

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cavitron Ultrasonic Surgical Aspirator (CUSA) compared to conventional pancreatic transection in distal pancreatectomy – study protocol for the randomized controlled CUSA-1 pilot trial
AUTHORS	Holze, Magdalena; Loos, Martin; Hüttner, Felix; Tenckhoff, Solveig; Feisst, Manuel; Knebel, Phillip; Klotz, Rosa; Mehrabi, Arianeb; Michalski, Christoph; Pianka, Frank

VERSION 1 – REVIEW

REVIEWER	Sakamoto , Katsunori Ehime University Graduate School of Medicine
REVIEW RETURNED	02-Dec-2023

GENERAL COMMENTS	Authors scheduled the RCT for pancreatic transection methods comparing stapler/scalpel and CUSA. The study is interesting and might provide important results for pancreatic surgeons. However, I have some comments for the authors as follows. 1. Although the previous studies indicated no difference in POPF rate among stapler and scalpel, I think it might differ. Therefore, the one study arm may be recommended to be unified to stapler or scalpel. 2. How is the rate of minimally invasive surgery in the hospital where the study is conducted? 3. Do the authors collect the data of pancreatic transection time?
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REVIEWER	McCarron , Frances N Mercy Health St Elizabeth Youngstown Hospital, Hepatobiliary and Pancreatic Surgery
REVIEW RETURNED	19-Dec-2023

GENERAL COMMENTS	First the discussion portion of the abstract states that CUSA may have a benefitable effect on POPF. This is also mentioned in the limitations section. I think it is more accurate to say that the benefit of CUSA assisted transection is unknown based on current literature. As stated in the manuscript, the literature to support this is severely limited and flawed. This seems to be the basis for the current study. Second, I think it is important to note that since there is no CUSA currently for minimally invasive surgery this RCT is limited to open distal pancreatectomy only. There is literature describing the benefits of MIS pancreatic surgery and at many centers this is the preferred approach. Thus a limitation should be acknowledged that this is not transferrable to patients undergoing laparoscopic or
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	robotic distal pancreatectomy. Consideration should also be given to adding the rationale for choosing open distal pancreatectomy over MIS for patients included in the study as there is potential for bias/confounding if open surgery is chosen for "more difficult cases" at this specific center. That being said, this is a very interesting study with potential for significant impact in the HPB community.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Katsunori Sakamoto, Ehime University Graduate School of Medicine

Comments to the Author:

Authors scheduled the RCT for pancreatic transection methods comparing stapler/scalpel and CUSA. The study is interesting and might provide important results for pancreatic surgeons. However, I have some comments for the authors as follows.

1. Although the previous studies indicated no difference in POPF rate among stapler and scalpel, I think it might differ. Therefore, the one study arm may be recommended to be unified to stapler or scalpel.

Answer: Thank you for this relevant comment, as you mentioned the previously published randomized controlled trials and meta-analyses comparing the stapler/ scalpel technique showed no differences in both surgical approaches (Diener et al., 2011, Probst et al., 2015). To compare the CUSA device with the existing evidence-based standard in clinical routine, we chose to define the control group according to the surgical standard so far. This means that, depending on the surgeon's preference, either a stapler or scalpel can be used for pancreatic transection in the control group. Based on the existing evidence, we do not anticipate that a control group using either a scalpel or stapler would make a significant difference in our study. Therefore, we have decided to employ both techniques to, for example, facilitate better recruitment. Additionally, in a future multicenter trial, the conventional transection method may also vary across different centers. Nevertheless, the transection method is currently being recorded in the pilot trial, and will be recorded in a future multicentre trial.

Furthermore, we would like to mention, that the standard transection method in our centre is stapling (Endo-GIA, 60mm black cartridge), but as there are some select cases such as chronic pancreatitis with calcifications, we also allow the use of scalpel, when needed or indicated by the operating surgeon.

2. How is the rate of minimally invasive surgery in the hospital where the study is conducted?

Answer: Thank you for the very relevant question, around 50% of all distal pancreatectomies are performed minimally invasive in our centre. We are aware of the fact that the CUSA can only be used in open surgeries so far, therefore we adjusted the sample size to the expected number of open distal pancreatectomies in the recruitment period. Nevertheless, as far as we are informed, Integra Lifesciences is currently working on a laparoscopically useable CUSA device, which will be supposedly commercially available this or the following year as well as Sörling Innovative Surgery provides a new HEPACCS transection device for open and laparoscopic tissue transection. Therefore, a future trial will definitely include minimally invasive distal pancreatectomies.

3. Do the authors collect the data of pancreatic transection time?

Answer: Thank you for this remark, as stated in the study by Suzuki et al. that the CUSA device had a longer transection time (23 vs 9 minutes), we already know that the CUSA will take significantly longer than for example a stapler. Therefore, we decided not to collect the data of the transection time. It is

rather interesting that the stapling took 9 minutes in the trial of Suzuki et al., as I am convinced that the stapling normally does not take longer than 3-5 minutes. We anticipated a CUSA transection time of around 20-30 minutes and we will see this difference in the general operation time. Nevertheless, we also collect data, experience of the surgeon, quality of pancreatic tissue, intraoperative blood loss and drainage placement.

Reviewer: 2

Dr. Frances N McCarron, Mercy Health St Elizabeth Youngstown Hospital

Comments to the Author:

First the discussion portion of the abstract states that CUSA may have a beneficial effect on POPF. This is also mentioned in the limitations section. I think it is more accurate to say that the benefit of CUSA assisted transection is unknown based on current literature. As stated in the manuscript, the literature to support this is severely limited and flawed. This seems to be the basis for the current study.

Answer: Thank you for your comment. We agree that the beneficial effect of the CUSA device could only be shown in a very limited body of evidence, nevertheless, the only study that offers any usable data shows striking results which leads to the impression that CUSA may actually have a beneficial effect on the development on POPF rather than none or only an unknown effect. It is of course arguable that the original study by Suzuki et al. included mostly patients with healthy pancreata but we believe that this is a key detail, as healthy pancreas tissue (i.e. ISGPS grade C/D pancreas) has a much higher risk of developing POPF and therefore CUSA may be useful especially in these patients. The idea of this study is, of course, based on the fact that the effect of the CUSA transection device on postoperative pancreatic fistula (POPF) occurrence has never been investigated in this patient cohort. However, our assumption is also based on the somewhat dated but nonetheless impressive results of the study by Suzuki et al. Our main objective was to examine a homogeneous patient population undergoing distal pancreatectomy due to pancreatic disease. Why no further study on this method has been conducted since 1999 remains unclear to us. However, we believe that the results of the initial study are certainly indicative of the need for further investigations in pancreatic surgery patients.

Second, I think it is important to note that since there is no CUSA currently for minimally invasive surgery this RCT is limited to open distal pancreatectomy only. There is literature describing the benefits of MIS pancreatic surgery and at many centers this is the preferred approach. Thus, a limitation should be acknowledged that this is not transferrable to patients undergoing laparoscopic or robotic distal pancreatectomy. Consideration should also be given to adding the rationale for choosing open distal pancreatectomy over MIS for patients included in the study as there is potential for bias/confounding if open surgery is chosen for "more difficult cases" at this specific center.

Answer: Thank you for this very important remark. We took up this point in the limitation section and added the sentence "the CUSA transection method is yet only applicable in open distal pancreatectomy" in the strength and limitation section. Therefore, see Comment 2 of reviewer 1. Based on the data from the presented study, a future confirmatory study will hopefully include minimally invasive operations, depending on the availability of a suitable device

That being said, this is a very interesting study with potential for significant impact in the HPB community.

We thank you very much for your kind comment, we are also confident that this first pilot study will provide promising data for further confirmatory investigations. We hope to generate a significant impact on the most relevant complication after distal pancreatectomy.