CURRENT THERAPEUTIC RESEARCH

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Gabexate Mesylate in the Prevention of Post-Endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Systematic Review and Meta-Analysis Update

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ABSTRACT

BACKGROUND: Acute pancreatitis is a common complication of endoscopic retrograde cholangiopancreatography (ERCP), and the benefit of pharmacologic treatment of the condition is unclear. Although prophylactic use of gabexate mesylate (GM) for the reduction of pancreatic injury after ERCP has been evaluated, uncertainty remains regarding the effectiveness of GM treatment in post-ERCP pancreatitis (PEP).

OBJECTIVE: The aim of this study was to determine through systematic review and meta-analysis the effectiveness and tolerability of GM in the prophylaxis of PEP.

METHODS: MEDLINE (January 1966–July 2007), EMBASE (January 1966–July 2007), the Cochrane Controlled Trials Register on The Cochrane Library (Issue 2, 2007), and the China Biological Medicine Database (January 1978–July 2007) were searched. We used the method recommended by The Cochrane Collaboration to perform a systematic review and meta-analysis of randomized controlled trials (RCTs) of GM in the prevention of PEP.

RESULTS: Of the 38 studies identified, 31 were excluded for the following reasons: they were reviews or editorials (9 articles); were meta-analyses (4); had differences in cointerventions (4); were nonrandomized controlled trials or had incorrect randomization (4); were repeat publications (2); lacked a placebo group (1); or other (7). Seven RCTs, totaling 2883 patients, conducted in a variety of languages were included in the meta-analysis. When the RCTs were analyzed, odds ratios for GM were 0.65 (95% CI, 0.36–1.18; $P = 0.16$) for PEP, 1.90 (95% CI, 0.54–6.65; $P = 0.32$) for severe PEP, 0.55 (95% CI, 0.17–1.77; $P = 0.32$) for the case-fatality ratio of PEP, 0.88 (95% CI, 0.74–1.05; $P = 0.16$) for post-ERCP hyperamylasemia, and 0.78 (95% CI, 0.49–1.25; $P = 0.30$) for post-ERCP abdominal pain. No evidence of publication bias was found.

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CONCLUSIONS: No beneficial effects of GM on acute pancreatitis, the PEP mortality rate, or post-ERCP abdominal pain or hyperamylasemia were found; therefore, GM cannot be recommended for the prophylaxis of PEP. (*Curr Ther Res Clin Exp.* 2008;69:288–304) © 2008 Excerpta Medica Inc.

KEY WORDS: gabexate mesylate, post-endoscopic retrograde cholangiopancreatography pancreatitis, prevention, randomized controlled trial, meta-analysis.

INTRODUCTION

Three meta-analyses published in 2007[1,2] and 2000[3] evaluated randomized controlled trials (RCTs) comparing gabexate mesylate (GM) with placebo. These studies assessed prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP), post-ERCP hyperamylasemia, post-ERCP abdominal pain, and the case-fatality ratio of PEP. One review[1] examined 4 RCTs published as full articles in peer-reviewed journals between 1996 and 2006 in 2 different countries. These studies included patients with high, average, and low risk for PEP. The studies found that in patients with PEP, GM did not prevent pancreatic injury after ERCP. In 2000, a meta-analysis[3] including 6 studies reported that patients who received GM after ERCP had PEP at an occurrence rate of 1.6% while 6.5% patients in the placebo group had PEP. Therefore, they concluded that GM use was associated with a significant reduction of PEP ($P < 0.001$). When they updated the meta-analysis in 2007,[2] they came to an opposite conclusion.

ERCP is an important procedure for the diagnosis and treatment of several biliary and pancreatic conditions.[4] However, ERCP can also cause acute pancreatitis and result in significant morbidity and mortality.[4,5] Depending on the definition used, it has been reported that the incidence of PEP was 1% to 40%, whereas post-ERCP hyperamylasemia was found to occur in up to 70% of patients.[6] Although most cases (90%) of PEP were mild, 10% of patients developed severe pancreatitis, a condition that can result in prolonged hospitalization and increased risk of mortality.[4]

Protease activation is recognized as the key event in the pathogenesis of acute pancreatitis; agents that inhibit proteolytic activity were assessed.[7–13] Several studies[8,11,13] found that GM was effective in reducing the incidence of PEP; however, other studies[9,10,12] did not find any benefit of GM therapy. The purpose of this study was to update previously published meta-analyses[1–3] with 3 trials[7,12,13] not previously included.

METHODS

SELECTION CRITERIA

MEDLINE (January 1966–July 2007), EMBASE (January 1966–July 2007), the Cochrane Controlled Trials Register on The Cochrane Library (Issue 2, 2007), and the China Biological Medicine Datadase (CBMdisc) (January 1978–July 2007) were searched using the exploded (exp) medical subject heading terms *exp pancreatitis* OR *exp post-ERCP pancreatitis* AND the exploded terms *gabexate* and *FOY*, and by limiting the search to reports of clinical trials in human patients. The search was performed by

database specialty personnel. Reference lists of pertinent reviews and retrieved articles were also checked to identify additional studies. In addition, we attempted to find data from poster presentations and by consulting several experts in the field; however, these methods yielded no additional information.

In the systematic review, the following inclusion criteria were established: (1) each trial should be a prospective clinical RCT; (2) the patient population should be aged >18 years; (3) the patients were to be scheduled to undergo ERCP and/or endoscopic sphincterotomy; (4) randomized comparisons of GM versus placebo or blank control should have been included, regardless of the initial time of treatment, treatment duration, dose, and administration route of the drug; and (5) cointerventions (including treating complications) were allowed if administered equally to all intervention groups. Two independent reviewers (M.-H.Z. and J.-L.B.) used these criteria to review each article identified.

A study was excluded if: (1) it was quasi-randomized or nonrandomized; (2) the patients had active acute pancreatitis, chronic pancreatitis, pancreatic cancer, or cancer of the papilla of Vater; (3) there were differences in the cointerventions between intervention arms; or (4) the report was repetitive (if >1 version of the same study was retrieved, only the most recent was used).

DATA EXTRACTION

The 2 reviewers independently extracted data from each matching study using a standardized form. To reduce bias, 1 of the reviewers (M.-H.Z.) was blinded to the source of the publication and to the authors' names. Inconsistencies between reviewers' data were resolved through discussion until a consensus was reached. Each RCT was scored for quality to assess validity using the Jadad scoring system,[14] which is used to evaluate studies based on randomization, blinding, and description of withdrawals and dropouts.[15] If the Jadad score of a study was ≥3, it was considered a high-quality study.[16] The extracted data included characteristics of the trial, patients, interventions, and outcomes (including 3 primary outcomes [PEP, severe PEP[6], and the case-fatality ratio of PEP] and 2 secondary outcomes [post-ERCP hyperamylasemia and abdominal pain]). Trial characteristics collected were the country of origin, methodologic quality, sample size calculations, and study setting. Patient characteristics collected were inclusion and exclusion criteria, mean age of included patients, proportion of men, etiology, number of patients, and number and reasons for dropouts and withdrawals.

STATISTICAL ANALYSIS

Meta-analysis was performed according to recommendations from The Cochrane Collaboration[17] and the quality of reporting of meta-analyses guidelines.[18] The effect measures estimated were odds ratio (OR) for dichotomous data and weighted mean difference for continuous data, both reported with 95% CIs. The OR represented the odds of an adverse event (AE) occurring in the GM group compared with the placebo group. An OR of <1 favored the GM group. The point estimate of the OR was considered statistically significant at $P < 0.05$ if the 95% CI did not include the value 1.

Studies that contained a zero in 1 cell for the number of events of interest in 1 of the 2 groups resulted in problems with the computation of ratio measurement; therefore, on the recommendation of a statistician, a value of 0.5 was added in both groups for those studies.

Heterogeneity was evaluated using the χ^2 test. $P < 0.1$ was considered significant for heterogeneity. Fixed-effect models were used throughout, unless statistical heterogeneity was significant, in which case a random-effects model was used.

Analysis was performed using the statistical software Intercooled Stata version 8.2 for Windows (Stata Corp., College Station, Texas) and Review Manager version 4.2 (The Cochrane Collaboration, Software Update, Oxford, UK).

RESULTS

The search strategy initially generated 31 studies, and 7 additional studies were identified from the reference lists of pertinent reviews and retrieved articles (**Figure 1**). Three studies[19–21] were excluded because they were not RCTs. One study[22] was excluded because it compared the effect of a short (6-hour) versus a long (12-hour) infusion and because a placebo group was lacking. One study[23] was excluded because of its incorrect randomization method and different cointerventions. Two articles[24,25] reported >1 version of the same study, and 4 meta-analyses[1–3,26] and 9 reviews were excluded. Eleven additional studies were excluded due to differences in cointerventions (3);

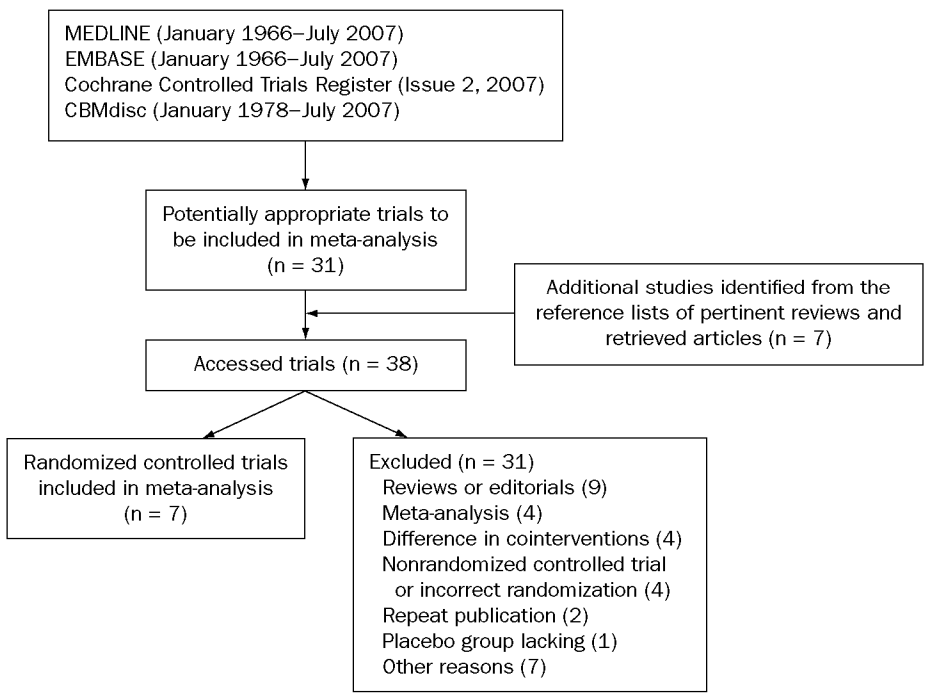

Figure 1. Identification of eligible randomized controlled trials. CBMdisc = China Biological Medicine Database.

incorrect randomization (1); and other reasons (7). Thus, 7 RCTs satisfied all of the inclusion criteria (**Tables I and II**).

PRIMARY OUTCOMES

In this meta-analysis, PEP (either general PEP or severe PEP[6]) was the primary outcome. General PEP was found in 6 of the RCTs.[8–13] These trials included 2827 patients, with 151 patients (5.3%) having PEP. Of the patients with PEP, 68 were treated with GM and 83 received placebo. There was significant heterogeneity among these studies (χ^2 = 13.94, degree of freedom [df] = 5; P = 0.02). However, analysis by random-effects model indicated a DerSimonian and Laird (DL) random-effect pooled OR of 0.65 (95% CI, 0.36–1.18; P = 0.16), with no significant association between the use of GM and the reduction of PEP (**Figure 2, Table III**). When stratified by the duration of treatment (group 1, ≥6 hours; group 2, <6 hours), there was no significant reduction in PEP in either group 1 (DL random-effect pooled OR, 0.63 [95% CI, 0.30–1.33]; P = 0.23) (**Figure 3A**) or group 2 (DL random-effect pooled OR, 0.64 [95% CI, 0.14–2.92]; P = 0.57) (**Figure 3B**). There was significant heterogeneity in both group 1 (χ^2 = 9.53, df = 3; P = 0.02) (**Figure 3A**) and group 2 (χ^2 = 3.99, df = 1; P = 0.05) (**Figure 3B**).

Severe PEP was reported in 4 trials[9,10,12,13] that included 2216 patients, 10 (0.5%) of whom had severe PEP (7 in the GM treatment group and 3 in the placebo group). The Q test of heterogeneity between studies was not significant (χ^2 = 2.46, df = 3). The meta-analysis did not indicate an association between GM use and reduction of severe PEP (inverse variance [IV] fixed-effect pooled OR, 1.90 [95% CI, 0.54–6.65]) (**Figure 2, Table III**). When studies were stratified by the duration of treatment, there was no significant reduction in severe PEP in either group 1 (IV fixed-effect pooled OR, 2.21 [95% CI, 0.53–9.23]; P = 0.28) (**Figure 3A**) or group 2 (IV fixed-effect pooled OR, 1.01 [95% CI, 0.06–16.26]; P = 0.99) (**Figure 3B**). There was no significant heterogeneity in group 1 (χ^2 = 2.38, df = 2; P = 0.30) (**Figure 3A**). Only 1 study[9] in group 2 reported severe PEP, so the result of the heterogeneity test was unavailable (**Figure 3B**).

The subgroup analysis of the case-fatality ratio of PEP is shown in **Figures 3A and 3B**. Data for the case-fatality ratio of PEP were extracted from 3 trials[8,10,13] that included 1802 patients, 11 (0.6%) of whom died (GM group, 4; placebo group, 7). The Q test of heterogeneity of effect sizes was not significant (χ^2 = 0.75, df = 2; P = 0.69). Moreover, there was no significant association between the use of GM and the reduction of the case-fatality ratio of PEP (IV fixed-effect pooled OR, 0.55 [95% CI, 0.17–1.77]; P = 0.32) (**Figure 2, Table III**).

SECONDARY OUTCOMES

The subgroup analysis of post-ERCP hyperamylasemia is shown in **Figures 3A and 3B**. Both post-ERCP hyperamylasemia and abdominal pain were considered as secondary outcomes in the meta-analysis. For post-ERCP hyperamylasemia, data were derived from 6 RCTs.[7–11,13] These trials included 2447 patients, with 851 (34.8%) patients having post-ERCP hyperamylasemia. Among these patients, 432 were treated

Table I. Randomized controlled trials of the use of gabexate mesilate (GM) for the prevention of pancreatic injury after endoscopic retrograde cholangiopancreatography (ERCP).

Reference	Setting	No. of Patients	Interventions	Outcomes	Allocation Concealment
Benini et al, 1985[7]*	Italy, single-center	56	GM 150-mg IV infusion from 1 hour before to 1 hour after ERCP, followed by 150 mg infused over 4 hours	Post-ERCP hyperamylasemia	Unclear
Cavallini et al, 1996[8]†	Italy, multicenter	418	GM 1-g IV infusion starting 30 to 90 minutes before endoscopy and continuing for 12 hours after	PEP, post-ERCP hyperamylasemia, post-ERCP abdominal pain, case-fatality ratio of PEP	Adequate
Andriulli et al, 2002[9]†	Italy, multicenter	396	GM 500-mg IV infusion starting 30 minutes before endoscopy and continuing for 2 hours after	PEP, severe PEP, post-ERCP hyperamylasemia, post-ERCP abdominal pain	Adequate
Andriulli et al, 2004[10]†	Italy, multicenter	776	GM 500-mg IV infusion starting 30 minutes before endoscopy and continuing for 6 hours after	PEP, severe PEP, post-ERCP hyperamylasemia, post-ERCP abdominal, pain, case-fatality ratio of PEP	Adequate
Xiong et al, 2006[11]†	China, single-center	193	GM 300-mg IV infusion starting 30 minutes before endoscopy and continuing for 4-1/2 hours after	PEP, post-ERCP hyperamylasemia, post-ERCP abdominal pain	Adequate
Benvenuti et al, 2006[12]*	Italy, multicenter	436	GM 1.2-g IV infusion starting 1 hour before endoscopy and continuing for 12 hours after	PEP, severe PEP	Unclear
Manes et al 2007[13]†	Italy, multicenter	608	GM 500-mg IV infusion starting 1 hour before endoscopy and continuing for 6 hours after or 1 hour after ERCP and continuing for 6 hours after	PEP, severe PEP, post-ERCP hyperamylasemia, post-ERCP abdominal pain, case-fatality ratio of PEP	Adequate

PEP = post-ERCP pancreatitis.
*Abstract.
†Full paper (complete report).

Table II. Jadad quality score of randomized controlled trials included in the meta-analysis.

Reference	Year of Publication	Randomization	Withdrawals and Jadad Blinding	Dropouts	Score[14]
Benini et al[7]*	1985	Not mentioned	Double	Unclear	2
Cavallini et al[8]†	1996	Centralized randomization schedule	Double	Clearly reported	5
Andriulli et al[9]†	2002	Computer-generated list	Double	Clearly reported	5
Andriulli et al[10]†	2004	Computer-generated list	Double	Clearly reported	5
Xiong et al[11]†	2006	Computer-generated randomized set of numbers	Double	Clearly reported	5
Benvenuti et al[12]*	2006	Randomization mentioned, but method not specified	Unclear	Clearly reported	2
Manes et al[13]†	2007	Computer-generated list	Double	Clearly reported	5

*Abstract.
†Full paper (complete report).

with GM and 419 received placebo. The Q test of heterogeneity of effect sizes was not significant ($\chi^2 = 2.94$, df = 5; $P = 0.71$). Although post-ERCP hyperamylasemia was noted in 32.8% (432/1318) of patients with GM and 37.1% (419/1129) of control patients, the results of the meta-analysis indicated no significant association between the use of GM and reduction of post-ERCP hyperamylasemia (IV fixed-effect pooled OR, 0.88 [95% CI, 0.74–1.05]; $P = 0.16$) (**Figure 2, Table III**).

The subgroup analysis of post-ERCP abdominal pain is shown in **Figures 3A** and **3B**. Data for post-ERCP abdominal pain were extracted from 5 RCTs,[8–11,13] which included 2391 patients. Two hundred seventy-six patients (11.5%) had post-ERCP abdominal pain; 143 were treated with GM and 133 were in the control group. The Q test of heterogeneity of effect sizes was significant ($\chi^2 = 11.95$, df = 4; $P = 0.02$). Although post-ERCP abdominal pain was noted in 11.1% of the patients in the GM group versus 12.1% in the placebo group, the results of meta-analysis showed that post-ERCP there was no significant association between the use of GM and the occurrence of abdominal pain as compared with placebo control (DL random-effect pooled OR = 0.78 [95% CI, 0.49–1.25]; $P = 0.30$) (**Figure 2, Table III**).

SENSITIVITY ANALYSIS

Sensitivity analysis of these trials was performed using 3 independent exclusion methods. We excluded the trials in which the allocation concealment was inadequate or unclear; those that were published as abstracts; and those that had a Jadad score <3.

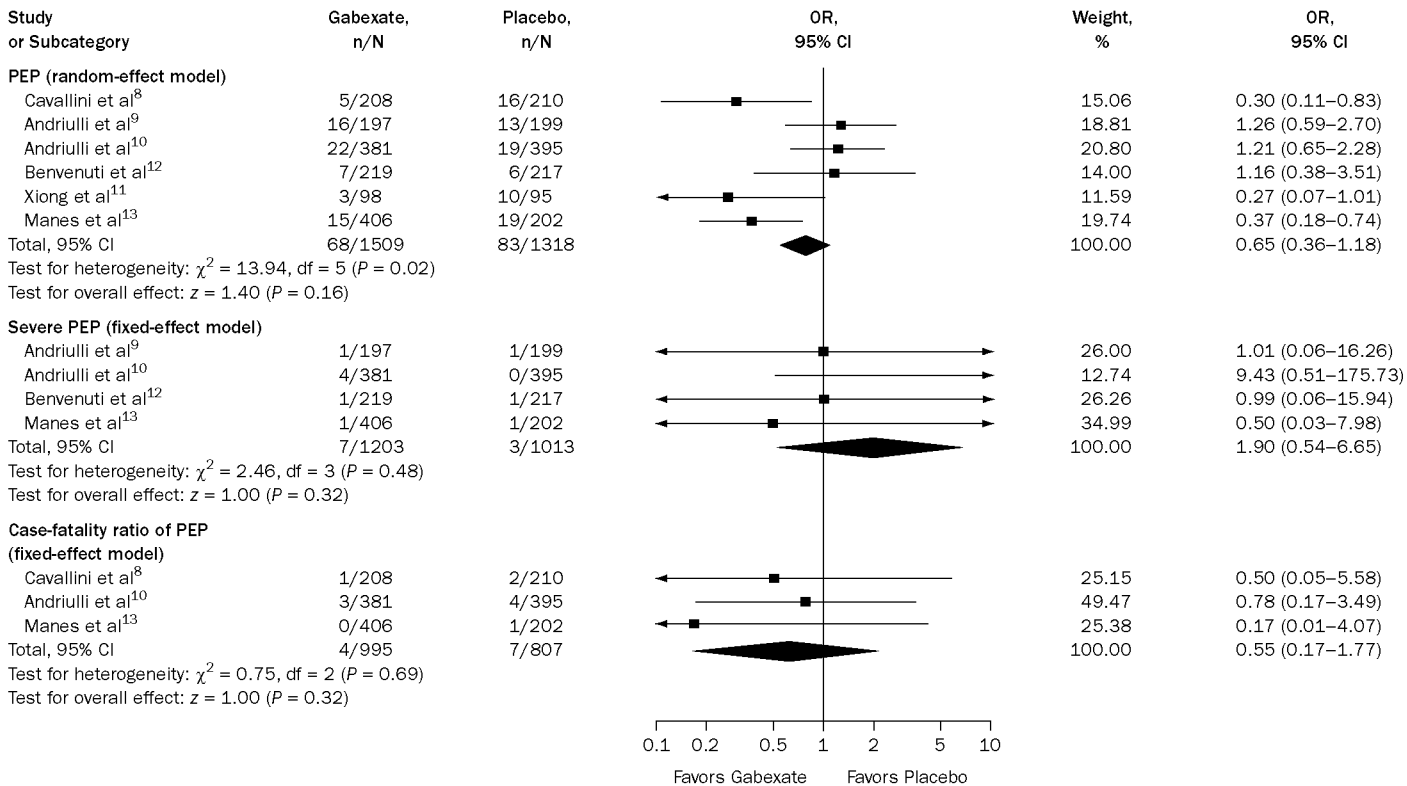

Figure 2. Forest plot illustrating results of the meta-analysis comparing gabexate mesilate with placebo. OR = odds ratio; PEP = post-endoscopic retrograde cholangiopancreatography pancreatitis; ERCP = endoscopic retrograde cholangiopancreatography; df = degree of freedom.

(continued)

Study or Subcategory	Gabexate, n/N	Placebo, n/N	OR, 95% CI	Weight, %	OR, 95% CI
Post-ERCP hyperamylasemia (fixed-effect model)					
Benini et al[7]	1/28	4/28		1.49	0.22 (0.02–2.13)
Cavallini et al[8]	134/208	142/210		19.39	0.87 (0.58–1.30)
Andriulli et al[9]	48/197	52/199		15.09	0.91 (0.58–1.43)
Andriulli et al[10]	120/381	129/395		33.46	0.95 (0.70–1.28)
Xiong et al[11]	33/98	42/95		10.91	0.64 (0.36–1.15)
Manes et al[13]	96/406	50/202		19.66	0.94 (0.64–1.39)
Total, 95% CI	432/1318	419/1129		100.00	0.88 (0.74–1.05)
Test for heterogeneity: $\chi^2 = 2.94$, df = 5 ($P = 0.71$)					
Test for overall effect: $z = 1.40$ ($P = 0.16$)					
Post-ERCP abdominal pain (random-effect model)					
Cavallini et al[8]	12/208	29/210		18.01	0.38 (0.19–0.77)
Andriulli et al[9]	27/197	27/199		20.83	1.01 (0.57–1.80)
Andriulli et al[10]	24/381	21/395		20.17	1.20 (0.65–2.19)
Xiong et al[11]	15/98	28/95		17.96	0.43 (0.21–0.88)
Manes et al[13]	65/406	28/202		23.03	1.18 (0.73–1.91)
Total, 95% CI	143/1290	133/1101		100.00	0.78 (0.49–1.25)
Test for heterogeneity: $\chi^2 = 11.95$, df = 4 ($P = 0.02$)					
Test for overall effect: $z = 1.03$ ($P = 0.30$)					

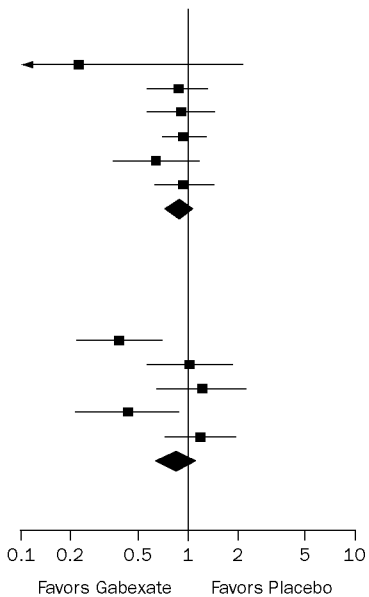

Figure 2 (continued). Forest plot illustrating results of the meta-analysis comparing gabexate mesilate with placebo. OR = odds ratio; PEP = post-endoscopic retrograde cholangiopancreatography pancreatitis; ERCP = endoscopic retrograde cholangiopancreatography; df = degree of freedom.

Table III. Results of the meta-analysis and the sensitivity analysis.

	Method	
Adverse Event	A*	B†
PEP		
N	2827	2391
Pooled OR (95% CI)	0.65 (0.36–1.18)	0.59 (0.30–1.16)
P	0.16	0.13
Severe PEP		
N	2216	1780
Pooled OR (95% CI)	1.90 (0.54–6.65)	2.22 (0.53–9.29)
P	0.32	0.27
Case-fatality ratio of PEP		
N	1802	1802
Pooled OR (95% CI)	0.55 (0.17–1.77)	0.55 (0.17–1.77)
P	0.32	0.32
Post-ERCP hyperamylasemia		
N	2447	2391
Pooled OR (95% CI)	0.88 (0.74–1.05)	0.89 (0.75–1.07)
P	0.16	0.20
Post-ERCP abdominal pain		
N	2391	2391
Pooled OR (95% CI)	0.78 (0.49–1.25)	0.78 (0.49–1.25)
P	0.30	0.30

PEP = post-endoscopic retrograde cholangiopancreatography pancreatitis; OR = odds ratio; ERCP = endoscopic retrograde cholangiopancreatography.
*Meta-analysis including all trials.[7–13]
†Sensitivity analysis in which the trials with inadequate or unclear allocation concealment, the trials that were published in abstract form, and the trials in which the Jadad score was <3 were excluded; all 3 methods excluded the same trials.[7,12]

The results of the 3 methods were the same; each method excluded the same 2 trials.[7,12] The overall estimates and the 95% CIs were similar between the meta-analysis and the sensitivity analysis (**Table III**).

PUBLICATION BIAS

Publication bias was assessed for all pooled ORs with 95% CIs using the Begg test.[27,28] The results are presented as a funnel plot of the treatment effects estimated from individual studies plotted on the horizontal axis (OR) against the SE of the estimate shown on the vertical axis (SE [log OR]) (**Figure 4**). All of the studies lay within the 95% CI and were uniformly distributed around the vertical axis, suggesting a low likelihood of publication bias.

Study or Subcategory	Gabexate, n/N	Placebo, n/N	OR, 95% CI	Weight, %	OR, 95% CI
PEP (random-effect model)					
Cavallini et al[8]	5/208	16/210		21.91	0.30 (0.11–0.83)
Andriulli et al[10]	22/381	19/395		29.50	1.21 (0.65–2.28)
Benvenuti et al[12]	7/219	6/217		20.46	1.16 (0.38–3.51)
Manes et al[13]	15/406	19/202		28.13	0.37 (0.18–0.74)
Total (95% CI)	49/1214	60/1024		100.00	0.63 (0.30–1.33)
Test for heterogeneity: $\chi^2 = 9.53$, df = 3 ($P = 0.02$)					
Test for overall effect: $z = 1.21$ ($P = 0.23$)					
Severe PEP (fixed-effect model)					
Andriulli et al[10]	4/381	0/395		17.22	9.43 (0.51–175.73)
Benvenuti et al[12]	1/219	1/217		35.49	0.99 (0.06–15.94)
Manes et al[13]	1/406	1/202		47.29	0.50 (0.03–7.98)
Total (95% CI)	6/1006	2/814		100.00	2.21 (0.53–9.23)
Test for heterogeneity: $\chi^2 = 2.38$, df = 2 ($P = 0.30$)					
Test for overall effect: $z = 1.09$ ($P = 0.28$)					
Case-fatality ratio of PEP (fixed-effect model)					
Cavallini et al[8]	1/208	2/210		25.15	0.50 (0.05–5.58)
Andriulli et al[10]	3/381	4/395		49.47	0.78 (0.17–3.49)
Manes et al[13]	0/406	1/202		25.38	0.17 (0.01–4.07)
Total (95% CI)	4/995	7/807		100.00	0.55 (0.17–1.77)
Test for heterogeneity: $\chi^2 = 0.75$, df = 2 ($P = 0.69$)					
Test for overall effect: $z = 1.00$ ($P = 0.32$)					
Post-ERCP hyperamylasemia (fixed-effect model)					
Cavallini et al[8]	134/208	142/210		26.74	0.87 (0.58–1.30)
Andriulli et al[10]	120/381	129/395		46.15	0.95 (0.70–1.28)
Manes et al[13]	96/406	50/202		27.11	0.94 (0.64–1.39)
Total (95% CI)	350/995	321/807		100.00	0.92 (0.75–1.14)
Test for heterogeneity: $\chi^2 = 0.13$, df = 2 ($P = 0.94$)					
Test for overall effect: $z = 0.75$ ($P = 0.46$)					
Post-ERCP abdominal pain (random-effect model)					
Cavallini et al[8]	12/208	29/210		30.24	0.38 (0.19–0.77)
Andriulli et al[10]	24/381	21/395		33.09	1.20 (0.65–2.19)
Manes et al[13]	65/406	28/202		36.68	1.18 (0.73–1.91)
Total (95% CI)	101/995	78/807		100.00	0.84 (0.43–1.66)
Test for heterogeneity: $\chi^2 = 7.82$, df = 2 ($P = 0.02$)					
Test for overall effect: $z = 0.49$ ($P = 0.62$)					

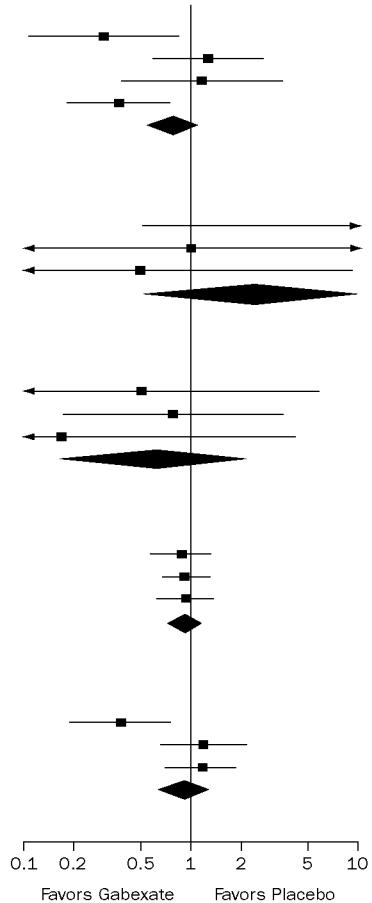

Figure 3A. Subgroup analysis for group 1 (duration of treatment ≥6 hours). OR = odds ratio; PEP = post-endoscopic retrograde cholangiopancreatography pancreatitis; df = degree of freedom; ERCP = endoscopic retrograde cholangiopancreatography.

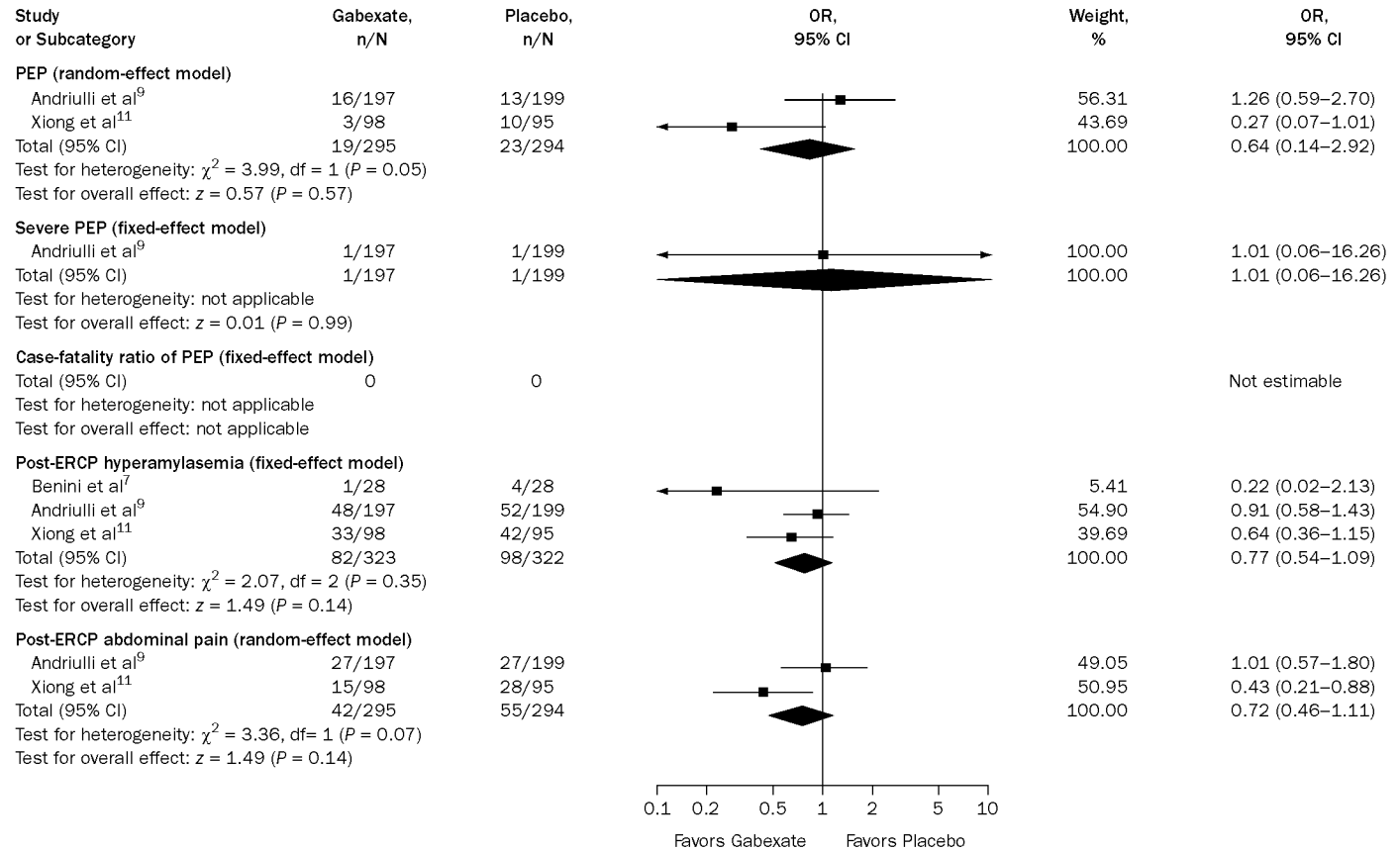

Figure 3B. Subgroup analysis for group 2 (duration of treatment <6 hours). OR = odds ratio; PEP = post-endoscopic retrograde cholangiopancreatography pancreatitis; df = degree of freedom; ERCP = endoscopic retrograde cholangiopancreatography.

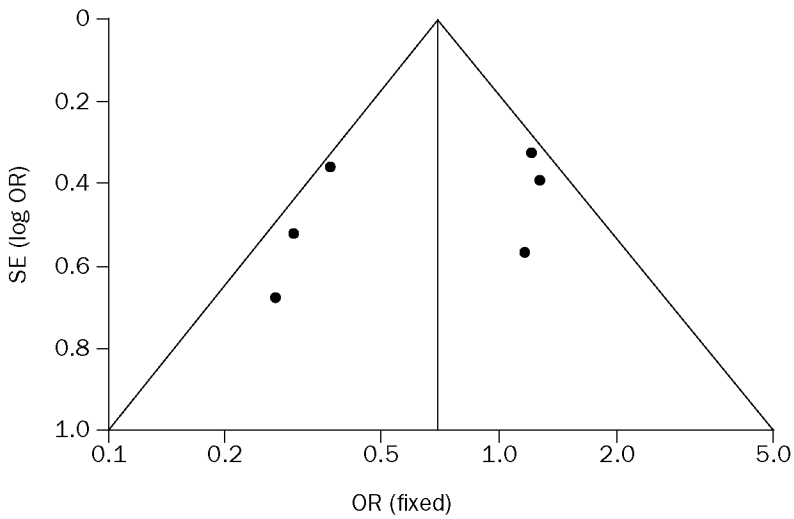

Figure 4. Funnel plot illustrating meta-analysis of the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis. SE (log OR) = standard error of the estimate; OR = odds ratio.

ADVERSE EVENTS

The AEs of GM were evaluated in the current study. Three trials found various AEs of GM.[8,11,13] In 1 trial,[8] 8 patients experienced AEs (2 in the GM group and 6 in the placebo group). In the GM group, 1 patient had mild nausea and vomiting and 1 had self-limiting dyspnea and a hypertensive crisis. The 6 patients in the placebo group experienced the following AEs: nausea (2 patients), vomiting (3), hypotension (1), sweating (1), and fatigue (1). All of the AEs resolved without treatment. In the study by Xiong et al,[11] symptoms (eg, bloating, nausea, vomiting, fever) were reported in both groups, with no statistically significant difference between the GM group and the placebo group. Manes et al[13] found no AEs in the GM group and concluded that there was no significant correlation between the use of GM and AEs.

DISCUSSION

Acute pancreatitis, the most frequent and serious complication of ERCP, cannot always be avoided.[4] A drug that can prevent pancreatic injury after ERCP remains an unmet clinical need. Most of the ongoing attempts to minimize the occurrence and severity of PEP have been disappointing. Studies with calcitonin, aprotonin, nifedipine, and glucagon found no decrease in post-ERCP hyperamylasemia or pancreatitis.[29–32] Several studies of the long-acting somatostatin analogue octreotide have produced conflicting results.[33–36] Meta-analyses of all prospective RCTs of corticosteroids and allopurinol have also found that these agents did not prevent pancreatic injury after ERCP.[37,38] Murray et al[39] found that diclofenac 100 mg administered as a suppository immediately after ERCP reduced the incidence of PEP (24 patients de-

veloped PEP, of whom 7 received rectal diclofenac and 17 received placebo [$P < 0.05$]). However, this finding has not been confirmed since no additional studies of this diclofenac regimen have been conducted.

Acute pancreatitis is an inflammatory process within the pancreas that may have systemic manifestations. The triggering event is thought to be the premature activation of proteolytic enzymes, resulting in cellular injury and autodigestion of pancreatic tissue.[40] As a protease inhibitor and a highly diffusible molecule, GM may be protective against intracellular trypsin activation. Once trypsin is activated, GM may also play a protective role by inhibiting activation of the other proteases.[41]

The activation of proteinase is one of the most important pathogeneses of pancreatic injury after ERCP. The efficacy of GM in preventing PEP was demonstrated in previous studies.[3,8,13] In the first large-scale prospective study, which was conducted in Italy, Cavallini et al[8] found that GM significantly reduced pancreatitis after ERCP compared with placebo (the occurrences of PEP were 2% and 8%, respectively; $P < 0.05$). Manes et al[13] reported that the decrease in the incidence of PEP when GM was administered immediately after ERCP was similar to the decrease that was achieved by pre-ERCP administration. The incidence of PEP was 3.9% in the preprocedure administration group, 3.4% in the postprocedure administration group, and 9.4% in the placebo group (both, $P < 0.01$ vs placebo). A meta-analysis[3] published in 2000 that included 6 studies (one of which was included in the present study[7]) also reported that patients who received GM after ERCP had a significantly lower incidence of PEP than the control group (1.6% vs 6.5%, respectively; $P < 0.001$). Favorable conclusions concerning the use of GM for the prevention of post-ERCP hyperamylasemia and post-ERCP abdominal pain were also drawn in this meta-analysis.

This updated meta-analysis of 7 prospective RCTs[7–13] that were published in different languages evaluated the effectiveness and tolerability of GM in the prevention of PEP. We found that the occurrences of PEP, post-ERCP hyperamylasemia, post-ERCP abdominal pain, and the case-fatality ratio of PEP did not correlate with the prophylactic use of GM. The results of the meta-analysis indicated that GM did not prevent pancreatic injury after ERCP. Moreover, there was no association between the prophylactic use of GM and AEs, although AEs were reported in 3 studies.[8,11,13] We also evaluated the quality of these RCTs using the Jadad score,[14] and found that the results of meta-analysis were consistent with the sensitivity analysis. Furthermore, the results were also similar to the outcomes of the meta-analysis that Andriulli et al[2] updated in 2007. The present meta-analysis and that of Andriulli et al differ in that ours included 3 additional RCTs, which covered more risk factors for PEP. Second, our study included patients with high, average, and low risk for PEP, while the other meta-analysis was limited to patients with average PEP risk. Therefore, the results of the effectiveness and tolerability of GM in the prophylaxis of PEP were supported.

However, the differing conclusions between the present study and the earlier study by Andriulli et al[3] might be due to the inclusion and exclusion criteria. In the present study, we included only clinical RCTs, while the other study included clinical controlled trials and relied heavily on the conclusion of one clinical controlled trial[8] because the other trials[7,19–21] had small sample sizes. In addition, discordance among the

large RCTs was recognized and ascribed to the heterogeneity of the study populations and to differences in experimental design (eg, patient selection, indication for ERCP, therapeutic maneuvers performed, and different routes of drug administration).[42] Patient heterogeneity and differences in experimental design could explain the divergence of the results. The duration of GM treatment might also have contributed to the different outcomes; however, in the current study, subgroup analyses were conducted after the studies were grouped by the drug administration schedule. GM was found to be ineffective when administered either as a short-term (<6 hours) or a long-term (≥6 hours) infusion (**Figures 3A** and **3B**). This result was also in accordance with the findings of Masci et al.[22]

CONCLUSIONS

No beneficial effects of GM on acute pancreatitis, the PEP death rate, or post-ERCP abdominal pain or hyperamylasemia were found; therefore, GM cannot be recommended for the prophylaxis of PEP.

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