

Format for ANSWERING REVIEWERS

February 25, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 15112-review.doc).

Title: Steps to consider in the approach and management of critically ill patient with spontaneous intracerebral hemorrhage

Author: Daniel Agustin Godoy, Gustavo Piñero, Patricia Koller, Luca Masotti, Mario Di Napoli

Name of Journal: *World Journal of Critical Care Medicine*

ESPS Manuscript NO: 15112

The manuscript has been improved according to the suggestions of reviewers:

Dear Editor in Chief

First of all I want to deeply thank the exhaustive work of the reviewers. We have taken and edited all your suggestions, which have clearly contributed to improving the quality of the manuscript. According to the editorial requirements below we respond point by point to the considerations of all reviewers, which will be highlighted in red for easy location.

Thank you very much again for the effort.

Reviewer 1

The manuscript is a thorough and scholarly review of the literature related to management of spontaneous intracerebral hemorrhage. While major grammar problems are present throughout, the manuscript is generally understandable. The provocative Step 1 to avoid nihilism is an interesting reminder that medicine combines both philosophy and science. Figure 8 presents some problems. The INR goal presented in the text (INR ≤ 1.5) is different from that in the figure (INR ≤ 1.2). Also, the INR in the figure is given as ≥ 1.2 or ≤ 1.2 . One of these equal signs needs to be removed. The INR value needs to be reconciled with the text. Also, the proposed pathway does not clearly take into account which anticoagulant is associated with the ICH. The decision branch point after CT confirmation of ICH and INR ≥ 1.2 is unspecified.

Response

Now, grammatical problems have been resolved. The text was entirely checked by a native English speaker. Figure 8 was made newly, correcting errors highlighted by the reviewer and in absolute agreement with the text.

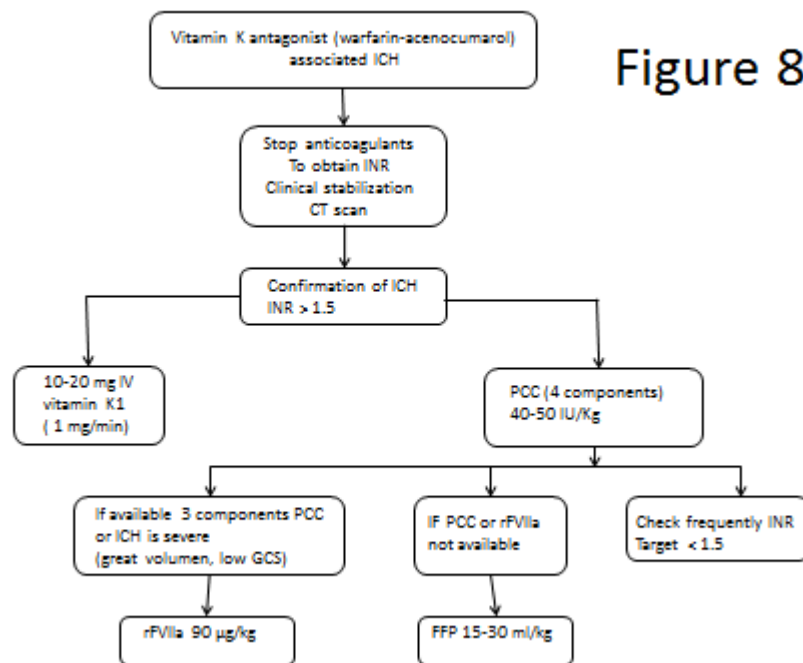


Figure 8. Algorithm to urgent reversal therapy in vitamin K antagonist related ICH
 ICH: intracerebral hemorrhage; INR: international normalization ratio; CT: computed tomography; IV: intravenous; PCC: prothrombin concentrate complex; IU: international units; kg: kilograms; GCS: Glasgow coma scale; rFVIIa: activated recombinant seven factor; µg: micrograms; FFP: fresh frozen plasma.

Reviewer 2: None suggestion.

Reviewer 3

Godoy et al submitted an interesting and extensive review dealing with the management of spontaneous intracerebral hemorrhage. I found their manuscript valuable and I believe that it deserves to be published in WJCCM. Some relatively minor corrections are necessary. Maybe the manuscript could be shortened. To avoid hyperthermia: No prospective study has been conducted. Please add that due to ethical concerns is very unlikely to be performed ever. Same page in sodium homeostasis, last line, change día per day. Gastrointestinal care. H2 receptors blockers are not recommended because.....until pneumonia 127. While I agree that these agents should be avoided in this setting, this is an ASSOCIATION rather than a causation. Please, state. Seizures control. The authors do not recommend any agent, but it should be stated that in the study by Naidech in 2009 phenytoin use was associated with more fever and worse outcomes after intracerebral hemorrhage. Hydrocephalus and ventricular extension of bleeding. Please, give more information of the design limitations of the CLEAR-IVH study. I believe that this recommendation has to be tone down. In my opinion, more (preliminary) evidence exists with lumbar drainage that deserves little comment in this review. Relaxation use in specific treatment of intracranial hypertension is used when it is strictly necessary. For respiratory purposes or as an intracranial hypertension treatment measure? Some grammar and style corrections are necessary. I also found problems with the superscript numbering of references and the spaces between words. In my opinion, the number of References is too high to support this review. The format of the references should be uniformly adapted to journal's recommendations. There is a problem with the numbering

and titles of figures/tables.

Response

Now, the manuscript was shortened in everything it was possible (from 8691 to 6383 words), without altering its essence. At the same time, grammatical and style corrections were undertaken. The manuscript was revised by a native English speaker. References were shortened too (from 262 to 134) and were formatted according to journal's recommendations. The numbering of tables and figures and the titles of them were corrected.

Legends of figures and tables

Figure 1. Steps to consider in the approach to the critically ill patient with spontaneous intracerebral hemorrhage (ICH)

Figure 2. Typical sites of bleeding in spontaneous ICH

Figure 3. Micro bleeds in Magnetic Resonance Imaging

Figure 4. Spot sign

Table 1. ICH Score. GCS: Glasgow coma scale; IVH: intraventricular hemorrhage; ICH: intracerebral hemorrhage.

Table 2. Secondary Insults. SIRS: Systemic Inflammatory Response Syndrome; DIC: Disseminated Intravascular Coagulation

Figure 5. Initial approach of the patients with suspected ICH.

GCS: Glasgow Coma Scale; ABC: Airway, Breathing, Circulation; EKG: electrocardiogram; CT: Computed tomography; ICH: intracerebral hemorrhage, SABP: Systolic arterial blood pressure; MABP: mean arterial blood pressure.

Figure 6. Physiological neuroprotection. 6 N Rules.

°C: Degrees Celsius; CVP: central venous pressure, WP: wedge pressure; SaO₂: oxygen arterial saturation; Na⁺: serum sodium levels; paCO₂: carbon dioxide arterial levels.

Figure 7. Algorithm suggested for venous thromboembolism prevention in ICH

ICH: intracerebral hemorrhage; CT: computed tomography; LMWH: low molecular weight heparin.

Figure 8. Algorithm to urgent reversal therapy in vitamin K antagonist related ICH

ICH: intracerebral hemorrhage; INR: international normalization ratio; CT: computed tomography; IV: intravenous; PCC: prothrombin concentrate complex; IU: international units; kg: kilograms; GCS: Glasgow coma scale; rFVIIa: activated recombinant seven factor; µg: micrograms; FFP: fresh frozen plasma.

Specific points

To avoid hyperthermia: according to reviewer suggestions, now the text is as follow: .." Until now, there is no a study that prospectively evaluated the impact of fever control on the outcome nor that is the most suitable method to control fever, and due to ethical concerns is very unlikely to be performed ever.

Sodium homeostasis: "dia was changed by day"

Gastrointestinal care: Now; ..." H₂ receptors blockers are not recommended because they are associated with encephalopathy, interaction with anticonvulsants and modify the local pH favoring bacterial colonization and pneumonia"...

Seizures control: In the text was added: ..." Phenytoin use was associated with more fever burden and worse outcomes after ICH".

Hydrocephalus and intraventricular hemorrhage: We follow strictly reviewer comments.

We tone down the topic and now the text is:" CLEAR-IVH study evaluated the strategy of external ventricular drainage more rtPA instillation, 3 mg twice daily versus optimal medical treatment. Resolution rates of clots were significantly higher with shorter permanence time of ventriculostomy in rtPA group. By contrast, symptomatic bleeding rate was higher in the group rtPA. Mortality rates not changed significantly. The study had several methodological limitations, for example; selection criteria for study inclusion did not include location of bleeding or extension of intraventricular hemorrhage; management of known factors that influence rates of bleeding such as blood pressure levels or coagulation state not were considered and the study was not designed to assess long-term functional outcome, a situation that is being evaluated in CLEAR III study.

Endoscopically removal of the clot and controlled lumbar drainage are promising therapeutic alternatives that need large-scale validation. Preliminary results indicate that lumbar drainage after radiological permeation of third and four ventricles was associated with a reduction in the need for permanent ventricular shunting.

Intracranial hypertension: Now..."We do not utilize neuromuscular paralysis unless strictly necessary for ICP normalization".

Reviewer 4

This was a very interesting review of an important topic. It does not claim to be a systematic review, and so there is no methodology given as to selection of papers. However, there is therefore a danger that this is merely an opinion piece. It would also be good to give clearer aims in the introduction. The paper is very long, and quite difficult to read (with a huge number of references). The language would certainly benefit from revision by a native English speaker. I wonder whether it would also be easier for the reader to see brief mini-summaries at the end of each section: for example, 'what is already known; what is controversial; what is currently being researched; final recommendations'. A couple of minor points: In Step 4, 'secondary injury', mention is made of 'rule 6N', but this isn't properly described (nor mentioned in figure 6). In the section 'glycemic control', final paragraph, the sentence beginning 'If it is clear the so-called...' doesn't make sense; there needs to be a '...then...' somewhere.

Response

The manuscript and references were shortened (see response to reviewer 1) and grammatical problems have been resolved. The text was entirely checked by a native English speaker. The aim of the paper was clarified in introduction as reviewer request. By restructuring the manuscript, shortening, the points requested by the reviewer have been entraining and clarified to make the article easier to read. At the end of each topic the reader will get recommendations and ongoing studies.

Now, 6N rule was properly described as follow: "the basis of therapeutic of any

neurological injury is to achieve organic homeostasis, which we call “physiological neuroprotection”. From a practical point of view and easy to remember is to maintain healthy 6 principal clinical variables (6 N rules), such as: euvolemia, paO_2 and paCO_2 levels, temperature, glycaemia and natremia. Target to achieve for each variable are depicted in Figure 6”.

Last paragraph of glycemic control topic was changed according to reviewer suggestions to: ...” Intensive insulin therapy (glucose levels between 80-110 mg/dl) is contraindicated, because at these levels starts cellular metabolic distress. The current trend is to maintain the lower limit of about 150 mg/dl and not higher than 200 mg/dl”.

A handwritten signature in black ink, appearing to be 'DAG' or similar, with a stylized flourish extending to the right.

Daniel Agustin Godoy, MD