Peer Review File

Article information: http://dx.doi.org/10.21037/atm-20-4719

Reviewer Comments:

Comment 1: What will you do if the fever is refractory to this medication? This HAS to be described! You may not leave them febrile I guess.

Reply: If the fever is refractory to this medication in the normothermia team, adjunctive cooling measures such as cooling blanket and ice packs were applied in the patients to maitain bladder temperature at 36-37°C. Sedative and analgesic drugs should be given when necessary. We have modified our text as advised(see Page10, Line194-197).

Comment 2: You may change the title to: "Targeted temperature management at 33 degrees Celsius in patients with high-grade aneurysmal subarachnoid hemorrhage".

Reply: Thanks for your valuable suggestion. We have modified the title to "Targeted temperature management at 33 degrees Celsius in patients with high-grade aneurysmal subarachnoid hemorrhage: a protocol for a multicenter randomized controlled study", and modified the text (see Page1, Line1-4).

Comment 3: Also state the WFNS grade you want include, because many centers will use also the WFNS grading for SAH patients.

Reply: Thanks for your valuable suggestion. We have added WFNS grades IV-V in the inclusion criteria and modified the text(see Page5, Line123-124).

Comment 4: You should add radiologic gradings into your inclusion criteria: mFisher grade (above 3?), global cerebral edema (Claassen et al.)? because we all know the

limitations of clinical gradings (WFNS, HH) alone.

Reply 4: Thanks for your carefulness. We have also added mFisher grades 3-4 and global cerebral edema in the inclusion criteria and modified the text(see Page7, Line123).

Comment 5: Why only Glasgow coma scale (GCS) 4-8 points at admission, what about GCS 3? I suggest to include them.

Reply 4: Thanks for your valuable suggestion. We have added GCS 3 in the inclusion criteria and modified the text (see Page7, Line126).

Comment 5: What does this mean in detail? surgical clamping or interventional embolization performed in the operating room immediately after admission or after resuscitation???

Reply 5: This sentence means: the aneurysms responsible for SAH should be treated by surgical clamping or interventional embolization as soon as possible when the patient's condition permits after admission or after resuscitation. We have modified the text (see Page7, Line126-128).

Comment 6: Please change the term therapeutic hypothermia to TTM at 33°C. A lower temperature may be harmful to patients. TTM to 33°C (intervention) TTM to 36-37.5°C (control) harbor the best evidence yet (mainly from TTM studies in cardiac arrest patients).

Reply 6: Thanks for your valuable suggestion. We have changed the term therapeutic hypothermia to TTM at 33°C and modified the text.

Comment 7: The term normothermia is not defined, neither abstract, nor manuscript.

Reply 7: We have defined the normothermia as 36-37°C of the bladder

temperature in "Treatment and management" par t(see Page9, Line190).

Comment 8: The conclusion should be changed to: TTM aiming 33°C in patients with high-grade aSAH MAY become a promising treatment strategy for improving 6-month outcome.

Reply 8: Thanks for your valuable suggestion. We revised the concludion according to your comments (see Page3, Line49-51).

Comment 9. In the Methods, Page 8, Randomization, please change the term "block" to "blocked randomization……using a computer generated random sequence", as this is suggested by the recent CONSORT guidelines (http://www.consort-statement.org/Media/Default/Downloads/CONSORT%202010%20Explanation%20and%20Elaboration%20Document-BMJ.pdf)

It is not clear, how the physicians are informed about the group assignment. Will they get an e-mail with the randomization details? Will patients be included only during working hours or also during night shifts or weekend shifts? Will there be a 24h hotline for the physicians if there are questions on patient inclusion?

Reply 9: Thanks for your valuable suggestion. We revised the text according to your comments (see Page7, Line138, 144-146).

During the trial, the physicians will be informed about the group assignment by cell telephone and e-mail. They will get an email with the randomization details. The patients will be included during working hours, night shifts and weekend ones. Yes, there will be a 24h hotline for the physicians if there are questions on patient inclusion.

Comment 10. Treatment: Where are your patients treated? Neuro-ICU? General ICU?

Stroke unit? If the patients are treated in different settings, you should provide a stratified analysis (e.g. Neuro-ICU stratum vs. general ICU stratum). Usually all patients with aneurysms are treated at an ICU and all WFNS grade IV and V patients will be ventilated.

Reply 10: Thank you very much for your reminder. The patients will be treated in Neuro-ICU, Stroke Unit or General ICU, and we will be provided a stratified analysis as you suggest. All WFNS grade IV and V patients will be ventilated. We hav modified the text (see Page8, Line149, and Page13, Line271)

Comment 10a. What will you use for sedation and analgesia? Only midazolam, or also sufentanil? To my opinion, it does not make any sense to limit the dosage of sedo-analgesia, because patient might be very different in their metabolism. It is better to clearly report the used dosage in your study (in mg/kgBW).

Reply 10a: We will use midazolam, propofol, dexmetomidine, remifentanil for sedation and analgesia. The doses of each drugs are midazolam 0.02～0.1mg/kg/h, propofol 4～12mg/kg/h, dexmetomidine 0.2～0.7μg/kg/h, remifentanil 0.02～0.15μg/kg/h, meperidine 0.03 ～ 0.06mg/kg/h, respectively. We revised the manuscript according to your comments (see Page9, Line179-181).

Comment 10b. Patient discomfort should be avoided. Shivering is an important limitation of TTM at 33°C. Please include a shivering protocol. A shivering protocol should be stepwise, please clarify that. How will you asses shivering? I recommend the shivering score by Badjatia et al., as this score is commonly used in comparable studies. Clonidine or dexmedetomidin are very useful drugs against shivering. Do you use Bair Hugger devices to treat shivering?

Reply 10b: We will assess shivering through the Bedside Shivering Assessment Scale[1]. The anti-shivering protocol is as follows: midazolam 0.02～0.1mg/kg/h,

propofol 4～12mg/kg/h, dexmetomidine 0.2～0.7μg/kg/h, remifentanil 0.02～0.15μg/kg/h, meperidine 0.03～0.06mg/kg/h, respectively, to maintain deep sedation as RASS -4, and regulate the doses to achieve adequate shiver control (BSAS≤1). We use dexmedetomidin against shivering, but not use clonidine because of side effect. We don't use Bair Hugger devices because we don't have the device (see Page9, Line178-181).

Comment 10c: Will you use muscle relaxans in your patients? If yes, bolus or continuous infusions?

Reply 10c: We generally don't use muscle relaxans in our patients because muscle relaxans easily cause impaired cough reflex and lead to pneumonia.

Comment 10d. Please discuss the advantages and disadvantages of rewarming speed (discussion section). Too slow rewarming might lead to more hypothermia related complications, too fast rewarming to rebound edema. What will you do if a patient gets severe vasospasm during rewarming? What procedures / cosequences? – Please describe this in your methods.

Reply 10d: Thanks for your valuable suggestion. As you said, a rapid increase in core body temperature can cause systemic vasodilation and hypotension, which can in turn trigger cerebral vasodilation, rebound edema and increased ICP [2], too slow rewarming might result in more hypothermia related complications. If a ptient gets severe vasospasm during rewarming, we will continue to maintain 33℃ for several days until relief of severe vasospasm. We have modified the manuscript (see Page14, Line298-301).

Comment 10e. Please clarify and ensure that the CPP of at least 50mmHg will be

measured /calculated with the MAP transducer at the level of foramen monroi (this makes a difference of at least 10 mmHg compared to atrium levels) and that these CPP targets are only used during the first 72 hours after aneurysm securing, because during vasospasm you might need 70-80mmHg CPP.

Reply 10e: Thanks for your valuable suggestion. We revised the manuscript according to your comments (see Page8, Line153-156).

Comment 10f. Recent Neurocritical Care society guidelines (2020) favor hypertensive saline (10%) instead of mannitol (Neurocritical Care volume 32, pages647–666(2020)). Please state if you use ICP guided bolus therapy or sodium targeted therapy (which would not be recommended).

Reply 10f: Thanks a lot. When ICP is elevated greater than 20mmHg, patients will be given an infusion of 4.2% HS at a dose of 125-250ml through a central venous catheter over 20 to 30 minutes. We generally do not use 10% HS. We modified the manuscript (see Page8, Line157)

Comment 10g. A blood flow velocity >120 cm/s in the middle cerebral artery (MCA) or the MCA/internal carotid flow velocity (Lindegaard ratio) >3 does only indicate an increased flow velocity, and is only a surrogate marker of vasospasm, which should be confirmed by additional angiogram.

Reply 10g: Thank you for your reminder. Transcranial Doppler (TCD) ultrasonography remains to be the primary noninvasive method for detection of vasospasm[3]. It is simple, fast, and reproducible. Many studies make use of TCD to detect vasospasm. Digital subtraction cerebral angiography would be performed to diagnose vasospasm if necessary because it is invasive.

Comment 10h. Avoid the term long-term hypothermia (this is misleading).

Reply 10h: Thank you very much for your advice. We have deleted the phrase" long-term" in the manuscript.

Comment 10i. Please state clearly, that it is a standard procedure to secure the aneurysm first, and then randomize the patients. Please describe how many patients are treated endovascular and how many are treated by clipping at your center (e.g. during the last 2 years). You may give this information in a supplementary file.

Reply 10i: Thank you very much. The standard procedure is to secure the aneurysm first, and then randomize the patients (see Page7, Line135-136). During the last 2 years, 1452 patients were treated by endovascular therapy and 234 ones were treated by clipping at our center.

Comment 10j. Concerning fever management: What physical methods do you use except ice packs? Pepper-mint washings? Cold i.v. fluids? Arctic sun?

Reply 10j: Common physical cooling measures we use includes cold iv. fluids, ice blanket except ice packs (see Page10, Line196).

Comment 10k. How do you investigate the cause of fever? How often do you perform chest X ray? There should be a routine urine examination and chest X ray before starting the cooling procedure. Antibiotics should be given according to the clinical situation after blood and urine cultures. Although these are basics, you should report the patient treatment as detailed as possible to have a good standard of care and synchronized treatment over your centers.

R**eply 10k: We investigate the cause of fever by physical, laboratory and imaging examination. Physical examination includes pulmonary auscultation et al. Laboratory examination includes blood routine test, PCT, blood culture, sputum culture, cerebrospinal examination and so on. Imaging examinatin includes chest**

X ray, chest CT and so on. We usually perform chest X ray once three days. Thank you very much for your advice. We add the details in the manuscript (see Page10, Line199-205).

References

[1] Jain A, Gray M, Slisz S, Haymore J, Badjatia N, Kulstad E. Shivering Treatments for Targeted Temperature Management[J]. J Neurosci Nurs,2018:1.

[2] Badjatia N. Therapeutic hypothermia protocols[J]. Handb Clin Neurol,2017,141:619-632.

[3] Durrant JC, Hinson HE. Rescue therapy for refractory vasospasm after subarachnoid hemorrhage[J]. Curr Neurol Neurosci Rep,2015,15(2):521.