Reply to Reviewer no 1 - (00069819)

The introduction section may be too long and needs to be shortened.

Introduction has been shortened to 300 words.

Answers to major comments:

1: Discussion section should start by stating the main results and their significance.

A1: Discussion section has been revised and now starts with the main results and their significance.
Text was revised: *"Our study has clearely shown that there are no significant differences for PEP rates between the standard NSAID profilaxis, double NAC and NSAID profilaxis, or split NSAID regimens. Nevertheless, increased levels of PEP in both secondary or tertiarry centers all around the world justify a continous search for better prophylaxis protocols".*

2: Discussion of the main results is somehow weak. The Authors need to expand on the pathophysiologic basis of their results as related to the different regimens used.

A 2. Discussion of main results has been revised with new comments on the pathophysiologic basis of the results.

3. There is no mention of what type of intravenous fluids was used in the study population. As the Authors probably know, the use of ringer lactate, as compared to normal saline, has been largely shown to be effective in reducing the incidence of PEP.

A3: The methods section has been revised by thorough mentioning of the type of intravenous fluids and regimens used.
Text was revised: "*No patient received aggresive intravenous hydration. All patients were administered standard local hydration protocol with 1.5ml/kg/h of lactate Ringer sollution during and for 8 hours after ERCP*"

4. The study strengths and limitations should be clearly stated by the Authors.

A 4: Study strengths and limitations were included.

Included text: "*Considering the absence of any significant difference in the prevention of PEP through different pharmacologic regimens alongside the relatively low morbidity and mortality associated with PEP in our patient groups, the main strength of our study resides on its prospective character, especially considering the paucity of prospective trials in ERCP. Moreover, our results suggest that various pharmacologic pathogenic preventive regimen locally available may be used for PEP prophylaxis, with similar efficacy and safety profiles. Nevertheless, the main limitation is that despite the presence of at least two alternative pharmacologic preventive measures: either intravenous NSAIDs or aggressive intravenous hydration, none of such alternative regimens were tested. Furthermore, in this respect, a double blind prospective randomized controlled trial would offer stronger evidence."*

Reply to Reviewer no 2 - (00504187)

1. “Introduction is too long and should be shortened“.

   A 1. Introduction has been shortened to 300 words.

2. “English language is relatively poor“.

   A2. **Text was revised**: The edited text was modified by two expert editors from Filipodia Publishing

3. “In Material and Methods, looking at the inclusion criteria, all patients had common bile duct stones. How many of them had previous pancreatitis or previous biliary colic or jaundice? Did they have a pancreatic evaluation by US or CT scan? “

   A3. **Text was revised**: *All patients were evaluated before inclusion in the study. Inclusion criteria consisted in: positive diagnosis of choledocholithiasis by magnetic resonance cholangiopancreatography (MRCP), age above 18 years old, willingness to participate in the study and legal capacity to sign the informed consent.*
   The exclusion criteria were represented by: the presence of acute or chronic ongoing pancreatitis or other inflammatory diseases at admission, history positive for acute or chronic pancreatitis, jaundice or recurrent upper right quadrant pain, the presence of pregnancy, contraindication for NSAID administration, recent episode of upper digestive bleeding (less than one month), hypersensibility to antioxidants hypersensibility to antioxidants, intra-procedural necessity of a prophylactic pancreatic stent insertion, and the inability to performe a proper prospective follow-up of patient.

4. “It is somewhat amazing that the control group had more or less the same number of patients of both Group A and B. There is some reason for this?

   A 4. The patient numbers were obtained after applying the inclusion and exclusion criteria in the main pool of patients initially refered for the study. Regarding the patients included in the control group, the number resulted from the simple randomization, while considering all the patients fulfilling the inclusion criteria during the enrollment period of the study. Through applying the suitable statistical analysis instruments, biases regarding the sample size are avoided.
   Text was revised: The study group A (n = 32) was administered 600 mg of NAC intravenously 15 min before the ERCP, as well as an intrarectal administration of 50 mg indomethacin both before and after the ERCP. The study group B (n = 56) received 50 mg of indomethacin per-rectum both before and after the ERCP.

5. “At page 8 and 9, the rised levels of amylasemia are referred as ”3-fold” rising or”asymptomatic hyperamylasemia”. These terms are confusing and an univocal definition should be used.

   A 5. **Text was revised:** Diagnosis of PEP was established after the criteria described by Cotton et al. [26] if the patient reported new onset of abdominal pain after ERCP, or worsening of preexistent abdominal pain, and at least three-fold increase of either serum lipase or amylase levels above upper normal value. Normal ranges of serum lipase and amylase reported by the local laboratory for adults were levels below 60 U/L and 100 U/L respectively. An asymptomatic increase of either serum lipase or amylase above upper normal value was not interpreted as PEP