Incidence, severity, and mortality of post-ERCP pancreatitis: a systematic review by using randomized, controlled trials

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Background: Data regarding the incidence and severity of post-ERCP pancreatitis (PEP) are primarily from nonrandomized studies.

Objective: To determine the incidence, severity, and mortality of PEP from a systematic review of the placebo or no-stent arms of randomized, controlled trials (RCTs).

Design: MEDLINE, EMBASE, and Cochrane databases were searched to identify RCTs evaluating the efficacy of drugs and/or pancreatic stents to prevent PEP.

Setting: Systematic review of patients enrolled in RCTs evaluating agents for PEP prophylaxis.

Patients: Patients in the placebo or no-stent arms of the RCTs

Intervention: ERCP.

Main Outcome Measurements: Incidence, severity, and mortality of PEP.

Results: There were 108 RCTs with 13,296 patients in the placebo or no-stent arms. Overall, the PEP incidence was 9.7% and the mortality rate was 0.7%. Severity of PEP was reported for 8857 patients: 5.7%, 2.6%, and 0.5% of cases were mild, moderate, and severe, respectively. The incidence of PEP in 2345 high-risk patients was 14.7% and the severity of PEP was mild, moderate, and severe in 8.6%, 3.9%, and 0.8%, respectively, with a 0.2% mortality rate. The incidence of PEP was 13% in North American RCTs compared with 8.4% in European and 9.9% in Asian RCTs. ERCPs conducted before and after 2000 had a PEP incidence of 7.7% and 10%, respectively.

Limitations: Difference in PEP risk among patients in the included RCTs.

Conclusion: The incidence of PEP and severe PEP is similar in high-risk patients and the overall cohort. Discrepancies in the incidence of PEP across geographic regions require further study. (Gastrointest Endosc 2015;81:143-9.)

ERCP was first introduced in 1968 as a diagnostic procedure. The number of ERCPs performed increased rapidly as the procedure evolved to include therapy for pancreaticobiliary disorders. However, the increased use of diagnostic MRCP and EUS resulted in a 16% decrease in the number of ERCPs performed from 2000 to 2009. Despite the decrease, it is estimated that approximately 700,000 ERCPs are performed annually in the United States

Abbreviations: PEP, post-ERCP pancreatitis; RCT, randomized, controlled trial; SOD, sphincter of Oddi dysfunction.

DISCLOSURE: *The following authors disclosed financial relationships relevant to this article: Dr Khashab is a consultant for Olympus and Boston Scientific. Dr Kalloo is an equity holder in Apollo Endosurgery. Dr Singh is a consultant for Santarus, D-Pharm, Abbvie, and Boston Scientific. All other authors disclosed no financial relationships relevant to this article.*

0016-5107/$36.00
http://dx.doi.org/10.1016/j.gie.2014.06.045

Received December 26, 2013. Accepted June 26, 2014.

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Presented as a poster in the ASGE: ERCP-2 session at Digestive Disease Week, May 20, 2013, Orlando, Florida (Gastrointest Endosc 2013;77:AB392).

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alone.[1] Given the high volume of ERCPs, the social and economic impact of post-ERCP pancreatitis (PEP) is substantial. Assuming a 5% incidence of PEP, there are approximately 35,000 cases of PEP annually in the United States with an estimated cost of $199,500,000.[2]

Although there are many studies detailing patient and procedural risk factors for the development of PEP, there are few studies that report the incidence, severity, and mortality of PEP. Previous studies have reported wide discrepancies in the incidence of PEP, ranging anywhere from 1% to 40%, with an incidence as high as 67% in high-risk patients.[3,4] PEP can range in severity from mild to severe, which includes fatal cases. The incidence of severe PEP has been reported to range anywhere from 0.13% to 12.6%.[3,5-9] The wide variation in the incidence of PEP and severe PEP is likely due to the fact that most previous studies are retrospective; furthermore, studies predating the consensus definition used different definitions for PEP and severe PEP. Prospective trials are less likely to underestimate the incidence of PEP because of the use of uniform definitions as well as closer follow-up and frequent contact with patients after ERCP.[10] Accurate figures for the incidence, severity, and mortality of PEP would help to guide the informed consent process for patients before ERCP.

The aim of this study was to determine the incidence, severity, and mortality of PEP in patients in non–risk-stratified and high-risk RCTs, based on a systemic review of the placebo or no-stent arms of RCTs.

METHODS

Medical literature search

This systematic review was conducted by using principles outlined in Cochrane Guidelines[11] and Agency for Healthcare Research and Quality Methods Guide[12] and reported in accordance with the PRISMA statement.[13] The PubMed, Embase, and Cochrane databases were searched by using a combination of MeSH terms, Emtree terms, and key words to identify RCTs evaluating the efficacy of drugs and pancreatic stents to prevent PEP (Appendix 1, available online at www.giejournal.org). The search had no language restrictions and included the period of inception of each database to June 30, 2013. Bibliographies of relevant systematic reviews in the *New England Journal of Medicine*, *Annals of Internal Medicine*, *Gastroenterology*, *Gastrointestinal Endoscopy*, *American Journal of Gastroenterology*, *Clinical Gastroenterology and Hepatology*, *Endoscopy*, *Gut*, *Pancreas*, and *Pancreatology* published between January 2012 and June 2013 were also hand searched to identify additional trials for inclusion.

Eligibility criteria

RCTs that evaluated patients undergoing ERCP, compared a drug and/or pancreatic stent with placebo or no stent to prevent PEP, and reported the incidence of PEP as an outcome were included. The placebo or no-stent arms were selected for this study to avoid the influence of an intervention on the development of PEP. Studies in which the placebo or no-stent arm included an agent to prevent or reduce the risk of PEP were excluded. Full-text publications published in any language and performed in any setting were included.

Article review and data abstraction

A systematic approach was used in the review of the search results, which was performed by 2 separate authors (B.K., V.A.). Two reviewers independently reviewed titles, abstracts, and full texts. In the title stage, any study having a title not related to ERCP was excluded if agreed on by both reviewers. During the abstract review, any trial that evaluated a drug or prophylactic stent placement in the setting of ERCP was included. During the full-text review, RCTs that reported on PEP after ERCP were eligible for data extraction. During the abstract and full-text reviews, conflicts were resolved by consensus among reviewers.

Trials that met the eligibility criteria were extracted by 1 reviewer with the extracted data reviewed and confirmed by a second reviewer. For studies that were not available in English, we recruited native speakers of the language with a scientific background to assist with determining trial eligibility and data abstraction. No trial was excluded for not being able to find a translator. We assessed study quality in terms of random sequence generation, allocation concealment, blinding of the patients and investigators, and a summary of assessment of bias across the study by using the Cochrane Collaboration's tool for assessing risk of bias in RCTs.[14]

Data abstraction from the placebo and no-stent arms was carried out by using pilot-tested data extraction sheets containing all the variables of interest including methodology, patient and study center characteristics, and outcomes.

Definitions

PEP was defined by the consensus criteria as a "clinical syndrome consistent with pancreatitis with an amylase level at least 3 times normal more than 24 hours after the procedure and requiring more than 1 night of hospitalization." The severity of PEP was also defined according to the consensus criteria: mild if length of hospitalization related to PEP was 2 to 3 days, moderate if it was 4 to 10 days, and severe if it was longer than 10 days and/or with the presence of pseudocyst, pancreatic necrosis, need for percutaneous drainage or surgery, or death.[15]

High-risk patients were identified by study authors. They included patients who met 1 or more of the following patient factors: a clinical suspicion of sphincter of Oddi dysfunction (SOD), a history of PEP, younger than age 50 years of age, female sex, and more than 2 episodes of pancreatitis. Procedural factors that placed patients at