PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	High versus low energy administration in the early phase of acute pancreatitis (GOULASH trial): Protocol of a multicentre randomized double-blind clinical trial
AUTHORS	Márta, Katalin; Szabó, Anikó; Pécsi, Dániel; Varjú, Péter; Bajor, Judit; Gódi, Szilárd; Sarlós, Patrícia; Mikó, Alexandra; Szemes, Kata; Papp, Maria; Tormai, Tamás; Vincze, Áron; Márton, Zsolt; Vincze, Patrícia; Lankó, Erzsébet; Szentesi, Andrea; Molnár, Tímea; Hágendorn, Roland; Faluhelyi, Nándor; Battyáni, István; Kelemen, Dezső; Papp, Róbert; Miseta, Attila; Verzár, Zsófia; Lerch, Markus; Neoptolemos, John; Sahin-Toth, Miklos; Petersen, Ole; Hegyi, Péter

VERSION 1 - REVIEW

REVIEWER	Srdan Novovic Department of Gastroenterology and Gastrointestinal Surgery, Hvidovre Hospital Denamrk
REVIEW RETURNED	07-Feb-2017

GENERAL COMMENTS	Thank you for the opportunity to review the submitted paper entitled "High versus low energy administration in the early phase of acute pancreatitis (GOULASH): A multicentre randomized double-blind clinical trial (Manuscript ID bmjopen-2017-015874)." The paper describes a multicenter randomized double blind, parallel arm, investigator initiated trial (1:1 randomisation). The objective is to compare to nutritional regimens; a: 'high energy nutrition' versus b: 'low-energy nutrition' in 957 patients admittedwith acute pancreatitis. The 'low energy' regimen consists of a gradually increased dose from 0 to 30 kcal/kg/day over four days from admission. The 'high energy' regimen consists of 30 kcal/kg/day from admission. Main concerns I agree with the investigators that we need large randomized trials to evaluate the interventions used for patients with acute pancreatitis. The group of investigators includes several distinguished researchers with extensive clinical experience. However, I respectfully disagree with the investigators regarding the relevance of the objective. As stated in the background section, early nutrition in the setting of severe acute pancreatitis is well known. Based on previous evidence (randomized controlled trials and meta-analyses), early high dose enteral nutrition is beneficial in acute pancreatitis. I am therefore not convinced that the submitted trial will add to previous evidence. It would be of interest for more precise rationale for the study. Both mild and severe cases of AP are included. Nutritional interventions for patients with mild pancreatitis are probably not needed. In particular, enteral feeding via tubes is not warranted and not standard clinical practice in most countries. Patients with mild

	acute pancreatitis have a discrete inflammatory response and no complications. The expected overall mortality is 0%. Minor comments The submitted paper is difficult to read. It took me several hours to identify the comparison group and design. The wording is confusing. Grammatical errors and spelling mistakes did not help. Assignment to the two groups seems not uniform in the different sections of the manuscript: In abstract, page 3, it is stated that patients will be assigned to group B (no energy administration in the first 24h of hospital admission). In methods, page 6, group B is low energy administration after 24 h of hospital admission. The wording should be consistent throughout the protocol. Abdominal pain > 120 hours is one of exclusion criteria. My suggestion would be to shorten this lag period to 72 hours, as five days seem too long when primary objective is (very) early nutritional intervention. The trial is designed with two primary outcomes (multiorgan failure and mortality). The sample size calculation should be adjusted accordingly. At present, one might suspect that the trial is seriously underpowered. The fact that there are 17 secondary endpoints is a concern. Spurious findings are likely to occur and several outcomes do not seem to add important/relevant clinical information. The planned design for costs calculations should be specified. A drop-out of 10% seems too high, as intervention is minimal and the patients are admitted through inclusion period. According to the manuscript, inclusion of patients has already been started, why it seems post-festum to optimize the design of the study.

REVIEWER	Pezzilli R Sant'Orsola-Malpighi Hospital, Bologna, Italy
REVIEW RETURNED	27-Feb-2017

GENERAL COMMENTS	The authors report the draft of a randomized, controlled two-arms double-blind multicenter trial on energy administration in patients suffering from acute pancreatitis. A combination of multi organ failure for more than 48h and mortality is defined as primary endpoint, whereas several secondary endpoints such as length of hospitalization or pain will be determined to elucidate more detailed differences between the groups. 1. The study is interesting and well supported by the calculated sample size. 2. The only question is that the study will include many patients with mild acute pancreatitis. Please add a comment on this topic. 3. There are some mistakes that should be corrected

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments to Author

Comment Major 1. I agree with the investigators that we need large randomized trials to evaluate the interventions used for patients with acute pancreatitis. The group of investigators includes several distinguished researchers with extensive clinical experience.

Answer: Thank you for your positive comment. Indeed, many researchers spent lots of time to prepare this trial. We had several personal, e-mail and skype conversations to design the best approach.

ACTION: NONE

Comment Major 2. Both mild and severe cases of AP are included. Nutritional interventions for patients with mild pancreatitis are probably not needed. In particular, enteral feeding via tubes is not warranted and not standard clinical practice in most countries. Patients with mild acute pancreatitis have a discrete inflammatory response and no complications. The expected overall mortality is 0%. However, I respectfully disagree with the investigators regarding the relevance of the objective. As stated in the background section, early nutrition in the setting of severe acute pancreatitis is well known. Based on previous evidence (randomized controlled trials and meta-analyses), early high dose enteral nutrition is beneficial in acute pancreatitis. I am therefore not convinced that the submitted trial will add to previous evidence. It would be of interest for more precise rationale for the study.

Answer: Thank you for your points which is a good sign for us that this part of the article needs better explanation. As you also pointed out we have clear evidences that enteral nutrition (via enteral tube feeding) is beneficial in severe AP (IAP/APA guideline statement G21 GRADE 1/B, strong agreement). We also know that enteral nutrition (oral feeding) should be started whenever the abdominal pain is decreasing and the inflammatory markers are improving (IAP/APA guideline statement G20 GRADE 2/B, strong agreement). Our meta-analyses also suggests that early (first 72h) enteral feeding is beneficial in mild, moderate and severe pancreatitis. However there is neither suggestion nor trial are available concerning the exact amount of energy intake. Moreover neither of the studies applied high energy in the first 24h. Therefore our study will be the very first one which will provide evidence concerning the necessity and amount of enteral feeding in the first 24h.

ACTION: The study introduction is now rewritten for better understanding.

Comment Major 3. Both mild and severe cases of AP are included. Nutritional interventions for patients with mild pancreatitis are probably not needed. In particular, enteral feeding via tubes is not warranted and not standard clinical practice in most countries. Patients with mild acute pancreatitis have a discrete inflammatory response and no complications. The expected overall mortality is 0%.

Answer: You are complete right. Nutritional interventions for patients with mild pancreatitis are probably not needed. However the main aim of the study is not to find new treatments in mild AP, but to prevent the development of severe pancreatitis. This is the reason why the severity and mortality are the primary endpoint. Please note that there is no accurate severity index at admission which can predict severe pancreatitis and/or mortality with high specificity and sensitivity. The Dutch Pancreatitis Study Group use 150mM CRP as cut off level between MAP and SAP which sensitivity is not too high at admission, especially when the symptoms started close to admission (PMID: 25409371). Others use the BISAP score which has been also showed very low sensitivity but high specificity for predicting the severity of acute pancreatitis (PMID: 26613249).

ACTION: The study introduction and discussion is now rewritten for better understanding.

Comment Minor 4. The submitted paper is difficult to read. It took me several hours to identify the comparison group and design. The wording is confusing. Grammatical errors and spelling mistakes did not help.

Answer: Thank you for this note.

ACTION: The paper is now rewritten. An English language editor has corrected the language mistakes in the ms.

Comment Minor 5. Assignment to the two groups seems not uniform in the different sections of the manuscript: In abstract, page 3, it is stated that patients will be assigned to group B (no energy administration in the first 24h of hospital admission). In methods, page 6, group B is low energy administration after 24 h of hospital admission. The wording should be consistent throughout the protocol.

Answer: Absolutely agree.

ACTION: The wording for group B is now uniformed.

Comment Minor 6. Abdominal pain > 120 hours is one of exclusion criteria. My suggestion would be to shorten this lag period to 72 hours, as five days seem too long when primary objective is (very) early nutritional intervention.

Answer: Thanks for the suggestion. This was one of the topics we have discussed a lot during the planning phase. Since our aim is to prevent the local necrosis and the development of severe AP one of the suggestions was to *shorten this lag period (even with higher extent) down to 24 hours. However, in the real life most of the patients (over 70%) come later. In addition, it would have decreased the number of patients we could have involved to the trial. Therefore, we decided to keep the longer period and perform subgroup analyses as described in the text. The study has been registered and already started, therefore it is too late at that stage to change the protocol.*

ACTION: None.

Comment Minor 7. The trial is designed with two primary outcomes (multiorgan failure and mortality). The sample size calculation should be adjusted accordingly. At present, one might suspect that the trial is seriously underpowered.

Answer: There is a single primary outcome which is a combination of multi organ failure for more than 48h and mortality. The sample size calculation has been adjusted accordingly.

ACTION: None.

Comment Minor 8. The fact that there are 17 secondary endpoints is a concern. Spurious findings are likely to occur and several outcomes do not seem to add important/relevant clinical information.

Answer: The 17 secondary endpoints have been aimed in order to get more information concerning the usefulness of energy intake in different groups of patients. We have chosen those parameters which have been shown to have relevance concerning the severity or mortality of AP.

ACTION: None.

Comment Minor 9. The planned design for costs calculations should be specified.

Answer: Agree

ACTION: It is now specified.

Comment Minor 10. A drop-out of 10% seems too high, as intervention is minimal and the patients are admitted through inclusion period.

Answer: Although the intervention is minimal, there could be several points how the patients can be dropped out. The most dangerous one is that 30% of the patients are alcoholics. We had several cases when the patient has left the department on his own risk. On the other hand if the patient status became more severe or ileus develops it may happen that one of the days the patients cannot get the planned energy.

ACTION: None.

Reviewer 2 Comments to Author

Comment 1. The study is interesting and well supported by the calculated sample size.

Answer: Many thanks for your positive comment.

ACTION: not needed

Comment 2. The only question is that the study will include many patients with mild acute pancreatitis. Please add a comment on this topic.

Answer: Many thanks for highlighting the necessity of better clarification of the specific aim of the study. Nutritional interventions for patients with mild pancreatitis are probably not needed, whereas it is crucially important in severe AP. Here, the main aim of the study is to prevent the development of severe pancreatitis with restoration of energy level. This is the reason why the severity and mortality are the primary endpoints. It would be also difficult to select the patients in advance since there is no accurate severity index at admission which can predict severe pancreatitis and/or mortality with high specificity and sensitivity. The Dutch Pancreatitis Study Group use 150mM CRP as cut off level between MAP and SAP which sensitivity is not too high at admission, especially when the symptoms started close to admission (PMID: 25409371). Others use the BISAP score which has been also showed very low sensitivity but high specificity for predicting the severity of acute pancreatitis (PMID: 26613249).

ACTION: We have added comments on this topic.

Comment 3. There are some mistakes that should be corrected.

Answer: Many thanks for that.

ACTION: We have checked the ms. and corrected several mistakes.

VERSION 2 – REVIEW

REVIEWER	Srdan Novovic, MD PhD Department of Gastroenterology and Gastrointestinal Surgery, Hvidovre Hospital, Copenhagen, Denmark
REVIEW RETURNED	01-Jul-2017

GENERAL COMMENTS	The authors have addressed all comments satisfactorily.