PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Finnish study of intraoperative irrigation versus drain alone after evacuation of chronic subdural haematoma (FINISH): a study protocol for a multicentre randomized controlled trial
AUTHORS	Tommiska, Pihla; Rahul, Raj; Schwartz, Christoph; Kivisaari, Riku; Luostarinen, T; Satopää, Jarno; Taimela, Simo; Jarvinen, Teppo; Ranstam, Jonas; Frantzen, Janek; Posti, Jussi; Luoto, Teemu M.; Leinonen, Ville; Tetri, Sami; Koivisto, Timo; Lönnrot, Kimmo

VERSION 1 – REVIEW

REVIEWER	Ron L Alterman, MD, MBA Beth Israel Deaconess Medical Center Harvard Medical School Boston, Massachusetts, USA
REVIEW RETURNED	11-Apr-2020

GENERAL COMMENTS	In this manuscript the authors present a clinical protocol designed to determine if irrigation during burr hole drainage of chronic subdural hematomas affects the rate of recurrence. This is a multi-center, prospective, non-inferiority trial in which 540 (270 per group) patients with symptomatic cSDH will be randomized to receive burr hole craniostomy and passive subdural drainage for 48 hours either with or without irrigation of the subdural space prior to placement of the drain. The primary outcome measure is the rate of re-operation for recurrent SDH over the ensuing 6 months. In addition, a number of secondary outcome measures are proposed as well as monitoring for serious and minor adverse events. Overall, this is a nicely designed and presented study that is properly powered to answer the question posed. The proposed statistical analysis is appropriate and research ethics are sound. I have no major criticisms of the paper. I do have one minor point that requires clarification. On page 13, line 5 it states: "Following randomisation, written consent will primarily be obtained from the patient." But, isnt consent to be obtained prior to randomisation? Best of luck with the study.

REVIEWER	Sami Ridwan Department of Neurosurgery, Bethel Clinic, Germany
REVIEW RETURNED	14-Apr-2020

GENERAL COMMENTS	I congratulate the authors on this suffisticated study to answer a question we all ask ourselves on a daily Basis in neurosurgical practice. My main concern is that 200ml is quite high as a cutoff. In

	my opinion, irrigation with 199ml can't be considered N-IR. I think this might pose as a limitation possibly falsifying your results. Please explain why you chose 200ml? In some cases less irrigation is enough for clearing the cavitiy, this should then rather be an IR case. Recurrence within 6 months appears too distant from initial surgery. Former also volumetric analysis data suggest that cSDH heal within 2-3 months, e.g. our study Ridwan et al. 2019 WNS.

REVIEWER	Giorgio Callovini Dep. Neurosurgery ,Ospedale San Giovanni Addolorata, Rome , Italy
REVIEW RETURNED	16-Apr-2020

GENERAL COMMENTS	The Authors present a protocol paper as multicentre randomised controlled trial to study whether no intraoperative irrigation and subdural drainage results in non-inferior outcomecompared to intraoperative irrigation and subdural drainage following burr-hole craniostomy. This is an interesting topic of strong practical relevance: if no irrigating treatment does not impact the frequency of recurrences and reduces adverse events. It should be better specified the type of passive drainage employed. This is a well-designed protocol, worthy of publication.

REVIEWER	Paul Brennan University of Edinburgh, Scotland, uk
REVIEW RETURNED	27-Apr-2020

GENERAL COMMENTS	The authors have submitted for publication the study protocol for a trial that will compare irrigation and no irrigation in surgical treatment of CSDH. It's a well written protocol. There is interest in reducing the rate of recurrence in CSDH. The process of irrigation in treatment of a CSDH takes a few minutes of most and it is intuitive to want to remove the blood from the subdural space. The authors suggest that not irrigating offers potential for time saving. Probably at best a few minutes. They suggest there are risks associated with irrigation. However, the primary end point of the surgery is neither time, nor risks, but recurrence. The study design is non -inferiority. If recurrence is not significantly worse then the tie saving will be worth it. Surgeons will not be prevented from irrigating in the non-irrigation group. they will just be required to use less irrigation. So even if the non-irrigation group meets its inferiority target, surgeons will still no necessarily know whether they can avoid irrigating at all. I am concerned that there is an exclusion based on GCS<8 and perceived inability to tolerate a drain in the peri-operative period. No rationale is given for the GCS restriction. By limiting the inclusion in this way the study limits assessment of the applicability of the study to the wider non-study population.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Ron L Alterman, MD, MBA

Institution and Country: Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA

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

In this manuscript the authors present a clinical protocol designed to determine if irrigation during burr hole drainage of chronic subdural hematomas affects the rate of recurrence. This is a multi-center, prospective, non-inferiority trial in which 540 (270 per group) patients with symptomatic cSDH will be randomized to receive burr hole craniostomy and passive subdural drainage for 48 hours either with or without irrigation of the subdural space prior to placement of the drain. The primary outcome measure is the rate of re-operation for recurrent SDH over the ensuing 6 months. In addition, a number of secondary outcome measures are proposed as well as monitoring for serious and minor adverse events.

Overall, this is a nicely designed and presented study that is properly powered to answer the question posed. The proposed statistical analysis is appropriate and research ethics are sound. I have no major criticisms of the paper. I do have one minor point that requires clarification. On page 13, line 5 it states: "Following randomisation, written consent will primarily be obtained from the patient." But, isnt consent to be obtained prior to randomisation?

Best of luck with the study

Thank you for the comment. The sentence you are referring to belongs to the context of "delayed consent", i.e. if the patient cannot himself/herself give written consent prior to randomisation and surgery. We have tried to specify this. Please see:

"*Due to the nature and emergency aspects of the disease (mass effect on the brain causing confusion and disorientation, lowered level of consciousness requiring urgent surgery), some patients will not be able to give written consent prior to randomisation. If the patient is unable to give written consent prior to the randomisation, delayed consent will be sought. In these cases, oral consent will be obtained from the next of kin after providing information regarding the trial. Following oral consent from the next of kin, the patient can be randomised. Following randomisation and surgery, written consent will primarily be obtained from the patient. However, in case of the patient being unable to give written consent due to neurological disability, written consent is obtained from the next of kin. In these cases, the next of kin has the right to withdraw the patient's consent at any time*."

Reviewer: 2

Reviewer Name: Sami Ridwan

Institution and Country: Department of Neurosurgery, Bethel Clinic, Germany

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

I congratulate the authors on this suffisticated study to answer a question we all ask ourselves on a daily Basis in neurosurgical practice. My main concern is that 200ml is quite high as a cutoff. In my opinion, irrigation with 199ml can't be considered N-IR. I think this might pose as a limitation possibly falsifying your results. Please explain why you chose 200ml? In some cases less irrigation is enough for clearing the cavitiy, this should then rather be an IR case. Recurrence within 6 months appears too distant from initial surgery. Former also volumetric analysis data suggest that cSDH heal within 2-3 months, e.g. our study Ridwan et al. 2019 WNS.

Thank you for the comment.

Up to date there is a lack of studies looking at the effect of the amount of irrigation and recurrence rates. A study from 2012 conducted in Dusseldorf, showed that (PMID: 22476866) the median intraoperative irrigation volume was 863 ml in those with recurrence and 1,500 ml in those without recurrence (p<0.001). In the same study, the multivariable analysis showed that irrigating less than 1,400 ml is associated with an 18.8 (95% CI 7.0–50.3) increased hazard ratio for recurrence. These irrigation volumes numbers are, however, very high. Thus, after a consensus meeting between study centers we set the target arbitrarily at 200 ml. Noteworthy is that we record the exact volume irrigated to enable subgroup analyses.

We would like to stress that 199 ml is NOT considered N-IR. If the patient is randomised to IR and for some reason only 180 ml irrigation is used, the patient stays in the randomized arm for the ITT analysis.

We suspect that the “compliance to treatment allocation and possible crossover” might have confused the reviewer. Thus, we have clarified this in that particular section. Please see: “The per protocol treatment is 0 ml of intracranial irrigation in the N-IR group and ≥200 ml (per operated side) of intracranial irrigation in the IR group. In the event of protocol breach, crossovers will be handled as follows:”

We would also like to stress that in order to declare non-inferiority, both the intention-to-treat and the per protocol analyses have to indicate non-inferiority. This minimizes the risk of potential cross-over influence of the final outcome.

Regarding the recurrence within 6 months. We agree that most of the recurrences happen within 1–3 months and recurrences after 3 months are rare (which we also showed in our out retrospective study, PMID: 31158547). Yet, several randomized controlled studies in the field of CSDH, are using 6-month follow up. For example, the study by Santarius and colleagues in 2009 (PMID: 19782872), the study by Schucht and colleagues (PMID: 30893542), the Dex-CSDH trial (PMID: 30514400), and the SIC! trial (PMID: 29021000) have used 6-month as the time point for the assessment of the primary outcome. Thus, we see no reason to deviate from this.

Reviewer: 3

Reviewer Name: Giorgio Callovini

Institution and Country: Dep. Neurosurgery, Ospedale San Giovanni Addolorata, Rome, Italy

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

The Authors present a protocol paper as multicentre randomised controlled trial to study whether no intraoperative irrigation and subdural drainage results in non-inferior outcome compared to intraoperative irrigation and subdural drainage following burr-hole craniostomy. This is an interesting topic of strong practical relevance: if no irrigating treatment does not impact the frequency of recurrences and reduces adverse events. It should be better specified the type of passive drainage employed. This is a well-designed protocol, worthy of publication.

Thank you for this relevant comment. For the subdural drainage, the type of the drain is not standardized but all centres use 10F drains that are connected to a passive ventricular drainage bag (through a non-return valve). Most drainage systems come with their own drainage bags and connection tubes. Since different hospitals may be using different systems, we did not want to completely standardise this, as it might limit the generalizability of our results.

We refer the reviewer to the "Surgical technique" section. The passive ventricular drainage bag is positioned at bed level and patient mobilization is allowed during drainage. We have clarified that during mobilisation, the drain is kept open.

Please see: "Patient mobilization is allowed during drainage (drain is kept open). Prophylactic antibiotics during drainage are not routinely used".

Reviewer: 4

Reviewer Name: Paul Brennan

Institution and Country: University of Edinburgh, Scotland, uk

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

The authors have submitted for publication the study protocol for a trial that will compare irrigation and no irrigation in surgical treatment of CSDH. It's a well written protocol.

There is interest in reducing the rate of recurrence in CSDH. The process of irrigation in treatment of a CSDH takes a few minutes of most and it is intuitive to want to remove the blood from the subdural space. The authors suggest that not irrigating offers potential for time saving. Probably at best a few minutes. They suggest there are risks associated with irrigation. However, the primary end point of the surgery is neither time, nor risks, but recurrence.

The study design is non-inferiority. If recurrence is not significantly worse then the tie saving will be worth it.

Surgeons will not be prevented from irrigating in the non-irrigation group. they will just be required to use less irrigation. So even if the non-irrigation group meets its inferiority target, surgeons will still no necessarily know whether they can avoid irrigating at all.

We'd like to correct this misunderstanding. Surgeons will NOT be irrigating in the N-IR group (=0 ml). We suspect that the "compliance to treatment allocation and possible crossover" might have confused the reviewer. Thus, we have clarified this in that particular section. Please see: "The per protocol treatment is 0 ml of intracranial irrigation in the N-IR group and ≥200 ml (per operated side) of intracranial irrigation in the IR group. In the event of protocol breach, crossovers will be handled as follows:"

I am concerned that there is an exclusion based on GCS<8 and perceived inability to tolerate a drain in the peri-operative period. No rationale is given for the GCS restriction. By limiting the inclusion in this way the study limits assessment of the applicability of the study to the wider non-study population.

Thank you for the comment. The reason for the GCS ≤8 criterion is that a matter of safety. For patients being unconscious the situation is often urgent and rapid evacuation of the CSDH is of highest priority. It is reasonable to assume that hematoma evacuation is slower in the N-IR group than in the IR-group. Thus, we and the ethics committee felt that these patients should be kept out and treated according to current standards. The same concern has been shared by RCTs, where one of the arms include a "slower" evacuation (e.g. DXM treatment PMID 30342554, NCT02111785, NCT02938468; MMA embolization NCT03307395; NCT04095819).

This has been clarified in the text. Please see: Exclusion criteria / "Comatose patients (GCS 8 or lower, absent motor responses to painful stimuli; decerebrate or decorticate posturing), where rapid hematoma evacuation is required"

VERSION 2 – REVIEW

REVIEWER	Sami Ridwan Paracelsus Klinik Osnabrück, Osnabrück, Germany
REVIEW RETURNED	16-May-2020

GENERAL COMMENTS	Thank you for clarifying the requested information. Good luck with your study, the results will bring us a step closer to finding some standard for treatment of this common disease .

REVIEWER	paul brennan University of Edinburgh, UK
REVIEW RETURNED	18-May-2020

GENERAL COMMENTS	The reviewers raised similar queries and the authors have largely made some clarifications as to what was already written in the text.