

Reviewer #1:

Specific Comments to Authors: The manuscript is well written, and the title reflect the main subject of the manuscript. Discussion is adequate and consistent with the finding. New and effective preventive measure to prevent PEP will of course open a new thinking and scope of further research in this sphere. However, I would like to suggest few corrections.

1. For the diagnosis of PEP, while doing imaging, CT is an option, especially in severe cases to rule out perforation (as per the consensus paper author referenced no 18). In the series, none required CT, it is astonishing while author encountered few severe cases. But they did CT as routine preprocedural procedure.

Response: Thank you for your insightful questions. Indeed, CT is a more valuable option than B ultrasound in evaluation of pancreatitis complications. However, CT requires higher coordination of patients. All the participants in this study were children; hence, sedation was required for most of the time. Moreover, parents often mind the radiation hazards from CT scanning. It is crucial that imaging evaluation of chronic pancreatitis focuses on whether there is morphological change in the pancreatic duct, pancreatic duct stone, etc. Therefore, in this study, more than 90% of children have MRCP as routine preprocedural procedure, only a few patients have CT examination as preoperative examination.

PEP was diagnosed if a child met two of the three following criteria after ERCP: a new onset of classical abdominal pain, a plasma amylase or lipase concentration exceeding three times the normal upper limit at 24 h postoperatively, and radiographic (B-type ultrasonography or CT) findings suggestive of pancreatitis. When pancreatitis occurs after ERCP procedure, PEP often can be diagnosed because of significant abdominal pain and elevated pancreatic enzymes; imaging examination of the pancreas is beneficial in the diagnosis of a few children with atypical clinical symptoms.

In consideration of the homogeneity and operability of the study, all patients

in this study were routinely examined with pancreatic B-mode ultrasonography 24 hours after ERCP.

In addition, according to Cotton's criteria, the severity of PEP is mainly defined according to the length of hospital stay after procedure (mild, additional hospitalization for 1-3 days; moderate, additional hospitalization for 4-10 days; and severe, hospitalization for >10 days and in cases of hemorrhagic pancreatitis, phlegmon, or pseudocysts). Therefore, we thought that B-scan ultrasound examination was feasible during the design of our experimental scheme.

2. Author could Cannulate in all cases (100%), that is another astonishing point.

Response: A few children with chronic pancreatitis after surgery, such as liver transplantation, duodenectomy, etc., have difficulties in cannulation; however, these children were excluded from this study. In addition, all ERCP procedures were conducted by an experienced digestive endoscopy specialist who performed >30,000 ERCPs; thus, in this study, success rate of intubation was 100%.

3. The incidence of PEP is higher in the blank group, author should find out other research work having such higher incidence specially in Asia region. (Please add the reference titled " Post-ERCP pancreatitis: Frequency and risk stratification from four tertiary care referral hospitals in South East Asia" PMID: 36042621 PMCID: PMC9410617 DOI: 10.1097/MD.00000000000030271

Response: We are grateful for your valuable suggestion.

PEP was identified in 19/66 pediatric Chinese patients (20.7%) (Deng Z, et al., 2021), whereas in a study on adult patients with pancreatic division (PD), the incidence of PEP was 15.7% and 5.6% in PD without CP and PD with CP groups, respectively (Meng QQ, et al., 2020). In another meta-analysis of randomized controlled trials, the overall incidence of PEP was 7.64% (47/615 patients) in

the indomethacin group and 15.15% (95/627 patients) in the placebo group (Shi N, et al., 2015). Therefore, the incidence of PEP is not low in Asia.

Based on your suggestions, we have made corresponding supplements and added references in the Discussion section.

4. There is wide variation in the definition for the diagnosis of PEP, some even considered serum lipase and amylase 5 times of upper limit of normal value. That might be a reason of higher PEP, as the author considered 3 times as per the consensus. Its Ok i think but this wide variation might be mentioned with reference (this reference might help, doi: 10.4103/ijabmr.ijabmr_192_21, PMID: 34912687 PMID: PMC8633690, " Role of 4-H Serum Lipase Level in Predicting Postendoscopic retrograde Cholangiopancreatography Pancreatitis").

Response: Thank you for your interesting question. I have carefully reviewed the literature you recommended and agree with the views in the paper.

In the patient management after ERCP in our center, we tested serum amylase levels and evaluated VAS scores at 3, 6, and 24 h, postoperatively, for all the patients routinely. If PEP was diagnosed, monitoring of serum amylase levels and VAS scores were continued at 48 h and 72 h.

From our experience, when pancreatitis occurs, the chief complaint of persistent abdominal pain is often more critical than the level of elevated trypsin. It is accurate that trypsin usually starts to rise within 3-4 hours after ERCP procedure. However, the accuracy of serum amylase levels and pain scores in early postoperative period may be affected by some factors, such as operation and anesthesia. Therefore, we believed it is a reasonable recommendation to take 24 hours after ERCP as the observation time point for the diagnosis of PEP, which may reduce the diagnostic error to a certain extent.

Reviewer #2:

Specific Comments to Authors: This is a multicenter randomized controlled trial to examine the usefulness of external use of Mirabilite to prevent PEP. This study is interesting. However, there are some concerns to be mentioned.

1. Pre-study calculation of sample size is essential because of a RCT. Did the authors perform sample size calculation in this study?

Response: Thank you for your critical suggestions.

We calculated the sample size according to our primary study. The PEP incidence rate in the control group was estimated to be 21% based on historical data from the study institution. Assume that preoperative prevention can reduce the risk of PEP by 50%, the target incidence of PEP in mirabilite external application group was estimated to not exceed 7%. Set $\alpha = 0.05$, two-sided test, $\beta = 0.20$. Calculated by PASS15.0 software, each group required 99 participants, the estimated dropout rate was 15%, and 117 patients would be included in each group.

We have added the sample size calculation information in the Materials and Methods section.

2. The authors should show how to use Mirabilite clearly in a Figure.

Response: Thank you for your suggestions. We have added the flow chart to show how to use mirabilite (Figure 1).

3. Does the endoscopist, who performed ERCP procedures in this study, really have 30,000 ERCP experiences?

Response: Yes, that is correct. All ERCP procedures in this study were conducted by Dr. Biao Gong, an experienced digestive endoscopy specialist. He has both adult and child ERCP licenses, has about 30 years of ERCP experience, and has performed > 30,000 ERCPs.

Revision reviewer:

Specific Comments to Authors: This manuscript is well revised.

Response: Thank you for your critical suggestions.