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Effect of somatostatin on prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis and hyperamylasemia: A systematic review and meta-analysis

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ABSTRACT

Objective: To perform a meta-analysis of all available studies on the effect of prophylactic somatostatin administration on prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) and post-ERCP hyperamylasemia (PEHA).

Methods: Electronic databases, including PubMed, EMBASE, the Cochrane library, and the Science Citation Index were searched to retrieve relevant trials. Randomized, placebo-controlled trials in adult patients that compared somatostatin versus placebo in prevention of PEP were included. Meta-analysis was performed using a random-effects model to assess the ratios of PEP, PEHA and post-ERCP abdominal pain.

Results: Total ratio of PEP of somatostatin group was significantly lower than that of placebo group. For the short-term injection or bolus injection there were no heterogeneity and no significance between the ratio of PEP of somatostatin group and placebo group. For the long-term injection subgroup there was heterogeneity, and the ratio of PEP of somatostatin group was significantly lower than that of placebo group. There was no significance between the ratio of PEP of somatostatin group and placebo group for the low-risk PEP subgroup, while the ratio of PEP of somatostatin group was significantly lower than that of placebo group for the high-risk PEP subgroup. The ratio of PEP of somatostatin group was significantly lower than that of placebo group for the long-term injection high-risk PEP subgroup. There was no significance between the ratio of PEHA of somatostatin group and placebo group for the short-term injection subgroup or bolus injection subgroup. The ratio of PEHA of somatostatin group was significantly lower than that of placebo group for the long-term injection subgroup. The total ratio of post-ERCP abdominal pain of somatostatin group was significantly lower than that of placebo group. The funnel plot of incidence of PEP and PEHA showed no asymmetry with a negative slope.

Conclusion: Prophylactic use of long-term injection of somatostatin can significantly reduce the incidence of PEP, PEHA and post-ERCP abdominal pain for the high-risk PEP patients, while it is not necessary to be used for the low-risk PEP patients.

Introduction

ERCP is a widely used procedure for the diagnosis and therapy for biliary and pancreatic disease [1]. PEP is the most common complication, with an estimated incidence of 3%–7% among average-risk patients and 15%–20% among patients at high-risk PEP [2]. Several factors, including hydrostatic injury, obstruction of

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pancreatic juice outflow, thermal injury from electrocautery current, and chemical or allergic injury associated previously with the development of PEP. However, irrespective of the triggering mechanisms, the pathophysiology of PEP implies premature acinar-cell-mediated activation of proteolytic enzymes, which leads to cellular injury and autodigestion of the pancreas [3]. The protease inhibitors (somatostatin, gabexate, octreotide, ulinastatin, and nafamostat mesylate) have been used to cure acute pancreatitis and would potentially reduce PEP, among which somatostatin was used most frequently [4]. However, their clinical benefits on reducing PEP were controversial. There were published meta-analysis and systematic review papers concluding that somatostatin could reduce the incidences of PEP and hyperamylasemia, but the papers were old (before 2015), and they had not assigned the patients into high-risk PEP and low-risk PEP subgroup [5–7]. Therefore, we reassessed the prophylactic effects of somatostatin on PEP pancreatitis with a meta-analytic approach by adding the recently published papers and assigning the patients into high-risk PEP and low-risk PEP subgroup.

Materials and methods

Literature search

We performed a computerized search to identify relevant trials using Medline (via PubMed), Embase (via Embase.com), Cochrane Central Register of Controlled Trials and Web of Science. The following key words were used: somatostatin, pancreatitis, endoscopic retrograde cholangiopancreatography, post-endoscopic retrograde cholangiopancreatography hyperamylasemia. PEP was defined as new or worsened abdominal pain and tenderness persisting for >24 h following ERCP, with an elevated serum amylase level >3 times the normal upper limit. SAP was characterized by one or more of the following characters: (1) systemic inflammatory response syndrome (SIRS); (2) persistent organ failure (defined by the Modified Marshall Scoring System) (>48 h); (3) CT scores of pancreas ≥6; (4) Acute Physiology and Chronic Health Evaluation II (APACHE II) scores ≥8. PEHA was defined as an elevation in serum amylase levels to at >2-fold higher the upper normal limit at 6 or 24 h following ERCP. Post ERCP pain was defined as the new occurrence of abdominal pain after ERCP [8].

Study selection

All studies comparing the effect of prophylactic somatostatin administration with a control in preventing PEP published in English were considered eligible. Articles or abstracts were included if they met the following criteria: (1) The study was a controlled trial wherein patients were grouped into 2 treatment arms to receive either somatostatin or a non-somatostatin control (placebo or nothing), with all other treatments and medications being the same or comparable; (2) patients in the study received ERCP; (3) the study reported on at least one of the following outcome measures: Incidence of PEP, PEHA or post-ERCP abdominal pain in the 2 groups. Cohort studies, case-control studies, case reports and case series were excluded. Subgroup analyses were performed based on the 2 following factors: (1) somatostatin infusion mode, including bolus injection (a single dose somatostatin 0.25 mg or 4 μg/kg intravenous injection); short-term injection (somatostatin 0.25 mg/h intravenous injection by drip or by pump for ≦4h); long-term injection(somatostatin 0.25 mg/h intravenous injection by drip or by pump for ≧10 h); (2) risk level of PEP, including high-risk PEP (① suspected sphincter of Oddi dysfunction, defined as a pre-ERCP suspicion of a functional or structural abnormality of the sphincter of Oddi, independent of any manometric findings, considered to be the potential cause of recurrent abdominal pain or pancreatitis, ② recent acute pancreatitis, ③ precut sphincterotomy, ④ cannulation attempted ≥ 3 times, ⑤ pancreatic duct injection) and low-risk PEP (none of the above risk factors for high-risk PEP) [3]. Data from the included studies were extracted and summarized independently by two of the authors. Any disagreement was resolved by the adjudicating senior authors. Sensitivity analysis further included change of the statistical model (a random-effects model). Publication bias in the analysis was determined using a funnel plot.

Quality of studies

The following information from each studies was extracted: first author, publication year, study location, study design, patient characteristics, sample size, intervention approaches (drug form, route, dose and timing), indications and severity criteria. Methodological quality of the included studies was evaluated by using criteria set forth by the Cochrane Collaboration tool for assessing the risk of bias. The quality of evidence was rated for each summary estimate through the GRADE framework, with main outcomes being ranked based on their relevance to clinical decision. RCT began as “high quality” evidence, but can be downgraded by one or two level in accordance with the following criteria: risk of bias, imprecision, inconsistency, indirectness, publication bias. “High quality” represented no more change in current conclusions for effect estimates, whereas “very low quality” suggested that it was very likely to change current conclusions for effect estimates in future.

Statistical analysis

Studies were combined using a random-effects model for the data. The pooled estimates were expressed as odds ratios of PEP, PEHA and post-ERCP abdominal pain with 95% confidence interval (CI). The summary results were represented by forest plots. Statistical heterogeneity between the studies was evaluated by using I^2-statistics. Funnel plots were constructed to evaluate potential publication bias and any association between the treatment estimates and sample size. The meta-analytic pooling was based on the inverse variance method for calculating weights, and the pooled proportion and its 95% CI were obtained using the DerSimonian-Liard random effects model. Heterogeneity of the pooled data was assessed using the Cochrane Q test and quantified with I^2 statistics. An I^2 value 50% was considered to indicate substantial heterogeneity [9]. For the statistical analysis, STATA version 11 (STATA Corporation, College Station, TX, USA) and R version 3.0.2 (The R Foundation for Statistical Computing, Vienna, Austria) were used. Begg and Mazumdar's rank correlation test were used to assess the potential publication bias.

Results

Baseline characteristics of patients and trials

As shown in Fig. 1, a total of 1503 articles were reviewed, of which 1193 were excluded because they were duplicated or not RCTs or not relevant. Of the 310 remaining studies with full-text assessment, 295 were excluded because they did not use somatostatin or were retrospective or economic analysis. Finally, 15 trials [10–24], fulfilled the selection. The characteristics of the 15 included studies are summarized in Table 1.

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