Early Endoscopic Retrograde Cholangiopancreatography Versus Conservative Treatment in Patients With Acute Biliary Pancreatitis

Systematic Review and Meta-analysis of Randomized Controlled Trials

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Objectives: The aim of the study was to evaluate the role of early endoscopic retrograde cholangiopancreatography (ERCP) in the treatment of acute biliary pancreatitis, in comparison with conservative treatment.

Methods: Systematic review via databases (MEDLINE [PubMed], Latin-American and Caribbean Health Sciences Literature database, Embase, Cochrane Central, and the [Brazilian] Regional Library of Medicine) is conducted. We analyzed 10 randomized controlled trials (1091 patients). Outcomes were the following: local and systemic adverse events; acute cholangitis; death; length of hospital stay; cost; abdominal pain; and time to a reduction in body temperature. For the meta-analysis, we used risk difference (RD) and mean with standard deviation as measures of variability.

Results: There was a statistically significant difference between the patients submitted to ERCP in terms of the following: local adverse events (RD, 0.74; 95% confidence interval [CI], 0.55–0.99), time to pain relief and time to a reduction in axillary temperature (RD, −5.01; 95% CI, −6.98 to −3.04, and RD, −1.70; 95 CI%, −2.33 to −1.08, respectively). Patients undergoing ERCP spent less time in hospital (RD, −11.04; 95% CI, −15.15 to −6.93). Cost was lower in the group treated with ERCP.

Conclusions: Early ERCP decreases local adverse events, shortening the time to pain relief, to a reduction in axillary temperature, hospital stays, and cost in patients with acute biliary pancreatitis.

Key Words: endoscopy, digestive system, pancreatitis, cholangiopancreatography, endoscopic retrograde, meta-analysis, randomized controlled trial

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Acute pancreatitis is an inflammatory disease involving the pancreatic parenchyma and the peripancreatic tissues. In cases that are more severe, distant organs, such as the kidneys, lungs, and heart, can be affected. The incidence of acute pancreatitis ranges from 5.4 to 79.8/100,000 population, depending on the region and population studied.[1]

The main cause of acute pancreatitis is the presence of stones in the gallbladder or bile duct. The migration of gallstones to the main biliary tract can cause temporary obstruction of the major duodenal papilla, and such obstruction is responsible not only for triggering acute pancreatitis but also for aggravating its evolution. In 1974, Acosta et al[2] stated that in acute biliary pancreatitis, most gallstones migrate rapidly from the main biliary tract, passing through the duodenal papilla, and can be found in the feces. The authors concluded that gallstone impaction is typically a transitory phenomenon.

Approximately 80% of patients who develop acute biliary pancreatitis present with a mild, self-limited form of the disease, in which the inflammatory disease regresses, with complete recovery of pancreatic function, within a few days. However, some patients develop the severe form, which is associated with multiple organ failure.[1] This severe presentation of pancreatitis should be considered a multisystemic disease, characterized by an inflammatory response syndrome with multiple organ dysfunction. The severe form, which typically develops within a few days after the onset of symptoms, has a mortality of approximately 20%.[3]

Because of the difficulty of obtaining an accurate prognosis of acute pancreatitis on the basis of clinical and biochemical parameters, various classifications and severity scales have been used:

- Ranson score[4]—The Ranson score is based on 11 clinical and biochemical criteria, of which 5 are evaluated at admission and 6 are evaluated within the first 48 hours thereafter. Patients who meet 3 or more of those criteria are classified as having severe pancreatitis.
- Acute Physiology and Chronic Health Evaluation II (APACHE II)[4]—The APACHE II is still one of the most widely used methods for stratifying the severity and mortality risk of acute pancreatitis. It uses 12 evaluation parameters, together with extra scores based on patient age and the presence of chronic diseases. Despite the large number of items that must be evaluated, the APACHE II score can be calculated within the first 24 hours after hospital admission and on a daily basis thereafter, to analyze the evolution of the patient.
- Osborne criteria[5]—The Osborne criteria are described as a prognostic factor classification system in which the age factor is removed and serum transaminases levels are considered of prognostic significance only if they are greater than 200 U/L within the first 48 hours after admission.
- Glasgow score[4]—Based on the Ranson score, the Glasgow score, which was first proposed by Imrie in 1984, links the specific clinical, biochemical, and radiological markers of acute pancreatitis with the severity of the condition and with its expected outcome. The Glasgow score can be calculated at any time within the first 48 hours of hospitalization and measures only 8 parameters. In the presence of 3 or more criteria at 48 hours, the presence of a severe case of acute pancreatitis is very likely.
- Atlanta classification[6]—The Atlanta classification combines clinical and tomographic imaging analyses in the initial phases and evolution of acute pancreatitis.

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The Atlanta classification, as updated in 2012,[6] is currently the most widely used system of classifying acute pancreatitis. The Atlanta classification is important because it allows the early identification of patients who are at risk for evolving to the severe form and who therefore require more intensive treatment.

The following groups have been defined:

- moderate acute pancreatitis
- moderately severe acute pancreatitis
- severe acute pancreatitis

The main parameters employed to distinguish each group are as follows:

- Transient organ failure (resolves within 48 hours)
- Persistent organ failure
- Local adverse events -
  - Pancreatic fluid collection
  - Pancreatic necrotic collection
- Systemic adverse events

In moderate acute pancreatitis, there is no organ failure or adverse events. Moderately severe acute pancreatitis is characterized by transient organ failure, with or without local or systemic adverse events. Severe acute pancreatitis is characterized by persistent organ failure. The organ failure can be single or multiple. According to the Atlanta consensus, the estimated mortality risk in the first days of evolution in patients with persistent organ failure is 36% to 50%.[6]

Currently, the recommended approach to acute pancreatitis is conservative treatment. Pain control, vigorous intravenous hydration, electrolyte replacement, and early oral nutrition are also recommended.[7] In some patients with recurrent nausea and vomiting, nasogastric decompression can improve patient comfort.[8]

There is no consensus regarding the use of prophylactic antibiotic therapy in acute pancreatitis, even in patients with severe acute pancreatitis. Although some randomized studies have shown the benefit of early initiation of antibiotic therapy, a recent double-blind study found that it provided no benefit in relation to the progression to infected pancreatic necrosis.[8]

Early decompression of the biliary tract through endoscopic retrograde cholangiopancreatography (ERCP), with papillotomy and removal of the stones can improve the course of the disease. However, this treatment can have adverse events such as worsening of the pancreatitis, perforation, and bleeding, all of which can increase morbidity and mortality.[9]

In the literature, there is a consensus that ERCP is indicated for patients with acute biliary pancreatitis accompanied by persistent cholangitis, with or without cholestasis.[10] However, the role of routine early ERCP in the treatment of acute biliary pancreatitis is still controversial.

Studies comparing the use of early ERCP with that of conservative clinical treatment in the initial approach to biliary acute pancreatitis in reducing morbidity and mortality have produced divergent or inconclusive results.[11] The following factors have hindered the interpretation of those results: the inclusion of heterogeneous populations; variations in the duration of the intervention; and the exclusion of patients with biliary tract obstruction, who would benefit from the procedure.[11]

In the literature, there are no concrete data showing real benefits of the early use of ERCP in the treatment of patients with acute biliary pancreatitis. Therefore, the aim of this meta-analysis was to perform a critical evaluation of the data available in the literature, to determine, in a categorical manner, whether and when ERCP should be performed in such patients. We also compared conservative treatment and early ERCP in terms of their ability to prevent or ameliorate the following: local and systemic adverse events; development of acute cholangitis; time to pain reduction; time to a reduction in axillary temperature; length of hospital stay; mortality; and total cost.

MATERIALS AND METHODS

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12] The review was registered with the International Prospective Register of Systematic Reviews under the identifier number CRD42016047001.[13]

Eligibility Criteria

Articles were considered eligible for inclusion in the review if they were randomized clinical trials evaluating the role of early ERCP in the treatment of acute biliary pancreatitis compared with conservative clinical treatment; had samples including patients 18 years or older who had been diagnosed with acute biliary pancreatitis; had a treatment arm involving the use of ERCP within the first 72 hours after admission (intervention arm) and a conservative treatment arm (control arm); did not include patients with pancreatitis of other causes; were available as full-text versions; and evaluated the following: local adverse events, including pancreatic necrosis, pancreatic abscess, and pancreatic pseudocyst; systemic adverse events, including respiratory failure, renal failure, cardiogenic shock, and disseminated intravascular coagulation (DIC); acute cholangitis; length of hospital stay; time to a reduction in abdominal pain; and time to a reduction in body temperature, death; and total cost. We did not impose any restrictions in terms of the language or date of publication.

Databases

We searched the following databases: MEDLINE (PubMed); Latin-American and Caribbean Health Sciences Literature; Embase; the Cochrane Central Register of Controlled Trials; and the (Brazilian) Regional Library of Medicine. We also conducted hand searches of the bibliographies of the selected studies and of previous systematic reviews evaluating the role of ERCP in acute pancreatitis.

Search Strategy

To perform the PubMed search, we used the search terms retrograde cholangiopancreatography, endoscopic cholangiopancreatography, retrograde endoscopy, endoscopic retrograde cholangiopancreatography, and ERCP, combined with pancreatitis through the Boolean operator "AND" ([Retrograde Cholangiopancreatography, Endoscopic OR Cholangiopancreatographies, Endoscopic Retrograde OR Endoscopic Retrograde Cholangiopancreatographies OR Retrograde Cholangiopancreatographies, Endoscopic OR Endoscopic Retrograde Cholangiopancreatography OR ERCP] AND Pancreatitis). The final step was the hand search, in which we reviewed the bibliographies to identify other RCTs.

Selection of Studies

Two reviewers, working independently, assessed the eligibility of articles and selected those that met the criteria. Disagreements between the two reviewers were resolved by consensus.

Risk of Bias in the Studies

The selected studies were classified by methodological quality, according to the descriptive risk of bias table for

therapeutic studies, which considers the question to be investigated and the form of randomization/allocation, as well as the blinding, losses, prognostic factors, outcome measures, and intention-to-treat analysis.

We also employed the Jadad score,[14] which considers randomization, masking (blinding of patients and investigators), and accountability (reporting of exclusions and losses).

Data Analysis

Data were extracted on an intention-to-treat basis. For each outcome measure, we considered the absolute risk difference (RD), with a 95% confidence interval (CI). The level of statistical significance was set at a P value f less than 0.05. We calculated the differences between the outcome measures using the RDs for dichotomous variables and the mean differences for continuous variables.

We analyzed the data with Review Manager software, Version 5.3 (RevMan 5.3; Cochrane Collaboration, Oxford, United Kingdom), using the Mantel-Haenszel method for categorical variables and the inverse variance (IV) method for continuous variables. We considered fixed and random effects.

We used the heterogeneity statistic I^2, with a cut-off point of 50%. When a value of 50% or more was found, we performed sensitivity analysis to identify any studies with a higher probability of a publication bias (outliers), using a funnel plot with a fixed-effects model. The objective of the sensitivity analysis is to identify publication bias that explains the heterogeneity observed with Egger test (funnel plot). When there was no publication bias, the random effect was used for the analysis. The results are shown in a forest plot.[15,16]

Outcome Measures

The following outcome measures were analyzed according to the data presented in each study: local adverse events, including pancreatic necrosis, pancreatic abscess, and pancreatic pseudocyst; systemic adverse events, including respiratory failure, renal failure, cardiogenic shock, and DIC; acute cholangitis; death; length of hospital stay; cost; time to a reduction in abdominal pain; and time to a reduction in body temperature.

RESULTS

A total of 5915 articles were retrieved (Fig. 1), and 14 articles were selected: 13 RCTs and 1 observational study. In our ancillary

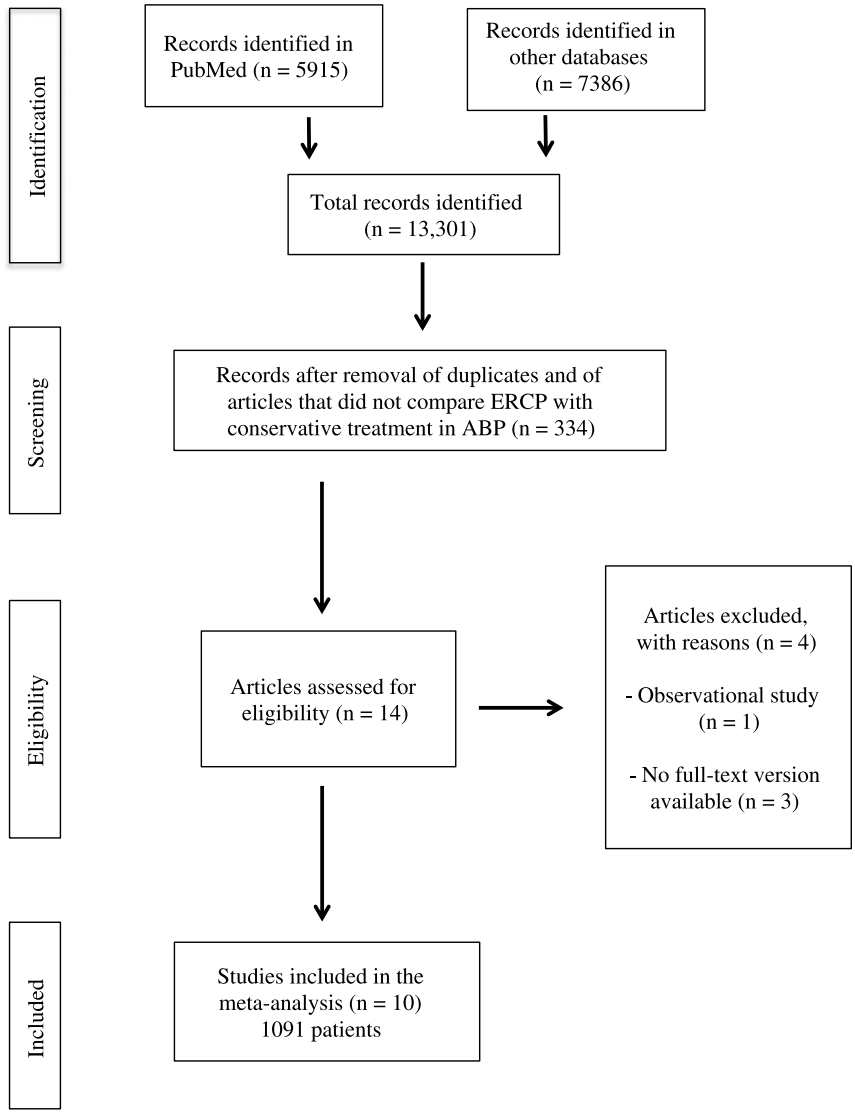

FIGURE 1. Selection of studies for inclusion in the meta-analysis. ABP indicates acute biliary pancreatitis.

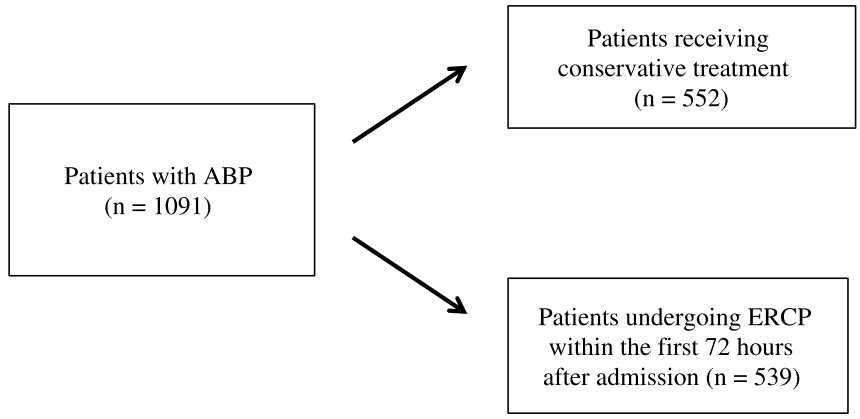

FIGURE 2. Collective sample and treatment arms of the studies included in the meta-analysis. ABP indicates acute biliary pancreatitis.

searches, we found 116 articles related to the theme in the Latin-American and Caribbean Health Sciences Literature database, compared with 2220 in Embase, 10 in the Cochrane Central Register of Controlled Trials, and 5040 in the (Brazilian) Regional Library of Medicine. However, there was no increase in relation to the number found in the PubMed search, because those studies were not RCTs.

After excluding duplicates and reading the titles, we selected 334 articles that evaluated the role of ERCP in the treatment of acute biliary pancreatitis. Of those, only 14 compared the use of ERCP with that of conservative treatment. We excluded 1 study because it was observational and another 3 studies because only the abstract was available.[17–20] Therefore, the final selection comprised 10 RCTs. The studies selected had been published between 1986 and 2012. All 10 RCTs evaluated the early use of ERCP (within the first 72 hours after admission). However, 1 trial evaluated its use within the first 48 hours and 2 evaluated its use within the first 24 hours.

The 10 RCTs selected collectively evaluated 1091 patients with acute biliary pancreatitis, of whom 539 underwent ERCP and 552 received conservative treatment only (Fig. 2). Although all of the patients evaluated had acute biliary pancreatitis, the inclusion and exclusion criteria differed across the trials. The study conducted by Fan et al[21] in 1993 was more comprehensive, including not only cases of acute biliary pancreatitis but also cases of acute pancreatitis of other causes. Some of the studies excluded patients with cholangitis,[11,22] pregnant patients,[3,11,22–25] or patients with severe comorbidities that made it impossible to undergo ERCP.[11,24]

In the collective study sample, 70 patients presented with pancreatic necrosis: 34 in the early ERCP group and 36 in the conservative treatment group. However, pancreatic necrosis was evaluated in only 6 of the RCTs evaluated.[11,21–24,26] In terms of the prevalence of pancreatic necrosis, we found no significant difference between the 2 treatment modalities (RD, −0.01; 95% CI, −0.05 to 0.03), although the meta-analysis showed high heterogeneity among them (I^2 = 50%). In the sensitivity analysis, using a funnel plot (Fig. 3), we identified 1 outlier study.[22] The objective of the sensitivity analysis is to identify publication bias that explains the heterogeneity observed with Egger test (funnel plot). After the outlier study had been excluded from the analysis (Fig. 4), no statistical difference was identified between ERCP and conservative treatment in terms of the occurrence of pancreatic necrosis (RD, 0.01; 95% CI, −0.03 to 0.05). The exclusion of that study also reduced the heterogeneity (I^2 = 0%).

There were 8 studies that evaluated pancreatic pseudocyst as a local adverse event.[11,21–27] Among those studies, there were 50 patients that presented with pancreatic pseudocyst: 19 in the early ERCP group and 31 having been in one of the conservative treatment group. In terms of the prevalence of pancreatic

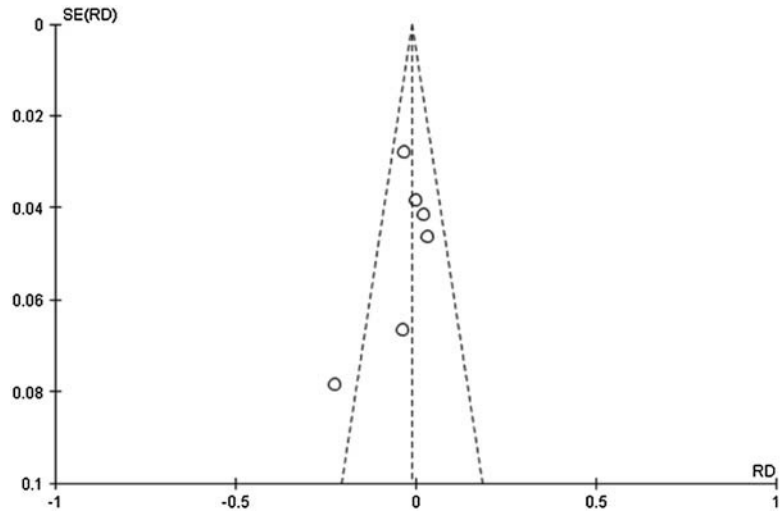

FIGURE 3. Funnel plot for pancreatic necrosis (Egger test).

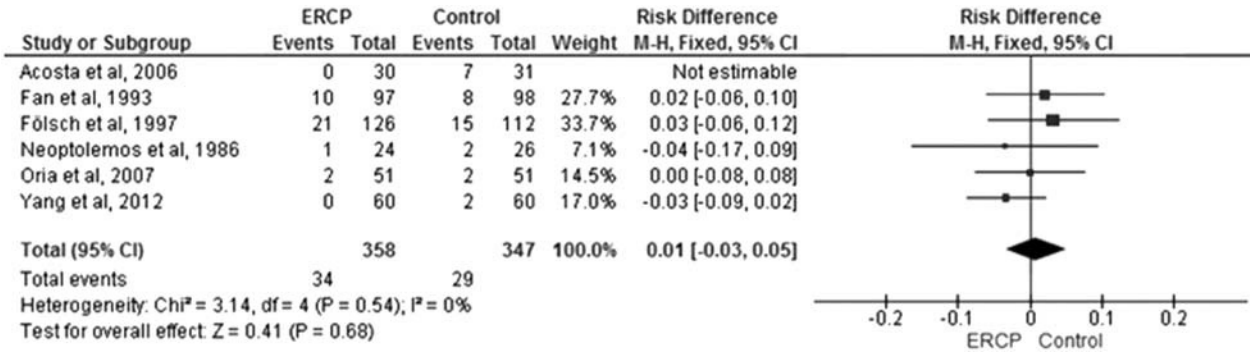

FIGURE 4. Forest plot for pancreatic necrosis (number of events), using a fixed-effects model, with the Mantel-Haenszel (M-H) method. *df* indicates degrees of freedom; I^2, heterogeneity statistic.

pseudocyst, there was no statistical difference between the early ERCP and conservative treatment arms (RD, −0.03; 95% CI, −0.05 to 0.00). The heterogeneity among those studies was relatively low (I^2 = 32%), as can be seen in Supplemental Digital Content 1, http://links.lww.com/MPA/A646.

The occurrence of pancreatic abscess as a local adverse event was evaluated in 5 of the RCTs.[21,23,24,27,28] Among those studies, there were 11 patients that presented with pancreatic abscess, of whom 8 had been treated with early ERCP and 3 had received conservative treatment only. In the meta-analysis of those 5 studies, no statistical difference was found between the ERCP and conservative treatment arms (RD, −0.01; 95% CI, −0.04 to 0.01). The heterogeneity among those studies was quite low (I^2 = 19%), as can be seen in Supplemental Digital Content 2, http://links.lww.com/MPA/A646.

Among the 10 RCTs evaluated,[3,11,21–28] the occurrence of at least 1 local adverse event (pancreatic abscess, pancreatic necrosis, pancreatic pseudocyst, bladder empyema, duodenal obstruction, peritonitis, or aneurysmal bleeding) was reported in a total of 152 patients: 65 in the ERCP group and 87 in the conservative treatment group. The meta-analysis showed that local adverse events were less common in the ERCP group than in the conservative treatment group, the difference being statistically significant (RD, 0.74; 95% CI, 0.55 to 0.99). The heterogeneity among the studies was low (I^2 = 27%), as shown in Figure 5.

Respiratory failure, as a systemic adverse effect, was evaluated in 5 of the 10 RCTs.[11,21,23–25,28] The meta-analysis of those 5 studies showed high heterogeneity (I^2 = 65%). The sensitivity analysis identified no outlier studies. Therefore, we adopted a random-effects model in the statistical analysis. A new meta-analysis, using the random-effects model (Fig. 6), identified no statistical difference between the use of early ERCP and that of conservative treatment in relation to the occurrence of respiratory failure as a consequence of acute biliary pancreatitis (RD, −0.01; 95% CI, −0.06 to 0.05).

The progression to renal failure, as a systemic adverse event, was evaluated in 5 of the RCTs.[11,21,23,25,28] Among those 5 studies, 32 patients progressed to renal failure—19 and 13 in the ERCP and conservative treatment arms, respectively—the meta-analysis showing no statistical difference between the 2 arms (RD, 0.01; 95% CI, −0.02 to 0.04). The meta-analysis of those 5 studies showed low heterogeneity (I^2 = 35%), as can be seen in Supplemental Digital Content 3, http://links.lww.com/MPA/A646.

The progression to cardiogenic shock, as a systemic adverse event, was evaluated in 4 of the RCTs.[11,21,23,25] Collectively, the event was reported in 30 patients: 13 having been in one of the ERCP group and 17 having been in one of the conservative treatment group. In relation to the progression to cardiogenic shock, the meta-analysis showed no statistically significant difference between the 2 arms (RD, −0.01; 95% CI, −0.05 to 0.02). The meta-analysis showed low heterogeneity (I^2 = 32%), as can be seen in Supplemental Digital Content 4, http://links.lww.com/MPA/A646.

Of the 10 RCTs selected, 4 evaluated DIC as a systemic adverse event.[11,21,23,25] Among those 4 studies, a collective total of

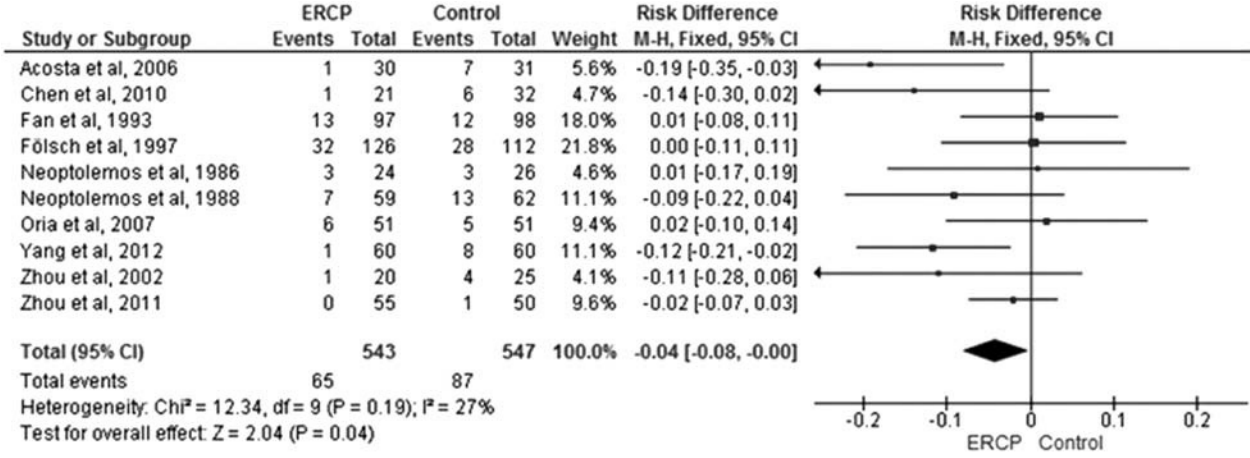

FIGURE 5. Forest plot for local adverse events (number), using a fixed-effects model, with the Mantel-Haenszel (M-H) method.

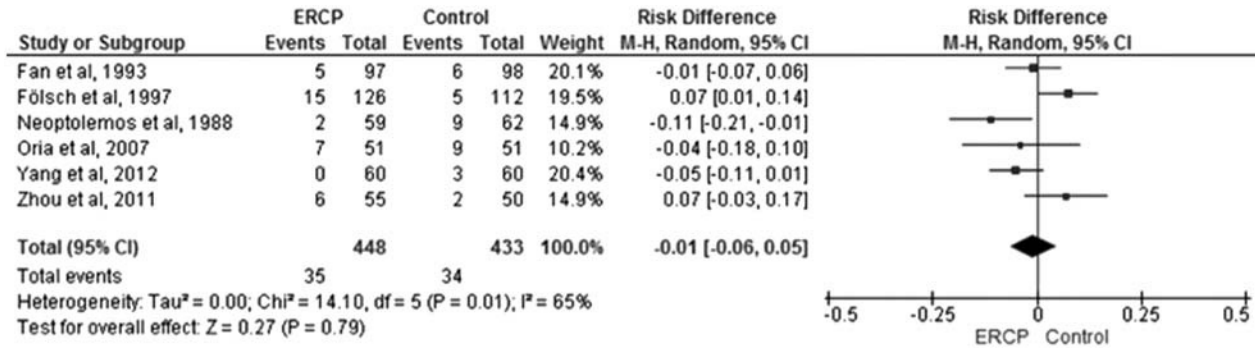

FIGURE 6. Forest plot for respiratory failure (number), using a random-effects model, with the Mantel-Haenszel (M-H) method.

15 patients developed DIC: 8 having been in one of the ERCP arms and 7 having been in one of the conservative treatment arms. The meta-analysis showed that for the occurrence of DIC, there was no statistically significant difference between the 2 treatment arms (RD, 0.00; 95% CI, −0.02 to 0.02). The meta-analysis showed no heterogeneity (I^2 = 0%), as can be seen in Supplemental Digital Content 5, http://links.lww.com/MPA/A646.

Systemic adverse events in general were evaluated in 6 RCTs.[11,21,23–25,28] Among those studies, a total of 228 patients experienced at least 1 such event: 111 having been in one of the ERCP arms and 117 having been in one of the conservative treatment arms. Considering all systemic adverse events reported in those studies (renal failure, respiratory failure, DIC, cardiogenic shock, stroke, ascites, portal vein thrombosis, pleural effusion, lumbar osteitis, sepsis, diabetes mellitus, acute myocardial infarction, and bronchopneumonia), the meta-analysis showed high heterogeneity (I^2 = 80%). The sensitivity analysis identified no outlier RCTs. Therefore, we adopted a random-effects model in the statistical analysis. A new meta-analysis, using the random-effects model (Fig. 7), identified no statistical difference between the use of early ERCP and that of conservative treatment in relation to the occurrence of systemic adverse events as a consequence of acute biliary pancreatitis (RD, −0.03; 95% CI, −0.15 to 0.08).

A collective total of 44 patients, in 4 RCTs,[21–23,27] presented with cholangitis: 17 having been in one of the ERCP arms and 27 having been in one of the conservative treatment arms. The meta-analysis showed relatively high heterogeneity (I^2 = 60%). The sensitivity analysis, using a funnel plot (Fig. 8), identified 1 outlier RCT.[21] After that study had been excluded from the analysis, no statistical difference was identified between the ERCP and conservative treatment arms in terms of the occurrence of cholangitis (RD, 0.00; 95% CI, −0.06 to 0.06). Exclusion of the outlier also reduced the heterogeneity (I^2 = 0%), as can be seen in Figure 9.

Of the 10 RCTs selected, 9 evaluated death as an outcome measure.[3,11,21–26,28] Among the patients included in those studies, a collective total of 57 evolved to death, 25 having been in one of the ERCP group and 32 having been in one of the conservative treatment group. The meta-analysis of those 9 studies showed no statistically significant difference between the 2 treatment arms (RD, −0.01; 95% CI, −0.04 to 0.01). The meta-analysis showed relatively low heterogeneity (I^2 = 40%), as can be seen in Figure 10.

Only 2 of the 10 RCTs selected evaluated the time to a reduction in abdominal pain.[3,24] The meta-analysis of those studies showed that the time to a reduction in abdominal pain was significantly shorter among the patients in the ERCP arms than among those in the conservative treatment arms (RD, −5.01; 95% CI, −6.98 to −3.04). Although the meta-analysis showed high heterogeneity (I^2 = 76%), the possibility that there was an outlier cannot be ruled out (Fig. 11).

The same 2 RCTs that evaluated the time to a reduction in abdominal pain also evaluated the time to a reduction in body temperature.[3,24] The meta-analysis of those studies showed that the time to a reduction in body temperature was also significantly shorter among the patients in the ERCP arms than among those in the conservative treatment arms (RD, −1.70; 95% CI, −2.33 to −1.08). The meta-analysis showed no heterogeneity (I^2 = 0%), as can be seen in Figure 12.

To evaluate the length of hospital stays among patients with acute pancreatitis, 2 of the RCTs considered all of the patients

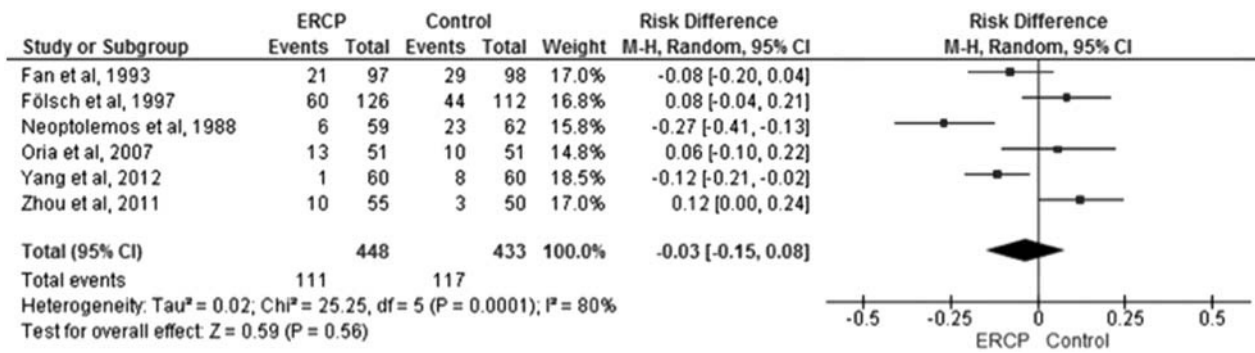

FIGURE 7. Forest plot for systemic adverse events (number), using a random-effects model, with the Mantel-Haenszel (M-H) method.

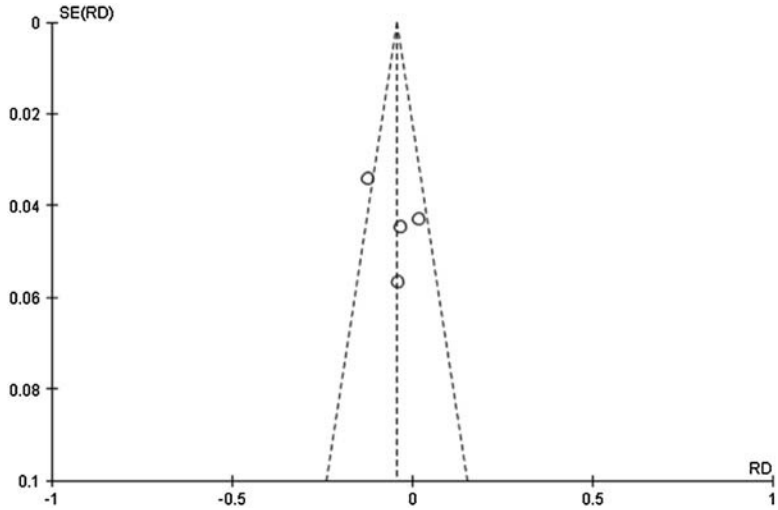

FIGURE 8. Funnel plot for cholangitis (Egger test).

together,[24,28] whereas 2 other RCTs stratified the patients, by severity, into 2 groups (moderate acute pancreatitis and severe acute pancreatitis).[25,27] According to the meta-analysis, with a random-effects model, hospital stays were shorter among the patients undergoing ERCP than among those receiving conservative treatment alone (RD, −11.04; 95% CI, −15.15 to −6.93). When the patients with severe pancreatitis were evaluated separately, the heterogeneity was high (I^2 = 99%). Using a random-effects model, we found no statistical difference between the 2 treatment groups in terms of the length of the hospital stay among the patients with the severe form (RD, −27.63; 95% CI, −66.93 to 11.67), as was the case among those with the moderate form (RD, −0.69; 95% CI, −2.68 to 1.31). Data from the 4 RCTs that evaluated the length of hospital stays are shown in Supplemental Digital Content 6, http://links.lww.com/MPA/A646.

Of the 10 RCTs included, only 2 compared ERCP and conservative treatment in terms of their costs.[27,28] One of those studies stratified the patients into 2 groups: those with moderate acute pancreatitis and those with severe acute pancreatitis.[27] In the group of patients with moderate acute pancreatitis, there was no statistical difference between ERCP and conservative treatment in terms of cost (Supplemental Digital Content 7, http://links.lww.com/MPA/A646). However, in the group of patients with severe acute pancreatitis (Supplemental Digital Content 8, http://links.lww.com/MPA/A646), as well as in the study that evaluated all of the patients together (Supplemental Digital Content 9, http://links.lww.com/MPA/A646), the cost was significantly lower for ERCP than for conservative treatment.

DISCUSSION

Although ERCP, which involves endoscopic cannulation of the papilla of Vater, was first described in 1968, it was not widely accepted until after the development of a new generation of duodenoscopes.[29,30] The first endoscopic papillotomies were performed in 1974, by Classen and Demling in Germany and by Kawaia et al in Japan.[31]

The development of devices and accessories allowed the use of ERCP to become more widespread and made it possible to customize the indications of the procedure as well as to minimize the occurrence of adverse events. However, cannulation of the papilla of Vater, which is a fundamental step in ERCP, correlates with numerous adverse events. Therefore, there has been much discussion about ERCP, especially regarding the benefit of its early use in the treatment of acute biliary pancreatitis. In patients with acute biliary pancreatitis, early ERCP could provide better outcomes than conservative treatment. Theoretically, using ERCP to unblock the biliary tract could prevent adverse events. However, some RCTs have found that ERCP provided no such benefit.

Despite the ERCP-related adverse events that can increase morbidity and mortality, the use of the procedure for decompression of the early biliary tract, through papillotomy, and for removal of the stones improves the course of acute biliary pancreatitis.[9]

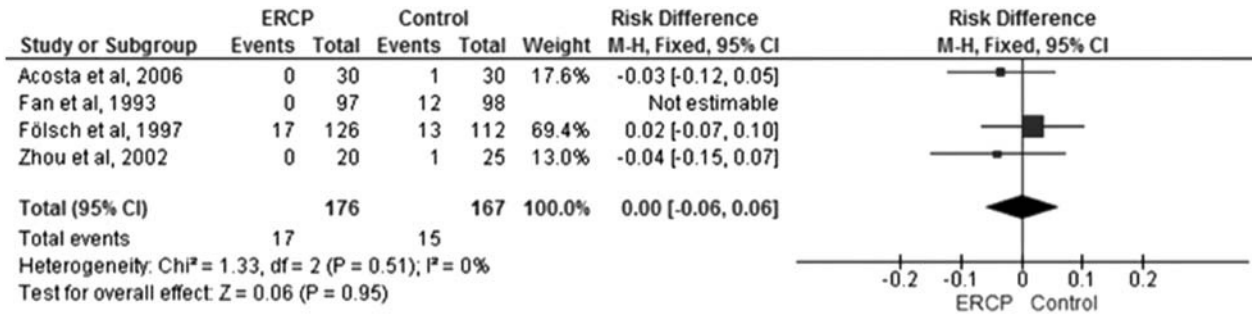

FIGURE 9. Forest plot for cholangitis (number of events), using a fixed-effects model, with the Mantel-Haenszel (M-H) method.

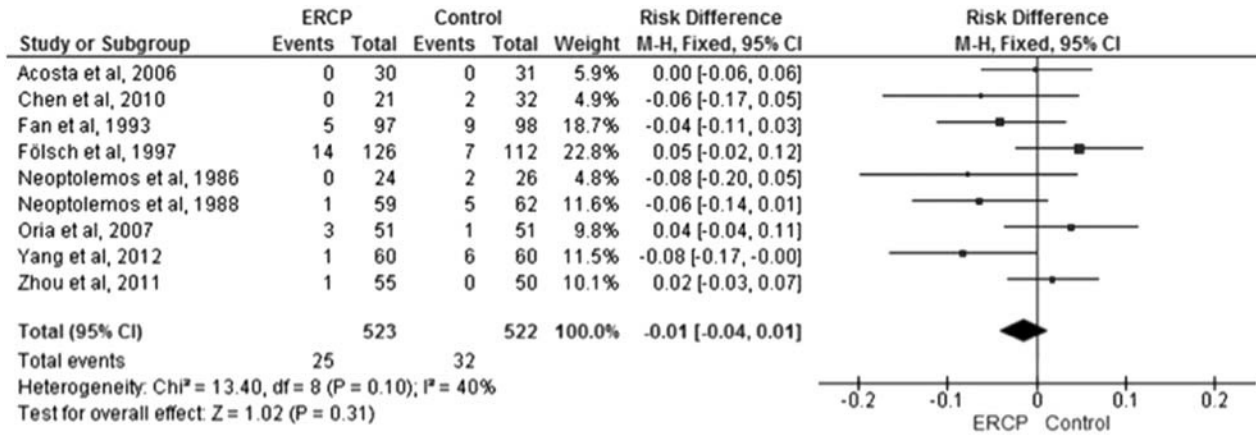

FIGURE 10. Forest plot for the outcome of death (number), using a fixed-effects model, with the Mantel-Haenszel (M-H) method.

According to the guidelines issued in 2005 by the UK Working Party on Acute Pancreatitis,[32] emergency ERCP is recommended in patients with any of the following:

- suspected or confirmed acute biliary pancreatitis
- cholangitis
- jaundice
- dilation of the biliary tract

The guidelines also state that the best results are obtained when ERCP is performed within the first 72 hours after the onset of pain.[32] Two other guidelines—the American Gastroenterological Association guidelines, issued in 2007,[33] and the Practice Guidelines in Acute Pancreatitis, issued in 2006[34]—defined the role of routine early ERCP in the treatment of acute pancreatitis as controversial, even in patients with severe or probably severe acute biliary pancreatitis, as have other studies.[20,32–34] The most recently published guidelines are the Japanese Guidelines for the Management of Acute Pancreatitis,[35] which state that early ERCP should be performed in cases of acute pancreatitis when cholangitis or cholestasis is suspected.

In the present meta-analysis, we compared early ERCP with conservative treatment in patients with acute biliary pancreatitis, attempting to determine whether early ERCP would provide a benefit to such patients. We found that there was no statistically significant difference between early ERCP and conservative treatment in terms of the occurrence of the main local adverse events resulting from acute pancreatitis (pancreatic necrosis, pancreatic abscess, and pseudocyst formation). In the patients classified as having a pancreatic pseudocyst, only the formation of acute pseudocysts was considered, because such pseudocysts should persist for at last 6 weeks to meet the criteria for the classic definition of the condition. None of the RCTs evaluated involved long-term follow-up of the patients.

When all local adverse events were analyzed together, including uncommon events evaluated in some studies (such as bladder empyema, duodenal obstruction, peritonitis, and aneurysmal bleeding), the meta-analysis of the data showed that the occurrence of such events was significantly less common among patients submitted to early ERCP than among those receiving conservative treatment.

Analyzing systemic adverse events, we observed the occurrence of respiratory failure, renal failure, cardiogenic shock, and DIC. There was no statistically significant difference between early ERCP and conservative treatment in terms of the occurrence of those specific systemic adverse events. Even when we analyzed all of the systemic adverse events reported, as a whole, the lack of a statistical difference persisted. In the analysis of mortality, there was also no statistical difference between the 2 treatment modalities.

Only 4 of the RCTs included in the present meta-analysis evaluated the development of cholangitis.[21–23,27] After the meta-analysis, 1 of those studies—the RCT conducted by Fan et al in 1993[21]—was considered an outlier, probably because it was the only one to show a large difference between the 2 groups analyzed (12 cases of cholangitis in the conservative treatment group and none in the early ERCP group). That was markedly different from what was reported in the remaining studies. After removing that study from the analysis, we identified no statistical difference between early ERCP and conservative treatment in patients with acute biliary pancreatitis, in terms of the development of cholangitis. However, that analysis cannot be generalized, because some of the RCTs applied the development of cholangitis as an exclusion criterion, given that it is well known that ERCP is an

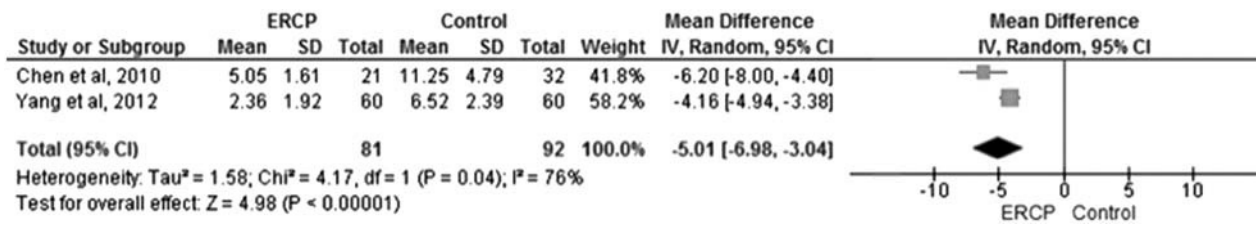

FIGURE 11. Forest plot for the time (in days) to a reduction in abdominal pain (number), using a random-effects model, with the IV method.

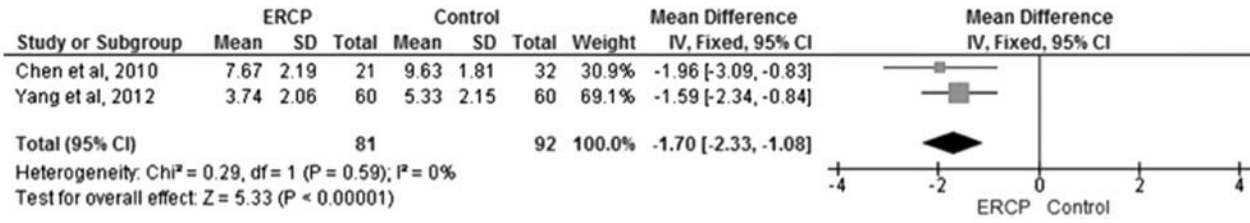

FIGURE 12. Forest plot for the time (in days) to a reduction in body temperature (number), using a fixed-effects model, with the IV method. *df* indicates degrees of freedom; I^2, heterogeneity statistic.

absolute indication when acute biliary pancreatitis is accompanied by acute cholangitis.

The time to a reduction in abdominal pain was significantly shorter among patients submitted to early ERCP than among those receiving conservative treatment alone, as was the time to normalization of the axillary temperature.

The 2 groups that evaluated the time to a reduction in temperature were Yang et al[24] and Chen et al.[3] In the study by Yang et al,[24] 1 of the inclusion criteria was having a temperature of 38.5°C or less. Chen et al[3] did not cite body temperature as a criterion of inclusion or exclusion.

The length of hospital stays was analyzed in only 4 of the 10 RCTs included in the present meta-analysis. In 2 of those studies, hospital stays were evaluated in all patients with acute pancreatitis,[24,28] whereas 2 other studies evaluating hospital stays stratified the patients into 2 groups—those with moderate acute pancreatitis and those with severe acute pancreatitis.[25,27] In the patients with acute pancreatitis, hospital stays were shorter among those submitted to ERCP. However, when the patients with moderate acute pancreatitis were analyzed separately from those with severe acute pancreatitis, neither group showed a statistical difference between early ERCP and conservative treatment regarding the length of hospital stays.

Only 2 of the RCTs evaluated presented cost analysis data.[27,28] One of those studies stratified the patients into 2 groups—those with moderate acute pancreatitis and those with severe acute pancreatitis.[27] In the moderate acute pancreatitis group, there was no statistical difference between early ERCP and conservative treatment in terms of their costs. In the study evaluating all acute pancreatitis patients together, the cost of ERCP was significantly lower than that of conservative treatment.

Despite the considerable number of RCTs included in this meta-analysis, all of which were considered to be of good methodological quality, the inclusion and exclusion criteria varied markedly across the trials. The studies conducted by Fan et al[21] and Zhou et al[28] did not mention the inclusion or exclusion criteria used in the selection of patients with acute pancreatitis. Neoptolemos et al[25] cited only exclusion criteria. Although the inclusion and exclusion criteria were mentioned in the remaining RCTs, they proved to be quite divergent. Some studies included febrile patients or patients with cholangitis, whereas others defined cholangitis as an exclusion criteria. As previously mentioned, some studies stratified patients by severity. Still other studies excluded patients with severe acute pancreatitis or included only such patients.[3,28]

The RCTs evaluated were also diverse regarding the classification of the severity of acute pancreatitis. Fan et al[21] and Acosta et al[22] used the Ranson score as a parameter of severity. The studies conducted by Zhou et al,[27] Oría et al,[11] Chen et al,[3] and Zhou et al[28] used the APACHE II score, whereas those conducted by Neoptolemos et al[25] and Fölsch et al[23] employed the Glasgow score. Only the study conducted by Neoptolemos et al[25] used the Osborne criteria,[26] and none of the RCTs used the criteria currently adopted, which are those of the Atlanta classification.

There were also differences among the RCTs evaluated regarding the type of conservative treatment employed. Most of the studies did not specify the basis of the conservative treatment given. Others augmented the conservative treatment with an additional treatment, such as Chinese herbal medicine, as in the 2 studies conducted by Zhou et al,[27,28] who also studied the use of nonsteroidal anti-inflammatory drugs in their ERCP group.

In this meta-analysis, we showed that early ERCP provides benefits in relation to certain outcomes of acute pancreatitis. However, ERCP still cannot be considered ideal for the early treatment of acute biliary pancreatitis, because additional randomized studies are needed. Such studies should have inclusion and exclusion criteria that are more standardized and should evaluate the various outcomes by subgroup (moderate acute pancreatitis vs severe acute pancreatitis), to analyzed the true benefits of ERCP in the treatment of acute biliary pancreatitis.

This meta-analysis has a number of limitations that should be noted. As previously mentioned, the inclusion and exclusion criteria varied across the RCTs evaluated. In addition, only a few of a studies evaluated the benefits of ERCP separately in moderate acute pancreatitis and severe acute pancreatitis. Furthermore, the criteria used to classify the severity of acute pancreatitis also varied across the studies selected.

In this meta-analysis, we found no statistical difference between early ERCP and conservative treatment in patients with acute biliary pancreatitis, in terms of the occurrence of systemic adverse events, the development of acute cholangitis, and evolution to death. Nevertheless, we were able to show that the use of ERCP early in the treatment of acute biliary pancreatitis minimizes the occurrence of local adverse events, as well as decreasing the time to pain relief and to a reduction in axillary temperature. In addition, hospital stays were shorter among patients undergoing ERCP than among those undergoing clinical treatment alone. Furthermore, the use of early ERCP in patients with acute biliary pancreatitis could result in cost reductions, regardless of the level of severity.

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