Is indomethacin and diclofenac combined with other drugs more effective in preventing pancreatitis after endoscopic cholangiopancreatography? Answers from a Bayesian network meta analysis

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Review question / Objective: Acute pancreatitis is the most common and worrying adverse event associated with endoscopic retrograde cholangiopancreatography (ERCP). It is reported that the incidence of post-ERCP pancreatitis (PEP) is 3.4-6.0% in the average risk group and 8-13.1% in the high-risk group, resulting in significant morbidity and mortality. Since 1977, more than 30 pharmacological drugs have been evaluated for their effectiveness in preventing PEP. However, most drugs have no definite and contradictory effects in the prevention of PEP. Recently, transrectal administration of indomethacin and diclofenac has been identified as potentially effective in preventing PEP in patients at high risk. Finally, a landmark trial in high-risk patients showed that rectal administration of indomethacin reduced the relative risk of PEP by 46%. However, rectal non-steroidal anti-inflammatory drugs are still ineffective in some patients. Recently new trials of rectal NSAIDs combined with other pharmacological drugs have been reported, including intravenous injection of somatostatin, sublingual administration of isosorbide dinitrate, duodenal epinephrine spray, double dose of rectal NSAIDs and so on. Therefore, we used network meta-analysis (NMA) to compare the combined effects of rectal 100mg indomethacin and diclofenac with other management measures directly and indirectly. Our goal is to determine whether the combined management of rectal 100mg NSAIDs is superior to rectal NSAIDs alone, and to evaluate the most effective combination for the prevention of PEP in patients who underwent ERCP.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 October 2021 and was last updated on 22 October 2021 (registration number INPLASY2021100086).
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Condition being studied: Some studies have shown that except indomethacin during ERCP, the incidence of PEP after rectal non-steroidal anti-inflammatory drugs intervention is low. Diclofenac before ERCP is the best way to prevent PEP, and diclofenac after operation may have the same effect as before operation. A recent network meta analysis of non-steroidal anti-inflammatory drugs for the prevention of PEP showed that rectal indomethacin combined with intravenous rehydration and rectal diclofenac combined with sublingual injection of nitrate were the most effective combination regimens for overall prevention of PEP. In view of the fact that several recent studies have been conducted to compare the efficacy of combined drugs, the results of this network meta analysis may be more accurate.

METHODS

Search strategy: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials. Search dates 7/7/2021 Language English.

Participant or population: Patients receiving ERCP. Inclusion criteria: a) a placebo study of indomethacin or diclofenac; b) a study of indomethacin or diclofenac combined management; c) a randomized controlled trial; d) a study with a complete outcome reported in the literature.

Intervention: 100 mg indomethacin or diclofenac alone; combined management of indomethacin or diclofenac.

Comparator: Control group: placebo group Inclusion criteria: a) a placebo study of indomethacin or diclofenac; b) a study of indomethacin or diclofenac combined management; c) a randomized controlled trial; d) a study with a complete outcome reported in the literature Exclusion criteria: a) retrospective studies, repetitive literature, animal experiments, cases, reviews, reviews and letters; b) secondary analysis of RCT. C) Research that data cannot be extracted.d) The data cannot be extracted or there are errors in inspection.e) The data cannot be extracted or there are errors in inspection.

Study designs to be included: Randomized controlled trial (RCT).

Eligibility criteria: Inclusion criteria: a) a placebo study of indomethacin or diclofenac; b) a study of indomethacin or diclofenac combined management; c) a randomized controlled trial; d) a study with a complete outcome reported in the literature Exclusion criteria: a) retrospective studies, animal experiments, cases, reviews, reviews and letters; b) secondary analysis of RCT. C) Research that data cannot be extracted.

Information sources: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials.
Main outcome(s): Incidence of PEP: Patients were evaluated for PEP according to the criteria described by Cotton et al., which included an increase in serum amylase levels 3 times greater than the ULN and new-onset or worsened abdominal pain lasting more than 24 h after the procedure.

Additional outcome(s): The Additional outcomes is an adverse event, including hyperamylasemia, bleeding, perforation, and other adverse event reported in the literature.

Data management: Select the study that meets the inclusion criteria, D.F. and S.H.X. independently extract data, the extracted data include: year, author, random assignment method, blind method, incomplete outcome data, registration, inclusion exclusion and exclusion criteria, control group, intervention group, population, total number of study, number of exclusion of study, number of intervention group, number of control group, age of intervention group, sex of intervention group, number of difficult cannulation. The diagnostic criteria of PEP, the number of PEP in the intervention group, the number of PEP in the control group, the number of mild, moderate and severe patients in the intervention group and the control group, and test-related adverse events. The uncertain data encountered in this process is discussed and determined by the whole team.

Quality assessment / Risk of bias analysis: The quality of the included studies was assessed independently by two authors (D.F. S.H.X.) according to the Cochrane Collaboration's tool for randomized controlled trials. R.L check the results of the evaluation. Study quality was assessed using ROB 2.0 tool. Risk of bias judgement was assessed in following domains: bias arising from the randomization process, bias due to deviations from intended intervention, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported results. Based on the results of risk of bias judgement, formal overall risk of bias judgement was characterized as “low risk of bias”, “some concern” and “high risk of bias”.

Strategy of data synthesis: Multiple treatment comparison NMA is a meta-analysis extension, including a comparison of direct and indirect randomized clinical trials (RCT). The Stata software based on mvmeta is used for NMA graphics tools, and ADDIS is used to execute random effect NMA based on Bayesian framework. Prior to NMA, we evaluated the transitivity hypothesis by examining the types of demographic and pharmacological drugs as potential therapeutic modifiers, as well as the comparability of bias risks (all associated with randomization, allocation concealment, and blindness risk of outcome evaluators). We use ratio OR to describe the results, analyze the mesh meta based on Bayesian framework, use ADDIS software to analyze, determine the OR value and 95% confidence interval between different intervention groups, describe it with inverted triangle diagram, and determine the order of different drug interventions based on consistency test. And use graphpadprism8 to draw the sorting diagram. The heterogeneity was analyzed by quantitative analysis I² test. If I² is less than 50%, the heterogeneity is low, otherwise the heterogeneity is high. Publication bias will be analyzed by meta by funnel chart and by Egger method. We will use ADDIS 1.16.6 and STATA software for statistical analysis of Windows v14.0 (STATA corp MP, College Station, Texas, USA) [module\“mvmeta\”].

Subgroup analysis: We set a subgroup of high risk people to analyze the incidence of PEP. This can significantly reduce clinical heterogeneity and provide guidance for future treatment plans.

Sensitivity analysis: None.

Language: English only.

Country(ies) involved: China.
Keywords: pancreatitis; endoscopic retrograde cholangiopancreatography; non-steroidal anti-inflammatory drugs.

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