

ANSWERING REVIEWERS

23 October 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (File name: WJG 20893 edited).

Title: [Suppository Naproxen Reduces Incidence and Severity of Post-ERCP Pancreatitis: Randomized Controlled Trial](#)

Authors: Fariborz Mansour-Ghanaei*, Farahnaz Joukar, Zahra Taherzadeh, Homayoon Sokhanvar, Tolou Hasandokht

ESPS Manuscript NO: 20893

We appreciate the comments of the Reviewers, and the manuscript has been improved according to the suggestions of Reviewers. All changes can be found highlighted within the revised version.

Reviewer No : 00068891

This study observed the efficacy of a single dose of suppository Naproxen to prevent PEP occurring. A reliable results are obtained and further studies are needed in a large population of the patients, including multiple centered studies in different regions worldwide. The majority of the literatures referred are not new enough and should be replaced by those recently published (from the year of 2010-2015).

Response: Thanks for your suggestion. We have now added 12 references in the manuscript.

Reviewed No: 00070271

Dear authors, we have read with interest your work about Naproxen in the reduction of incidence and severity of PEP. However there are some major subjects that need to be assessed.

Response: We thank the Reviewer for these comments. Revision has been made according to the suggestions of the reviewer.

It is strongly necessary to update the references made in your study, because several original studies and meta-analyses have been done in the last 5 years stating the use and effectiveness of NSAIDs in the prevention of PEP. Studies made by Freeman ML, Elmunzer BJ, Balmadrid B, The European Society of Gastrointestinal Endoscopy (ESGE), The American College of Gastroenterology, Mazaki T, Testoni PA, Cheon YK, Dumonceau JM, Hanna MS, Dai HF, Rustagi T, Otsuka T, D?br?nte Z, Abu-Safieh Y, Ding X, Akbar A, Yaghoobi M, Sun HL, Sethi S, Ahmad D, Puig I, Choksi NS, among others, because the use of a suppository of naproxen seems interesting, but the information given in the manuscript is outdated.

Response: We have now added new references in the Introduction and discussion.

Abstract • *Some minor issues regarding grammar and structure of the abstract are recommended.*

Response: Corrected

Introduction • The incidence of PEP mentioned in the manuscript is 1 to 10%, however recent studies have shown that the incidence is higher. This should be addressed with the new references suggested to review.

Response: Corrected with new references

• In the last paragraph you state “A single dose of intraduodenal indomethacin during ERCP does not decrease the incidence and severity of PEP”. A study conducted by Andrade-Dávila et al. published in *BMC Gastroenterology* in 2015 contradicts this affirmation. It can be accessed in the following link: <http://www.biomedcentral.com/1471-230X/15/85>. Please assess this matter referencing that study, that goes along with the updated bibliography suggested.

Response: Corrected

• In the same paragraph you state “Despite these benefits, the efficacy of NSAIDs for the prevention of PEP is unclear”, and “Although a recent meta-analysis indicated that rectal diclofenac or indomethacin reduce the incidence and severity of PEP, the authors stated that further study is needed for comparisons among these and other various NSAIDs”. Since 2010, the European Society of Gastrointestinal Endoscopy (ESGE) (along with more recent meta-analyses) has stated in their Guidelines that “Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce the incidence of PEP; effective PEP prophylaxis has only been demonstrated using 100 mg of diclofenac or indomethacin administered rectally (Evidence level I++). Routine rectal administration of 100 mg of diclofenac or indomethacin, immediately before or after ERCP, is recommended (Recommendation grade A)”. An Evidence level I++ and a recommendation grade A contradict your statements. You must assess that.

Response: Despite these benefits of NSAIDs and findings of the recent meta-analysis indicated that rectal diclofenac or indomethacin reduce the incidence and severity of PEP, results of the several studies appear to contradict these conclusions. Tilak Shah et al mentioned several questions in this area; comparison between various NSAID, higher dose of drug and different rout of administration. Additionally, there are some study reported NSAIDs can cause acute pancreatitis with the highest risk for diclofenac (OR 5.0, 95% CI: 4.2-5.9) and the lowest for naproxen (OR 1.1, 95% CI: 0.7-1.7).

Material and methods • There is no statement whether or not a Stent was used during the procedures. Either if it was used or not, you must state it in the manuscript.

Response: We did use pancreatic duct stenting in the nobody of study subjects

Results • It would be good to mention the lapse of time given to the patients for subsequent or late complications.

Response: All patients with prolonged pancreatitis symptoms (> 48 h) were assessed for complications of pancreatitis (abscess, pseudocyst, or fluid collection) by CT.

• Authors must show the results of the risk factors for developing PEP with raw numbers, proportions, mean and standard deviations and the P value that result from an Univariate analysis, determining the relative risk and confidence intervals 95% (not odds ratio).

Response :OR , RR(95%CI),RRR and AR were added in the table 3. The table 2 was revised.

Discussion • The Discussion section is too short. You need to make more emphasis in your discoveries and the impact that your method could reach. • Again (as with the rest of the text), you need to make a comparison with the LATEST studies published, for your manuscript to have impact. Your manuscript would be worthless if your comparing a good method with the ones made 10 years ago. We will gladly review the manuscript once the changes are made.

Response: We revised the sections of discussion with new references.

Reviewed No: 02823396

I have the opportunity to review this clinical trial focused on the efficacy of naproxen suppository to prevent post-ERCP-pancreatitis. The authors have confirmed this effect, demonstrated in previous studies with diclofenac or indometacine

Response: Thank you for reviewing our paper.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Fariborz Mansour-Ghanaei, M.D, AGAF, Professor of Medicine

Address: Gastrointestinal and Liver Diseases Research Center (GLDRC) Razi hospital, Sardarjanganal Ave. Rasht, 41448 -95655, Iran Tel: +98-131-5535116

Fax:

+98-131-5534951

E-mail: ghanaei@gums.ac.ir ghanaie@yahoo.com