4 4 3 25 	Plac al Event 3 2 5 5 8 6 1 5 0 2 5 2	ebo <u>s Tota</u> 8 199 2 135 6 122 3 395 0 49 4 255	Weight 9 11.4% 5 22.1% 2 27.5% 5 21.2% 9 7.6% 5 10.2%	Risk Ratio <u>M-H. Fixed, 95% C</u> 1.13 [0.70, 1.82] 0.67 [0.47, 0.96] 0.69 [0.52, 0.92] 0.68 [0.45, 1.03] 0.80 [0.46, 1.39] 1.38 [0.84, 2.26]	I Year 2002 2003 2004 2004 2004 2008 2014	Favours [Sc	Risk M-H. Fix	Ratio ed, 95% Cl	icebo]	
Test for overall effect: Z Study or Subgroup Andriulli 2002 Poon 2003 Arvanitidis 2004 Andriulli 2004 Chan 2008 Concepción-Martín 2014 Total (95% CI)	Somat <u>Events</u> 29 35 44 32 13 33	< 0.000 ostatin <u>s Tot</u> ;) 18 5 13 4 11 2 35 3 4 3 25 108	Plac al Event 3 2 5 5 8 6 1 5 0 2 5 2 2 2	ebo <u>s Tota</u> 8 199 2 135 6 122 3 395 0 49 4 255 1155	Weight 11.4% 27.5% 27.5% 521.2% 7.6% 10.2%	Risk Ratio M-H. Fixed, 95% C 1.13 [0.70, 1.82] 0.67 [0.47, 0.96] 0.69 [0.52, 0.92] 0.68 [0.45, 1.03] 0.80 [0.46, 1.39] 1.38 [0.84, 2.26] 0.81 [0.69, 0.96]	2002 2003 2004 2004 2008 2014	Favours [Sc	Risk M-H. Fix	Ratio ed. 95% CI	(cebo]	
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FIGURE 7 | Forest plot of RR of ERCP-induced hyperamylasemia SOM was administrated at high (\geq 3000 µg) (A) and low dose (<3000 µg) (B). l^2 and P is the criterion of heterogeneity test, \blacklozenge pooled risk ratio, $-\blacksquare$ risk ratio and 95% CI.



by Omata summarized that the preventive efficacy of SOM was more prominent in cases high-dose administration over 12 h, or bolus injection (Omata et al., 2010). Kubiliun et al. (2015), Qin et al. (2015), two meta-analyses further confirmed that the benefit of SOM has been demonstrated more consistently with bolus administration than with infusion. Apart from bolus administration seemed to be the prominent method, the benefits from other administration methods, duration and dosage of SOM were inconsistent. In addition, two new clinical trials were further published from 2014 to 2015. We therefore conducted this meta-analysis to find out more accurate result of SOM on PEP.

Eleven high-quality RCTs involving a total of 4192 participants receiving SOM or placebo during ERCP were included in our study. The result showed a significant decline in incidence of PEP and hyperamylasemia based on the pooled data of SOM. It indicated that SOM might be effective on PEP. Further outcomes were analyzed to evaluate the preventive efficacy of subgroups according to area, treatment schedule and dosage. The pooled data indicated a remarkable decrease of PEP treated with SOM

in Asia, whereas, there appeared no change between SOM and placebo treatment in Europe. The hyperamylasemia was in accordance with the change of PEP. Therefore, SOM might be more efficient for Asian than European. This is the first time to demonstrate the relationship between the efficacy of SOM and area. Moreover, we also explored the four subgroups according to schedule of treatment such as bolus, short-term infusion, long-term infusion and bolus plus continuous infusion to assess its preventive efficacy. SOM demonstrated significant decline of PEP and hyperamylasemia with both bolus and longterm infusion. The result is in according with previous study. Surprisingly, SOM was not effective applied with neither shortterm infusion nor bolus plus continuous infusion. Moreover, SOM even presented the opposite trend to increase the incidence of PEP compared with placebo with short-term infusion. Why could single bolus be effective than short-term infusion? As a possible explanation, we supposed that single bolus of SOM was able to achieve the peak at a critical point which enabled SOM exert its protective efficacy of PEP. This critical point is possibly the introduction of the catheter to the papilla. On the contrary, the short-term infusion of SOM failed to yield the peak and resulted in ineffectiveness. The previous used to pointed out that there was a significant efficacy of SOM on PEP with highdose over 12 h. We further investigated the relationship between dosage and efficacy. It was confirmed that SOM could decrease the incidence of PEP at no less than 3000 µg. In addition, SOM was also proved to be able to reduce hyperamylasemia in our study.

There are several limitations in our study. Firstly, we disregarded few non-English-language literatures. This might be one of the reasons for publication bias in our meta-analyses. Secondly, due to limited or missing data about subsets in current trials, there are still several details such as sex, age, reasons for

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ERCP and so on were unable to be analyzed in subgroups. Finally, the promising result of this study still need further confirmation by the most practical and likely cost-effective approach.

CONCLUSION

The current meta-analytic data on efficacy of SOM on patients undergoing ERCP varied from area to dosage. It is clear from our study that the beneficial efficacy of SOM used in Asia was more likely to reduce the incidence of PEP and hyperamylasemia. Moreover, when given as a single bolus or long-term injection, SOM still maintains its role in this field. High dosage of SOM demonstrated the obvious efficacy than low dose. However, highquality clinical trials are still needed to improve the residual doubts.

AUTHOR CONTRIBUTIONS

JH, P-LL, and TZ performed the search and contributed to manuscript writing. J-PC, Y-JH, and ZY contributed to data interpretation. P-LL and TZ performed the data extraction. J-PW, DZ, and X-FT amended the paper. JH designed the study and supervised the study operations. All authors read and approved the final manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://journal.frontiersin.org/article/10.3389/fphar. 2016.00489/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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