PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Endoscopic sphincterotoMy for delayIng choLecystectomy in mild acute biliarY pancreatitis (EMILY study): protocol of a multicenter randomized clinical trial
AUTHORS	Kucserik, Levente; Márta, Katalin; Vincze, Áron; Lázár, György; Czakó, László; Szentkereszty, Zsolt; Papp, Maria; Palatka, Károly; Izbéki, Ferenc; Altorjay, Áron; Török, Imola; Barbu, Sorin; Tantau, Marcel; Vereczkei, András; Bogár, Lajos; Dénes, Márton; Németh, Imola; Szentesi, Andrea; Zádori, Noémi; Antal, Judit; Lerch, Markus; Neoptolemos, John; Sahin-Toth, Miklos; Petersen, Ole; Kelemen, Dezső; Hegyi, Péter

VERSION 1 - REVIEW

REVIEWER	Dr E.J.M. van Geenen Radboud UMC The Netherlands
REVIEW RETURNED	15-Dec-2018

GENERAL COMMENTS	I´d like to compliment the EMILY consortium for designing this International multi-center (equivalence OR non-inferiority RCT. Most parts are scientifically well designed with a clinically relevant research question. Though, some questions did arise reviewing this manuscript: 1. ´previous ES or cholecystectomy will also be excluded´ this is contradictory compared to the inclusion criteria, please specify. 2. In the methods the authors mention: an equivalence trial (non-inferiority). Non-inferiority trial is different from an equivalence trial in it´s hypothesis and power-calculation. Power calculation was performed for a non-inferiority trial. Please change this part. 3. If this is a non-inferiority trial OR equivalence trial, do we accept a max difference of 14% based on the H0 hypothesis (5% in each group), why? This is a substantial deviation of the primary hypothesis, please clarify. 4. Inclusion criteria: patients with predicted mild ABP who underwent an ERCP during the attack of ABP. To excluded any inclusion-bias the indication of ERCP during an ABP attack must be crystal clear. Performing a routine ERCP in mild ABP is not recommended by any guideline. Therefore, ERCP is performed in symptomatic CBD stones (cholangitis, jaundice, biliary colicky pain). During the attack of an ABP the pain and jaundice can be cause by the pancreatitis itself and therefore difficult to distinguish from biliary pain/jaundice. Will they receive MRCP or EUS before the ERCP to differentiate CBDS form pancreatic head compression of the CBD, or to diagnose CBDS? I would recommend that this important inclusion criterium is defined more specifically.

	5. Limitations section: this study answers the question about a small subgroup of patients (ie those who underwent and ERCP+ES in the course of mild ABP). 6. This trial is designed as a pragmatic trial. Therefore, you could consider to include patients with a previous ERCP+ES. Of course, a risk of ES stenosis must be outweighed against a increased study population (and clinical relevance).

REVIEWER	Sang Hyub LEE Seoul National University Hospital, Korea
REVIEW RETURNED	19-Dec-2018

GENERAL COMMENTS	Thank you for contributing a good trial. major question> Several studies have investigated the effect of routine ERCP/ES in ABP. The UK guidelines for the management of ABP advocate urgent therapeutic ERCP. The indications for early ERCP in the AGA Institute review on ABP are more restricted. According to these guidelines, early ERCP should be performed in patients with cholangitis or when there is suspicion of persistent common bile duct stone. In patients with mild or resolved acute biliary pancreatitis who are scheduled for cholecystectomy, there is usually little need for preoperative ERCP because the risk of persistent common bile duct stones is low. And in selected patients with ABP, EUS and MRCP can safely replace diagnostic ERCP in the management. But, your study is design for the patients with mild ABP, there is no indication for urgent ERCP/ES in patients with mild pancreatitis without cholangitis. In your study, all patients have to get ES, so some patients with passed stones or sludge will get an unnecessary procedure and ERCP/ES itself may also be associated with complications in up to 10 % of patients. In other article (APEC trial), they wrote references about ABP with high probability of a biliary etiology and they suggested reference for ES (even in the absence of gallstones or visible sludge in the common bile duct). But APEC trial was designed to investigate whether early ERCP/ES improves outcome in patients with ABP without cholangitis who are at high risk for complications. So, I think that you must write evidences of benefits for early ERCP/ES in mild ABP. Also, repeated liver function tests for study within 24 hours after presentation and availability of EUS or MRCP will be helpful to your study design for exclusion of the passed stone. I think that cholangitis is the exact indication for ERCP/ES with mild ABP. How about to add cholangitis in inclusion criteria? minor question> 1. within 6 days after ES vs. within 5-6 days after ES ? 2. reference 31 --> main text inclusion criteria (3), figure 1 3. figure 1. reference (34)? spirit 2013 guideline 4. however in case of acute cholecystitis acute cholecystectomia ?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments

1) ´previous ES or cholecystectomy will also be excluded´ this is contradictory compared to the inclusion criteria, please specify.

Answer: We are sorry for the inaccurate description. We wanted to exclude patients who had ES or cholecystectomy before the current admission.

Action: We took in consideration your and the other reviewers comments and we decided to include patients who had ES in the medical history as well. Therefore we updated the manuscript.

2) In the methods the authors mention: an equivalence trial (non-inferiority). Non-inferiority trial is different from an equivalence trial in it´s hypothesis and power-calculation. Power calculation was performed for a non-inferiority trial. Please change this part.

Answer: We totally agree with you, thank you for the comment.

Action: We corrected the type of the trial.

3) If this is a non-inferiority trial OR equivalence trial, do we accept a max difference of 14% based on the H0 hypothesis (5% in each group), why? This is a substantial deviation of the primary hypothesis, please clarify.

Answer: We are sorry for the inaccurate description.

Action: We revised as requested.

4) Inclusion criteria: patients with predicted mild ABP who underwent an ERCP during the attack of ABP. To excluded any inclusion-bias the indication of ERCP during an ABP attack must be crystal clear.

Answer: We totally agree with you, thank you for your comment.

Action: We have inserted a more detailed description concerning the indication of ERCP. Of course, the protocol will follow the IAP/APA guideline. We added this statement to the manuscript (line 157; 218-219).

Performing a routine ERCP in mild ABP is not recommended by any guideline. Therefore, ERCP is performed in symptomatic CBD stones (cholangitis, jaundice, biliary colicky pain). During the attack of an ABP the pain and jaundice can be cause by the pancreatitis itself and therefore difficult to distinguish from biliary pain/jaundice. Will they receive MRCP or EUS before the ERCP to differentiate CBDS form pancreatic head compression of the CBD, or to diagnose CBDS? I would recommend that this important inclusion criteria is defined more specifically.

Answer: Thank you for your comment, we totally agree with you. EUS/MRCP will be performed in case of suspected common bile duct obstruction as suggested by the guideline (IAP/APA Q27).

Action: We added this statement to the manuscript (line 157; 219-220).

5) Limitations section: this study answers the question about a small subgroup of patients (ie those who underwent and ERCP+ES in the course of mild ABP).

Answer: Indeed. Thank you for your awareness

Action: It is now corrected.

6) This trial is designed as a pragmatic trial. Therefore, you could consider to include patients with a previous ERCP+ES. Of course, a risk of ES stenosis must be outweighed against a increased study population (and clinical relevance).

Answer: Thank you for your comment. Excellent idea. Indeed, your suggestion will elevate the number of patients in which the study results can be useful in the future.

Action: We modified the protocol accordingly.

Reviewer 2 Comments

1) Several studies have investigated the effect of routine ERCP/ES in ABP. The UK guidelines for the management of ABP advocate urgent therapeutic ERCP. The indications for early ERCP in the AGA Institute review on ABP are more restricted. According to these guidelines, early ERCP should be performed in patients with cholangitis or when there is suspicion of persistent common bile duct stone.

Answer: Thank you very much, we totally agree with you.

Action: We have inserted a more detailed description concerning the indication of ERCP. Of course, the protocol will follow the IAP/APA guideline. We added this statement to the manuscript (line 157; 218-219).

In patients with mild or resolved acute biliary pancreatitis who are scheduled for cholecystectomy, there is usually little need for preoperative ERCP because the risk of persistent common bile duct stones is low.

Answer: Agree.

Action: We broaden the inclusion criteria to elevate the number of patients fulfilling the inclusion criteria. We will not only include patients who had on admission EST but also those who had previous intervention.

And in selected patients with ABP, EUS and MRCP can safely replace diagnostic ERCP in the management.

But, your study is design for the patients with mild ABP, there is no indication for urgent ERCP/ES in patients with mild pancreatitis without cholangitis. In your study, all patients have to get ES, so some patients with passed stones or sludge will get an unnecessary procedure and ERCP/ES itself may also be associated with complications in up to 10 % of patients.

Answer: We are sorry for the inaccurate description. Of course, we will perform ERCP/ES only in case of cholangitis or common bile duct obstruction as suggested by the guideline (IAP/APA Q25 “indicated or probably indicated”). In suspected common bile duct obstruction we will perform EUS/MRCP only (IAP/APA Q27).

Action: We revised the manuscript accordingly.

In other article (APEC trial), they wrote references about ABP with high probability of a biliary etiology and they suggested reference for ES (even in the absence of gallstones or visible sludge in the common bile duct). But APEC trial was designed to investigate whether early ERCP/ES improves outcome in patients with ABP without cholangitis who are at high risk for complications.

So, I think that you must write evidences of benefits for early ERCP/ES in mild ABP.

Answer: See our answers above. Of course we do not want to perform ERSP/ES in mild ABP without cholangitis or obstruction.

Action: None.

Also, repeated liver function tests for study within 24 hours after presentation and availability of EUS or MRCP will be helpful to your study design for exclusion of the passed stone.

I think that cholangitis is the exact indication for ERCP/ES with mild ABP. How about to add cholangitis in inclusion criteria?

Answer: Agree. In case of mild ABP without cholangitis but common bile duct obstruction liver function test will be repeated next day. Patients with improved liver function test will not undergo ERCP/ES. Concerning the inclusion criteria we will add the IAP/APA guideline information to the text.

Action: The protocol is now modified as described above.

2)within 6 days after ES vs. within 5-6 days after ES ?

Answer: Agree.

Action: We corrected the ms. according to ‘6 days after ES’.

3) figure 1. reference (34)? spirit 2013 guideline

Answer: Thank you for your awareness.

Action: We corrected the ms. accordingly.

4) however in case of acute cholecystitis acute cholecystectomia ?

Answer: Agree. Patients with acute or chronic cholecystitis during the hospitalization should be excluded.

Action: Please see the exclusion criteria (line: 160-161).

VERSION 2 – REVIEW

REVIEWER	Erwin van Geenen Radboud University Medical Center The Netherlands
REVIEW RETURNED	31-Jan-2019

GENERAL COMMENTS	The authors of the EMILY trail present a clinically relevant topic in pancreatico-biliary endoscopy and surgery. The protocol is overall well designed, with clear: in/exclusion, primary/secondary endpoints, study type, and study population Minor issues: 1. the abstract lacks information about the study population, i.e. patients who underwent an ERCP + ES during an attack of mild ABP 2. Patients with a medical history of an ES can be potentially different from `fresh ES`patients, i.e. older ES can potentially lead to fibrosis of the papilla, with all its associated gallstone complications (the primary endpoint). Additionally, the former ES did not protect them from pancreatitis, why should it protect them after the initial period of mild acute biliary pancreatitis? Perhaps from cholangitis, colicky pain (cholecystitis)? See also 3. 3. ES is the main protective mechanism to decrease complications (= hypothesis) after an attack of mild ABP, is this intervention standardized? How can you retrieve information about patients who´d already had an ES (experienced operator, cutting direction, minimal cutting distance, current used ect). Perhaps it is wise to standardize this intervention. 4. Mild pancreatitis, according to the revised Atlanta criteria? if so please ad the reference. 5. Why should you remove CBD stones from the CBD in the patient has no cholangitis or severe colicky pain? Most stones will pass spontaneously within 2-3 days. Will you perform an EUS before ERCP? 6. Power calculation: drop-out rate of 5% is quite optimistic 10-15% is perhaps more common in this type of studies

REVIEWER	Sang Hyub Lee Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul, 110-744 South Korea
REVIEW RETURNED	19-Feb-2019

GENERAL COMMENTS	Thank you for good response. The desion of study seems to have been improved and clarified in a better way.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1 Comments

Reviewer: 1

Reviewer Name: Erwin van Geenen,The Netherlands

Please state any competing interests or state 'None declared': None

Answer: Agree.

Action: The statement of competing interests is added to the manuscript.

Minor issues:

1. the abstract lacks information about the study population, i.e. patients who underwent an ERCP + ES during an attack of mild ABP

Answer: Thank you for your comment, we agree with you.

Action: We added it to the manuscript.

2. Patients with a medical history of an ES can be potentially different from `fresh ES`patients, i.e. older ES can potentially lead to fibrosis of the papilla, with all its associated gallstone complications (the primary endpoint). Additionally, the former ES did not protect them from pancreatitis, why should it protect them after the initial period of mild acute biliary pancreatitis? Perhaps from cholangitis, colicky pain (cholecystitis)? See also 3.

Answer: Thank you for your comment. You are right. We cannot exclude the possibility of fibrosis after ES. The original protocol contained patients only with fresh ES, however, we agreed with referee 2 that the applicability of the study would be higher, if patients having earlier ES would not be excluded. Notably, this study is to understand the timing of cholecystectomy in patients having intact or cuted sphyncter and not whether ES would prevent from RAP. Since the event rate of fibrosis is relatively low after ES, we would leave the study protocol as is. However we would include an additional interim subgroup analysis when the 50% of the study is completed. If the results obtained from the interim analysis indicate that there could be significant difference between earlier and fresh ES, we will modify the trial protocol from the single-population two-arm (two groups) set up to a two-population two-arm set up (four groups). The required patients' number will be adjusted in both populations accordingly.

Action: We updated the manuscript accordingly.

3. ES is the main protective mechanism to decrease complications (= hypothesis) after an attack of mild ABP, is this intervention standardized? How can you retrieve information about patients who´d already had an ES (experienced operator, cutting direction, minimal cutting distance, current used ect). Perhaps it is wise to standardize this intervention.

Answer: You are right. It will be standardized. However, as you mentioned we will have no information concerning the earlier procedure. To avoid procedure bias in the earler ES group we will perform an interim analysis described above. If the interim analysis will show no difference between the results of

index ES vs earlier ES we will continue the study with the single-population two-arm set up. If the interim analysis indicates, we will modify the set up as described in point 2.

If ES is provided during the index admisson it will be performed according to the European Society of Gastrointestinal Endoscopy (ESGE) guidelines, by trained gastroenterologist (>50 ES completed within a year).

Action: None.

4. Mild pancreatitis, according to the revised Atlanta criteria? if so please ad the reference.

Answer: Yes.

Action: We added the reference to the ms.

5. Why should you remove CBD stones from the CBD in the patient has no cholangitis or severe colicky pain? Most stones will pass spontaneously within 2-3 days. Will you perform an EUS before ERCP?

Answer: Of course if only the laboratory parameters suggest common bile duct obstruction or choledocholthiasis we will perform either EUS or MRCP before the ERCP which is in accordance with the IAP/APA guideline. ERCP will be performed only in case of cholangitis, or image-proven choledocholithiasis (if EUS/MRCP confirmed it). See „Diagnosing and treating ABP" in the ms.

Action: none.

6. Power calculation: drop-out rate of 5% is quite optimistic 10-15% is perhaps more common in this type of studies

Answer: OK, accepted.

Action: We modified the drop-out rate to 10%. Since this does not alter the original sample size calculation, no additional calculation is needed.

Reviewer 2 Comments

Reviewer: 2

Reviewer Name: Sang Hyub Lee , South Korea

Please state any competing interests or state 'None declared': None declared

Answer: Thank you for your comment.

Action: The statement of competing interests is added to the manuscript.