## PEER REVIEW HISTORY



## ARTICLE DETAIL

| | |
|---|---|
| **TITLE (PROVISIONAL)** | Safety and Efficacy of Herbal Medicine for Acute Intracerebral Hemorrhage (CRRICH): A Multicenter Randomized Controlled Trial |
| **AUTHORS** | Zeng, Liling; Tang, Guanghai; Wang, Jing; Zhong, Jianbin; Xia, Zhangyong; Li, Jiexia; Chen, Guangsheng; Zhang, Yongbo; Luo, Saihua; Huang, Gan; Zhao, Qianshan; Wan, Yue; Chen, Chaojun; Zhu, Kaiyun; Qiao, Hanzi; Wang, Jian; Huang, Tao; Liu, Xian; Zhang, Qixin; Lin, Rongming; Li, Haijun; Gong, Baoying; Chen, Xiuyan; Zhou, Yuexiang; Wen, Zehuai; Guo, Jianwen |

## VERSION 1 - REVIEW

| | |
|---|---|
| **REVIEWER** | Dimitre Staykov<br>Hospital of the Brothers of St. John, Eisenstadt, Austria |
| **REVIEW RETURNED** | 30-Aug-2018 |

| | |
|---|---|
| **GENERAL COMMENTS** | The present manuscript reports on a multicenter placebo controlled RCT that investigated the safety of different herbal medicine treatments in patients with spontaneous ICH. I have several comments for the authors to consider.<br><br>1.The paper needs language editing by a native speaker.<br><br>2.The dose of each herb should be provided (weight unit, which part of the plant included, dried or other condition etc.)<br><br>3. Why did the authors use ABC/2 for assessment of the primary outcome parameter, given the fact that this formula is inaccurate as compared to planimetric assessment (that was used for research already in the FAST trial program more than 10 years ago). I think that this is a major weakness of the methodology.<br><br>4. Furthermore, why did the authors choose such a high cutoff value (>12cc) for the definition of ICH growth (see e.g. Al-Shahi et al Lancet Neurology 2018 using 6ml), especially considering the low baseline mean ICH volume in all groups?<br><br>5. Mean absolute ICH volumes, percentage of volume growth (related to baseline volume) and comparisons at 24h should be provided for all groups in table 2 for more clarity, rather than only rates related to affected patients.<br>6. The authors use different acronyms for the same term (AICH, ICH, HICH), please use consistent terms throughout the abstract and the manuscript text. |

| | |
|---|---|
| | 7. Why did the authors use an unusual definition of poor clinical outcome i.e. mRS 5 or 6? Most ICH studies use a cutoff between mRS 0-3 and 4-6, or 0-2 and 3-6.<br><br>8. The patients included have rather small ICH although the inclusion criteria did not restrict the population to this subgroup. The authors try to explain that there was a certain pre-selection as to which patients were preferably included in the trial, however, the provision of a screening log would be interesting for the reader to better understand which patients were not included. Otherwise this may be a major source of bias. |

| | |
|---|---|
| **REVIEWER** | Lily Lai<br>University of Southampton, United Kingdom |
| **REVIEW RETURNED** | 20-Oct-2018 |

| | |
|---|---|
| **GENERAL COMMENTS** | Thank you for the opporutnity to review this interesting paper. This is an under-researched area and that this multi-centred RCT on Chinese herbal medicines was carried out to investigate this area further. I have some comments for the authors which would strengthen the manuscript and improve clarity for readers.<br><br>The SRQR reporting checklist that the authors have submitted is irrelevant for this study as the checklist is for a qualitative study and not for an RCT.<br><br>Language and grammatical errors throughout need to be corrected. For example<br>Page 3, line 9 'To evaluated the safety and efficacy' should be 'To evaluate the safety and efficacy'<br>Line 43 'assessed on 90 days after symptom onset' should be 'assessed at 90 days after symptom onset'.<br>Line 38 refers to 'the secondary outcome endpoint' but the common term is either 'the secondary outcome' or 'the secondary endpoint'.<br>Page 5 line 17 'HICH' is referred to but the authors refer to 'AICH' in the earlier text. Please keep consistent or explain terminology in full before introducing in the text.<br>Please proofread carefully before resubmitting.<br><br>The Introduction section provides interesting scene-setting – however the writing style is not always consistent with the scientific writing style expected by readers of this journal. For example page 5 line 11 'RBS herbal medicine maybe promotes hematoma absorption' could be replaced with 'It is possible that RBS herbal medicine promotes hematoma absorption'.<br><br>To claim that an intervention has been proven to be effective previously is difficult for readers to accept without seeing arguments to demonstrate why this evidence is strong. The manuscript would be strengthened if the authors replaced terms such as 'proven' with such arguments and demonstrating specifically how previous studies have supported the hypothesis that RBS herbs could be helpful for HICH. In this case, drawing from evidence presented in the meta-analysis or from the |

| | |
|---|---|
| | retrospective study that the authors refer to would be particularly helpful.<br><br>Page 6 Line 37 – I'm interested in knowing more about obtaining informed consent from the patient. For patients to enrol onto this study, a GCS score of 6 or greater is required and it sounds like these patients may have varying capacity for consent. How did the team manage this variability? Did HICH patients truly have the capacity to provide signed consent given potential cognitive limitations? If a representative of the patient provided informed consent on behalf of the patient in these circumstances, this detail would be welcome in the manuscript.<br><br>Page 7 Line 46 onwards – when referring to the herbal medicines use, the common names (e.g. Rhubarb) are at times used instead of the standardised Latin scientific name, whilst in other cases the scientific name is used. Please amend it such that all herbs are referred to by the scientific name for consistency.<br><br>Page 7 line 44 onwards – there is insufficient detail provided regarding the interventions. Please can the authors provide specific information regarding these formulae. For example, dosage of the herbs, method of preparation of the herbs (it appears to be dried herbs that are decocted in boiling water?). This information does not appear to be present in either your Trial Registration or your Protocol documents. There is also no rationale for using these herbs in particular and why two particular formulae were used – was it based on the previous studies that the authors refer to, or the experience of certain clinicians? There lacks description of important elements of this herbal RCT such as which company produced the herbs, whether these companies adhered to GAP and GMP guidelines, where the herbal preparation was carried out and who by, confirmation that processes adhered to GCP, whether a reference sample was available, what the herbal preparation looked like and how it compared visually to the placebo (to ensure that participant blinding remained secure).<br>In Page 12, the authors discuss having carried out an ITT and FAS analysis – however, it is not clear from the results section reported subsequently whether it refers to the ITT or the FAS. Since both datasets are reportedly available, I would recommend the authors present both sets of results.<br><br>Page 17, Line 47 Table 2 – as this is a 3-arm study, it would be helpful if the authors could clarify which groups are referred to in the between-group differences that are described in the final column.<br><br>Page 19, line 3 –the authors have explained clearly in the Methods section what the primary outcome enlargement rate relates to and how this was measured but this is not that clear from the way it is presented in the results section, either in this table or descriptively in Page 15 line 51. Referring to the 'volume enlargement rate of ICH' as being 7.8% in the placebo group in the Results section implies that the cerebral haemorrhage volume was (presumably on average) 7.8% for participants in the placebo group. However, the authors are actually reporting that 7.8% of the participants in the placebo group experienced an increase in haematoma volume of greater than 33% or 12.5ml as measured by CT. Could the |

| | |
|---|---|
| | authors use different terminology here to make this clearer to the readers, especially since this is the primary outcome?<br><br>Page 19 Line 3 Discussion paragraph refers to a statement describing the effects of 'RBS administration' – for clarity, the authors should refer to the two interventions ICH-1 and ICH-2.<br><br>Page 19 Line 13 – the three serious bleeding events that is reported to have occurred in the ICH-1 group is unfortunately followed by a generic statement that all RBS treatment is a safety concern. However, this is not backed up by the results of this study – if this was the case ICH-1 and ICH-2 would lead to similar numbers of serious bleeding events which is not seen. The authors could improve on the presentation of their findings by relating more specifically to what their data shows.<br><br>Information presented in Page 21, lines 14 onwards describing the justification for using herbal medicine in this study should be presented in the Introduction section.<br>Whilst I understand that the authors are not able to provide definitive information regarding why administering ICH-1 or ICH-2 failed to improve the primary and secondary outcomes, the Discussion section would benefit from exploration of possible factors influencing the poor outcomes of using RBS within 6h of onset versus within 24 h onset. This would be especially helpful if it relates to specific herbs within either ICH-1 and ICH-2 and a critical analysis of why differences between ICH-1 and ICH-2 existed or did not exist. |

| | |
|---|---|
| **REVIEWER** | Thomas Cook<br>University of Wisconsin-Madison |
| **REVIEW RETURNED** | 20-Nov-2018 |

| | |
|---|---|
| **GENERAL COMMENTS** | The authors have described results of a multicenter randomized controlled trial of<br>safety and efficacy of herbal medicine for acute intracerebral hemorrhage. Overall, the analysis are described clearly and the analyses appear to be correct.<br><br>My major comment is that the safety results seem to be overstated. Specifically, the test for difference in the overall AE rate among the three groups yields a p-value of 0,022. While less than 0.05, this p-value is far from conclusive. Furthermore, comparisons ot the two ICH groups do not individually yield statistically significant differences with placebo. It is not clear that there is any real difference between groups. Of course, in the absence of any evidence of benefit, it is unclear whether potential differences in AE rates are of interest.<br><br>Similarly, while bleeding rates are numerically higher for the ICH-1 group, again it is unclear whether this is due to chance or an adverse effect of ICH-1, although it may be consistent with the RBS nature of ICH-1.<br><br>Specific comments (using page numbers at the bottom of each page): |

| | |
|---|---|
| | Page 10, around line 31, "The hematoma enlargement rate on days 10-14 (primary end point) and mortality between the three groups were compared using Fisher's exact test." How is Fisher's exact test used to compare 3 groups? It is generally only used for 2 group comparisons. Furthermore, The pairwise comparisons do not appear to be shown in any of the tables.<br><br>Top of page 17, "There were 35 AEs reported by investigators, and 22 AEs may have been TAEs. All AEs occurred during the double-blinded treatment period (within 2 weeks)." If all AEs occured during the double-blind period, aren't they all TAEs? Do you mean that the 35 AE occurred in 22 patients? I.e., Table 2 reports 6, 3, and 13 AEs in the three groups, which I assume refers to patients with at least 1 AE. (If in fact this table refers to total AEs, some of which occur in the same patient, then the p-value is wrong.)<br><br>Page 17, starting near line 38 "There were no differences in the incidence or type of serious AEs leading to death". I think you probably mean that there were no statistically significant differences among groups (the are likely to be numerically different).<br><br>Page 19, starting near line 9, "Conversely, the incidence of AEs increased significantly." It is unclear what "increased" means. As previously noted, the incidence of TAEs in the ICH-1 group is not statistically significantly larger than placebo.<br><br>Figure 2: Given the small number of deaths, it's not clear if this figure is useful. Furthermore, the numbers in the caption don't seem to match the figure. E.g., from the figure, the ICH-2 group seems to have only one death around day 17, and the latest death day in the caption is day 9, whereas there appear to be at least 4 deaths beyond this time in the figure. Finally, the caption statest "A possible small benefit of treatment with ICH 1,ICH 2 was evident from 10 to 90 days after treatment." It is unclear what this means. Please explain. |

**VERSION 1 – AUTHOR RESPONSE**

Response to review 1:

Dear professor Staykov,

We appreciate your comments. These comments are all valuable and helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied the comments carefully and have made correction which we hope meet with your approval.

Comment 1: The paper needs language editing by a native speaker. Answer: We are very sorry for the poor English writing. We have asked a native speaker for helping in editing language. Thanks again..

Comment 2: The dose of each herb should be provided (weight unit, which part of the plant included, dried or other condition etc.) .

Answer: We have made a table showing the detailed information about the herbals(one dose) involved in the intervention. And we have also supplemented the details in the supplemental material( shown in S4 Table in the online-only Data Supplement).

| TCM ID | Plant/animal parts included | Condition | dosage(gram) | dosage form |
|---|---|---|---|---|
| Hirudo nipponica Whitman | entire body | dry | 1.0 | granules |
| Tabanus bivittatus Matsumura | entire body | dry | 1.0 | granules |
| Rheum officinale Baill | rhizome | dry | 1.5 | granules |
| Typha angustifolia L | pollen | dry | 1.5 | granules |
| Trichosanthes kirilowii Maxim. | seed | dry | 1.5 | granules |
| Panax notoginseng （Burk.） F. H. Chen | rhizome | dry | 1.0 | granules |
| Acorus tatarinowii Schott | rhizome | dry | 1.0 | granules |
| Chinemys reevesii (Gray) | shell | dry | 1.5 | granules |

Comment 3: Why did the authors use ABC/2 for assessment of the primary outcome parameter, given the fact that this formula is inaccurate as compared to planimetric assessment (that was used for research already in the FAST trial program more than 10 years ago). I think that this is a major weakness of the methodology.

Answer: We really appreciate this comment. Considering that the study was conducted at 14 hospitals with different levels of services, planimetric assessment was hard to perform due to the limitation of radiology. So we chose the ABC/2 method that is easy to implement. Maybe, this is one potential limitation of this study. There may be is an deviation between the two methods, but the minor deviation make little effect on the results.In addition, the ABC/2 formula is still widely used in many clinical trials of ICH, such as the following two trials (Rodriguez-Luna D, Neurology 2016; Demchuk AM, Lancet Neurol.2012). So we consider it is reasonable to use ABC/2 for assessment of the primary outcome parameter.

The related literature with ABC/2 method:

1) Rodriguez-Luna D, Coscojuela P, Rubiera M, et al. Ultraearly hematoma growth in active intracerebral hemorrhage. Neurology 2016;87:357–364. 2) Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, et al..Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study.[J].Lancet Neurol.2012,11(4):307-14.

3) Divani, A. A., Majidi, S., Luo, X., Souslian, F. G., Zhang, J., Abosch, A., &

Tummala, R. P. (2011). The ABCs of Accurate Volumetric Measurement of Cerebral Hematoma. Stroke, 42(6), 1569–1574.

Comment 4: Furthermore, why did the authors choose such a high cutoff value

(>12cc) for the definition of ICH growth (see e.g. Al-Shahi et al Lancet Neurology 2018 using 6ml), especially considering the low baseline mean ICH volume in all groups?

Answer: It's usually to choose the two cutoff values (>12.5 or >6ml ) for the definition of ICH growth. But only when the volume of hematoma increased by 12.5ml, the ICH growth could affect the clinic prognosis(see e.g Dowlatshahi D et.al., Neurology 2011). Since we assessed the the poor outcome, we chose the cutoff values (>12.5 ml) for the definition of ICH growth. In addition, the trials INTERACT2 and ATACH Ⅱ also choose the cutoff values (>12.5 ) for the definition of ICH growth.

The related cited references as follows:

1) Dowlatshahi D, Demchuk AM, Flaherty ML, Ali M, Lyden PL, Smith EE. Defining hematoma expansion in intracerebral hemorrhage: Relationship with patient outcomes. Neurology 2011; 76: 12

2) Carcel C, Wang X, Sato S, et al. Degree and Timing of Intensive Blood Pressure Lowering on Hematoma Growth in Intracerebral Hemorrhage: Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial-2 Results. Stroke. 2016. 47(6): 1651-3.

Comment 5: Mean absolute ICH volumes, percentage of volume growth (related to baseline volume) and comparisons at 24h should be provided for all groups in table 2 for more clarity, rather than only rates related to affected patients.

Answer: We have provided more detail about the hemorrhage volumes in the table 2 showed as the follows. The mean absolute ICH volumes, percentage of volume growth (related to baseline volume) and comparisons at 24h have been added to the table 2 and are marked in red.

Table 2 Primary outcome and secondary outcomes

| | Placebo | ICH-2 | ICH-1 | Between-Group Differences P Value |
|---|---|---|---|---|
| Primary outcome: the incidence of hematoma enlargement at 24 h and at day 14 | | | | |
| At 24 h | 8/104(7.8) | 8/108(7.5) | 13/107(12.3) | 0.409 |
| On days 10-14 | 1/92(1.1) | 3/97(3.1) | 1/91(1.1) | 0.625 |
| Hemorrhage Volumes（ml）at Baseline and Follow-up | | | | |
| At baseline | 9.82±7.45 | 11.56±9.67 | 11.57±11.55 | 0.284 |
| At 24 h | 9.71±6.94 | 11.97±10.02 | 14.44±19.33 | 0.313 |
| percent increase from baseline- mean% (95% CI) | -14.1(4.5-32.7) | 3.4(0.2-6.5) | 41(9.4-91.4) | 0.22 |
| milliliters of increase from baseline | -0.13±1.41 | 0.22±2.24 | 3.13±16.10 | 0.168 |
| Secondary outcomes: | | | | |

| | | | | |
|---|---|---|---|---|
| NIHSS# at 3 months | 3.58±5.32 | 3.58±5.32 | 3.58±5.32 | 0.475 |
| Mortality at 3 months | 4/104(3.8) | 1/108(0.9) | 3/107(2.8) | 0.328 |
| Poor prognosis (mRS ≥5) | 7/99(7.1) | 5/105(4.8) | 6/100(6.0) | 0.783 |
| Total TEAEs | 6/104(5.8) | 3/108(2.8) | 13/107(12.1) | 0.022 |

The values are expressed as n/N(%) within group or the means±SD; # denotes the number of patients at 3 months: 104 in the placebo group, 107 in the ICH-2 group, and 105 in the ICH-1 group; P value vs. placebo.

---

Comment 6: The authors use different acronyms for the same term (AICH, ICH, HICH), please use consistent terms throughout the abstract and the manuscript text.

Answer: We have uniformly used the acronyms, AICH, throughout the abstract and the manuscript text.

Comment 7: Why did the authors use an unusual definition of poor clinical outcome i.e. mRS 5 or 6? Most ICH studies use a cutoff between mRS 0-3 and 4-6, or 0-2 and 3-6.

Answer: Actually, we had analyzed the data using a cutoff between 0-2 and 3-6.The following table shows the result (data not shown in the manuscript).

Since the differences aren't significant, we want to assess the worst endpoint(mRS 5 and 6 represent severe disability and death, respectively) and regard the severe disability and death rates as the second outcome.

| mRS | Placebo (n=105) | ICH-2 (n=99) | ICH-1 (n=100) | □2 | P* |
|---|---|---|---|---|---|
| 3-6 | 20（20.2） | 30（28.6） | 26（26.0） | 1.98 | 0.371 |
| 0-2 | 79（79.8） | 75（71.4） | 74（74.0） | | |

* Chi-squared Test

Comment 8: The patients included have rather small ICH although the inclusion criteria did not restrict the population to this subgroup. The authors try to explain that there was a certain pre-selection as to which patients were preferably included in the trial, however, the provision of a screening log would be interesting for the reader to better understand which patients were not included. Otherwise this may be a major source of bias.

Answer: The following DHI-S shows the provision of a screening log (Picture 1 used Chinese, Picture 2 translated into English ).We also have stated the study inclusion and exclusion criteria in the supplemental material( shown in S1 Table in the online-only Data Supplement),and we have stated the screening results in the Result section of the manuscript.Thanks again for your valuable comments.

# 自发性脑出血病人筛查表

提示：凡是头颅 CT 显示急性脑出血的患者均要进行筛选！

筛选号：_____

筛选医院：_____

A1 姓名 □□□□　　A2 出生日期：□□□□年□□月□□日

A3 性别：女性 □ 男性 □　　A4 民族：汉族 □ 其他 □

A5 发病至入院时间（24 小时计）□□时□□分

A6.既往疾病和用药史： 有 □ 否 □　　（如无，跳向问题 B）

是否有高血压？　　有 □ 否 □

既往 1 月内是否有急性脑梗塞、心绞痛、心肌梗塞、下肢动脉血栓　　有 □ 否 □

抗凝药物：华法林　肝素　低分子肝素　有 □ 否 □

抗血小板：阿司匹林　氯吡格雷　有 □ 否 □

B 发病时头颅 CT

检查时间　|__|__|月|__|__|日|__|__|时|__|__|分

出血量：按多田氏公式:血肿体积=ABC×1/2 计算

_____□□□ ml

C 凝血功能：PT_____ APTT_____ FIB_____INR_____

D 纳入标准：

1. 头颅 CT 提示脑出血；
2. 年龄大于 18 周岁；
3. 起病时间 6h 之内；
4. 无脑疝。
5. 知情同意；

E 排除标准

1. 经检查证实脑出血由脑肿瘤、脑外伤、血液病、脑血管畸形(先天异常)或动脉瘤等引起；1 月内有急性脑梗塞、心绞痛、心肌梗塞、下肢动脉血栓者；
2. 发病时有严重消化道出血，需禁食和胃肠减压不宜口服中药者；
3. 起病 6 小时内需急诊手术者；
4. 患者伴有严重的心、肝肾功能损害；
5. 发病初期即表现为严重脑疝患者；

F 结论：是否纳入？ □是 □否

医生签名：

筛选时间：

Picture 1 DHI-S used Chinese

Screening inventory for patients with spontaneous cerebral hemorrhage

Note: All patients with acute cerebral hemorrhage demonstrated by head CT should be screened

Screening of number: _____

Screening of hospital: _____

A1 Name:□□□□ A2 Date of birth: □□□□year□□month□□day

A3 Gender: Female☐ Male☐ A4 Nationality: Han nationality □ Other□

A5 Onset to admission time（calculated by 24h）□□Hour(s)□□Minute(s)

A6.Previous medical history and medication history: YES □ NO □ （If NO, jump to question B）

Hypertension YES □ NO ☐

Had acute cerebral infarction, angina pectoris, myocardial infarction, and lower limb artery thrombosis in the previous 1 month

YES □ NO ☐

Anticoagulate: warfarin heparin low molecular heparin YES □ NO ☐

Antiplatelat: Aspirin clopidogrel YES □ NO ☐

B Head CT at onset

Inspection time

|__||__|month(s)|__||__|day(s)|__||__|hour(s)|__||__|minute(s)

Volum of hematoma:calculated by coniglobus formula:Volum of hematoma=ABC×1/2

□□□ml

C Coagulation function: PT_____ APTT_____ FIB_____INR_____

D Inclusion criteria

1. Head CT indicates cerebral hemorrhage;
2. Age＞18 year;
3. The onset time is within 6h
4. Without brain herniation
5. Informed consent.

E Exclusion criteria

1. According to the examination, cerebral hemorrhage is caused by cerebral tumor, traumatic hematopathy, cerebral vascular malformation (congenital abnormality) or aneurysm. Patients with acute cerebral infarction, angina pectoris, myocardial infarction and lower limb artery thrombosis within 1 month;
2. Patients with severe gastrointestinal bleeding and need fasting and gastrointestinal decompression should not take oral Chinese medicine;
3. Emergency surgery within 6 hours after onset;
4. The patient is associated with severe cardiac, hepatic and renal dysfunction;
5. The initial presentation was severe cerebral hernia;

F Conclusion: including or not? YES □ NO ☐

Signature of the doctor:

The time of screening:

Picture

2 DHI-S translated into English

Response to review 2:

Dear professor Lai,

We appreciate your comments. These comments are all valuable and helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied the comments carefully and have made correction which we hope meet with your approval.

Comment 1: The SRQR reporting checklist that the authors have submitted is irrelevant for this study as the checklist is for a qualitative study and not for an RCT.

Answer: We are very sorry for uploading the irrelevant document, and we have remove the irrelevant file SRQP when we resubmitted. Thanks very much. Comment 2: Language and grammatical errors throughout need to be corrected.

Answer: We are very sorry for the poor English writing. We have asked a native English speaker to help us in proofreading carefully the manuscript. Any changes were highlighted by using the track changes mode in the manuscript. Comment 3: To claim that an intervention has been proven to be effective previously is difficult for readers to accept without seeing arguments to demonstrate why this evidence is strong. The manuscript would be strengthened if the authors replaced terms such as‘proven’with such arguments and demonstrating specifically how previous studies have supported the hypothesis that RBS herbs could be helpful for HICH. In this case, drawing from evidence presented in the meta-analysis or from the retrospective study that the authors refer to would be particularly helpful. Answer: Thanks for the particularly helpful comment. It' really helpful to improve our paper, after drawing from evidence presented in the meta-analysis or from the retrospective study. We have modified the text in the manuscript according your opinion.

The evidences was cited in the manuscript as follows:

‘Meta-analysis showed that RBS herbal therapy for AICH could improve the neurological function deficit, reduce the volume of hematoma and perihematomal edema, and lower the mortality rate and dependency.’ Comment 4: Page 6 Line 37–I'm interested in knowing more about obtaining informed consent from the patient. For patients to enrol onto this study, a GCS score of 6 or greater is required and it sounds like these patients may have varying capacity for consent. How did the team manage this variability? Did HICH patients truly have the capacity to provide signed consent given potential cognitive limitations? If a representative of the patient provided informed consent on behalf of the patient in these circumstances, this detail would be welcome in the manuscript.

Answer: We are very sorry that we have not given enough details about informed consent in the manuscript. If the participants don't have the capacity to sign the informed consent for serious condition or illiteracy, the researcher will explain the informed consent to the patients or their authorized immediate family. Weighing the pros and cons of both sides,their immediate family will decide whether to sign the informed consent on behalf of the patient. The informed consent has stated this information. We have added more detailed information to the manuscript.

Comment 5: Page 7 Line 46 onwards – when referring to the herbal medicines use, the common names (e.g. Rhubarb) are at times used instead of the standard Latin scientific name, whilst in other cases the scientific name is used. Please amend it such that all herbs are referred to by the scientific name for consistency.

Answer: Thank for the kind comment and we have amended it and named all herbals by the standard Latin scientific name.

Comment 6: Page 7 line 44 onwards–there is insufficient detail provided regarding the interventions. Please can the authors provide specific information regarding these formulae. For example, dosage of

the herbs, method of preparation of the herbs (it appears to be dried herbs that are decocted in boiling water?). This information does not appear to be present in either your Trial Registration or your Protocol documents. There is also no rationale for using these herbs in particular and why two particular formulae were used–was it based on the previous studies that the authors refer to, or the experience of certain clinicians? There lacks description of important elements of this herbal RCT such as which company produced the herbs, whether these companies adhered to GAP and GMP guidelines, where the herbal preparation was carried out and who by, confirmation that processes adhered to GCP, whether a reference sample was available, what the herbal preparation looked like and how it compared visually to the placebo (to ensure that participant blinding remained secure).

Answer:

(1) the ICH-1 formula and herbals

The formulae of ICH-1(including the two particular RBS herbals drugs) is based on the experience of the national medical master professor Jixue

Ren(1926-2010) and based on the previous studies (Liu Hai-yan, Ren Ji-xiang, Wang

Jian, Zhang Ying, Lv Zhi-guo, Zhao Jian-jun, Pharmacoeconomic evaluation of herbal decoctions for activating blood circulation to remove blood stasis and filling essence and nourishing marrow to treat cerebral hemorrhage at the acute stag. Beijing Journal of Traditional Chinese Medicine,2015,34 (7):

513-517).

The ICH-1 formula is composed of 8 herbals. The detailed information about the herbals in the ICH-1 formula(one dose) is showed in the following table. And we have supplemented the details in the supplemental material( shown in S4 Table in the online-only Data Supplement).

| TCM ID | Plant/animal parts included | Condition | dosage(gram) | dosage form |
|---|---|---|---|---|
| Hirudo nipponica Whitman | entire body | dry | 1.0 | granules |
| Tabanus bivittatus Matsumura | entire body | dry | 1.0 | granules |
| Rheum officinale Baill | rhizome | dry | 1.5 | granules |
| Typha angustifolia L | pollen | dry | 1.5 | granules |
| Trichosanthes kirilowii Maxim. | seed | dry | 1.5 | granules |
| Panax notoginseng （Burk.） F. H. Chen | rhizome | dry | 1.0 | granules |
| Acorus tatarinowii Schott | rhizome | dry | 1.0 | granules |

| | | | | |
|---|---|---|---|---|
| Chinemys reevesii (Gray) | shell | dry | 1.5 | granules |

(2)The interventions

The following table shows the detailed information of the three interventions. The details were stated in the Method section. We have also supplemented the details in the supplemental material( shown in S3 Table in the online-only

Data Supplement)..

GroupsandInterventions

| Groups | Interventions | Direction |
|---|---|---|
| ICH-1 | 8 herbal, including 2 herbals of RBS (Hirudo and Tabanus), | one dose, bid, by oral or nasogastric tube for 10 days |
| ICH-2 | 6 herbals(remove the 2 herbals of RBS | one dose, bid, by oral or nasogastric tube for 10 days |
| Placebo Comparator | placebo herbal medicine (with dextrin, farina and so on) | one dose, bid, by oral or nasogastric tube for 10 days |

*RBS, removing blood stasis

(3)The prepared method of the formula:

1) The process was performed with GMP guideline. Firstly, took Trichosanthes kirilowii Maxim. and Acorus tatarinowii in a medicine bag. Then put the medicine bag and Typha angustifolia.L. into a multi-functional extraction tank together. Added the drinking water and extracted with heating three times. After that, kept the micro boiling state for an hour before adding the drinking water with ten times the amount of medicine at the first time. At the last two times, the micro boiling state lasted 45 minutes and the amount of drinking water added was eight times larger than the amount of medicine. 400 meshes of liquid were filtered and concentrated to a relative density of 1.30 or more, the liquid was placed in a vacuum drying box, dried and collected at a vacuum of negative 0.06 to negative 0.08MPa and below 70 degrees Celsius; 2) Got Rheum palmatum L. and Panax notoginseng crushing into 80-100 mesh fine powder by universal crusher. Set aside;

3) Took one dry paste and crushed it into 80 to 100 mesh fine powder with universal crusher. Set aside;

4) Put the powders from step 2 and 3 together into the trough mixer, started up and run for 5 minutes, then added proper amount of 95% ethanol to make suitable soft material. After 14 mesh sieve was dried below 75 degrees Celsius, paid attention to not closing the oven door when heating at first, and then closed it after ethanol evaporates completely, continued drying until it was dry. After 14 mesh sieve, the dry particles were collected, weighed and tested to be qualified in the laboratory.

(4)which company produced the herbs, whether these companies adhered to

GAP and GMP guidelines.

The herbals were produced by Kangyuan pharmaceutical co. LTD (Kangyun). The company produced the herbals and prepared the formula adhered to GAP and GMP guidelines. The certificate of GMP of pharmaceutical products is showed as following:

中华人民共和国

# 药品GMP证书

CERTIFICATE OF GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS
PEOPLE'S REPUBLIC OF CHINA

证书编号：GD20160518
Certificate No.

企业名称：广州市康源药业有限公司
Manufacturer: Guangzhou Kangyuan Pharmaceutical Co., Ltd.

地　址：广州市南沙区榄核镇民利工业区
Address: Minli IndustrialPark, Lanhe town, Nansha district, Guangzhou city

认证范围：片剂，硬胶囊剂，颗粒剂，茶剂，丸剂(水蜜丸)，合剂，口服溶液剂，中药前处理及提取车间(口服制剂)
Scope of Inspection: Tablets, Capsules, Granules, Medicinal Teas, Pills(water honey pills), Mixture, Oral Solution, Chinese Crude Drugs processing and extraction workshop(oral preparations)

经审查，符合中华人民共和国《药品生产质量管理规范》要求。
特发此证。
*This is to certify that the above-mentioned manufacturer complies with the requirements of Chinese Good Manufacturing Practices for Pharmaceutical Products.*

有效期至 2021 年 02 月 02 日
*This certificate remains valid until 02/02/2021*

发证机关：
*Issued By*

*Date for Issuing* 03/02/2016　　2016 年 02 月 03 日

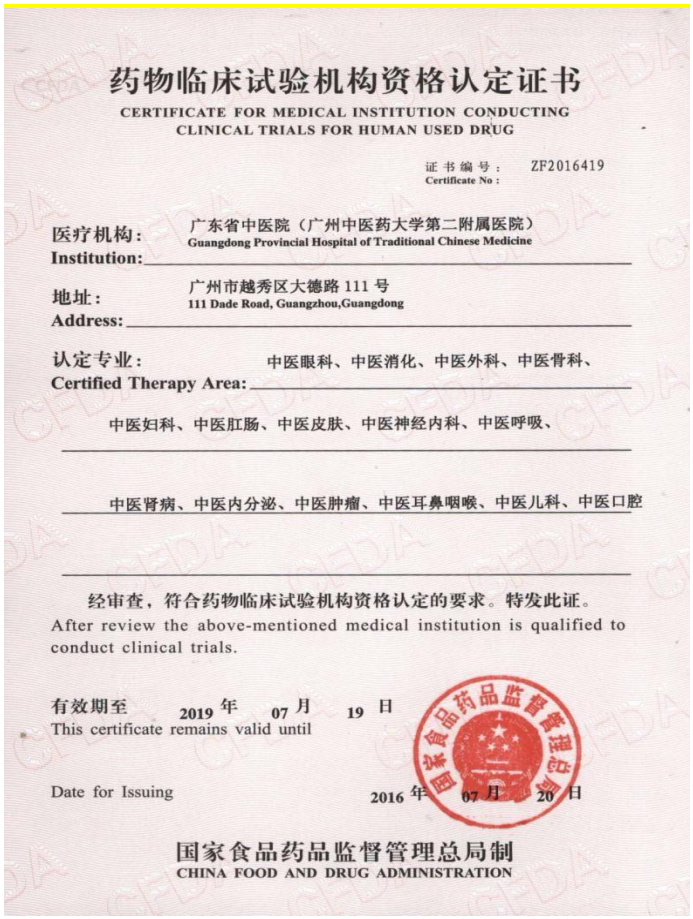
国家食品药品监督管理总局制
CHINA FOOD AND DRUG ADMINISTRATION

(5)where the herbal preparation was carried out and who by, confirmation that

processes adhered to GCP, whether a reference sample was available:

The herbal drugs were manufactured by Kangyuan pharmaceutical co. LTD (Kangyun) under the guideline of GMP, where lies in minli industrial Park, lanhe town, Nansha district, Guangzhou. And the drugs were carried out from Kangyun to the 14 clinical trial sites. The reference sample of the 3 groups' drug was available in Kangyuan for 10 years (2013-2022). Professor Weixiong

Liang, who is the administrator of the Guangdong Provincial Hospital of Chinese Medicine, supervised the processes adhered to GCP (No.ZF2016419). The GCP is showed as follows:



药物临床试验机构资格认定证书

CERTIFICATE FOR MEDICAL INSTITUTION CONDUCTING CLINICAL TRIALS FOR HUMAN USED DRUG

证书编号： ZF2016419
Certificate No :

医疗机构： 广东省中医院（广州中医药大学第二附属医院）
Institution: Guangdong Provincial Hospital of Traditional Chinese Medicine

地址： 广州市越秀区大德路 111 号
Address: 111 Dade Road, Guangzhou,Guangdong

认定专业： 中医眼科、中医消化、中医外科、中医骨科、
Certified Therapy Area:

中医妇科、中医肛肠、中医皮肤、中医神经内科、中医呼吸、

中医肾病、中医内分泌、中医肿瘤、中医耳鼻咽喉、中医儿科、中医口腔

经审查，符合药物临床试验机构资格认定的要求。特发此证。
After review the above-mentioned medical institution is qualified to conduct clinical trials.

有效期至 2019 年 07 月 19 日
This certificate remains valid until

Date for Issuing 2016 年 07 月 20 日

国家食品药品监督管理总局制
CHINA FOOD AND DRUG ADMINISTRATION

(6)what the herbal preparation looked like and how it compared visually to the

placebo (to ensure that participant blinding remained secure):

The herbal preparation looked like coffee powder which was packaged with aluminium foil bag. We prepared the placebo with caramel and bittern, which color, smell, and appearance looked like the ICH-1 or ICH-2 drug. We had tested the consistency among three groups' drug samples, with neurologists, nurse and patients before the clinical trial started.

Comment 7: In Page 12, the authors discuss having carried out an ITT and FAS analysis – however, it is not clear from the results section reported subsequently whether it refers to the ITT or the FAS. Since both datasets are reportedly available, I would recommend the authors present both sets of results.

Answer: We appreciate your comment. But before we get started, let's clear up one point: The ITT( intent-to-treat) not an analytical method but a principle and the FAS analysis (full analysis set) should be according to the intent-to-treat (ITT) principle, which was stated in the Statistical Analyses section in the manuscript. Since the result of FAS analysis is consistent with that of PPS( per-protocol population set) in the study, it's usually to show the result of the FAS analysis. So we just showed the result of FAS analysis in the manuscript. In the Statistical Analyses section, we have stated that we carried out FAS analysis based on ITT principle in the manuscript.

Comment 8: Page 17, Line 47 Table 2 – as this is a 3-arm study, it would be helpful if the authors could clarify which groups are referred to in the between-group differences that are described in the final column. Answer: We are sorry for the unclear clarification. Thanks for your helpful comment. In the table 2, the data were compared among three groups, and the table shows the differences between all 3 groups. We have clarified that in the final column. Thanks again.

Comment 9: Page 19, line 3–the authors have explained clearly in the Methods section what the primary outcome enlargement rate relates to and how this was measured but this is not that clear from the way it is presented in the results section, either in this table or descriptively in Page 15 line 51.

Referring to the'volume enlargement rate of ICH' as being 7.8% in the placebo group in the Results section implies that the cerebral haemorrhage volume was (presumably on average) 7.8% for participants in the placebo group. However, the authors are actually reporting that 7.8% of the participants in the placebo group experienced an increase in haematoma volume of greater than 33% or 12.5ml as measured by CT. Could the authors use different terminology here to make this clearer to the readers, especially since this is the primary outcome?

Answer: Thanks for your helpful comment. We have considered your comment carefully. We think it will be better that the terminology 'the incidence of hematoma enlargement', replaces the terminology 'volume enlargement rate of ICH'. The primary outcome, namely, the incidence of hematoma enlargement, was defined as the percentage of participants experienced hematoma enlargement.

Comment 10: Page 19 Line 3 Discussion paragraph refers to a statement describing the effects of 'RBS administration' – for clarity, the authors should refer to the two interventions ICH-1 and ICH-2.

Answer: we are so sorry to make you confused. RBS administration just refers to the intervention ICH-1.The intervention ICH-1 contains the RBS herbal (Hirudo nipponica Whitman and Tabanus bivittatus Matsumura), and the intervention ICH-2 did not contains the two special herbal drugs. The S3 table in the online-only Data Supplement shows the difference between the interventions ICH-1 and ICH-2.

S3 table in the online-only Data Supplement

| Groups | Interventions | Direction |
|---|---|---|
| ICH-1 | 8 herbal, including 2 herbals of RBS (Hirudo nipponica Whitman and Tabanus bivittatus Matsumura) | one dose, bid, by oral or nasogastric tube for 10 days |
| ICH-2 | 6 herbals(removed the 2 herbals of RBS from the ICH-1 formula) | one dose, bid, by oral or nasogastric tube for 10 days |
| Placebo Comparator | placebo herbal medicine (with dextrin, farina and so on) | one dose, bid, by oral or nasogastric tube for 10 days |

Comment 11: Page 19 Line 13 – the three serious bleeding events that is reported to have occurred in the ICH-1 group is unfortunately followed by a generic statement that all RBS treatment is a safety concern. However, this is not backed up by the results of this study – if this was the case ICH-1 and ICH-2 would lead to similar numbers of serious bleeding events which is not seen. The authors could improve on the presentation of their findings by relating more specifically to what their data shows.

Answer: RBS treatment just refers to the intervention ICH-1, because ICH-1 contains the RBS herbal (Hirudo nipponica Whitman and Tabanus bivittatus

Matsumura). The AEs (including the three serious bleeding events) incidence of the group of ICH-1were more than that of other groups. The intervention ICH-2 is also the control group in the study.

Comment 12: Information presented in Page 21, lines 14 onwards describing the justification for using herbal medicine in this study should be presented in the Introduction section.

Answer: Thanks for your careful attention to the details of our manuscript. Your comment can be helpful for our writing. But sudden adjustment in the order of the arrangement will affect the thought in writing. In addition, we had also described the justification for using herbal medicine in the Introduction section. And in the Discussion section, we want to emphasize that again. After weighing the pros and cons, we haven't made a big adjustment. We are very sorry and we beg your understanding.

Comment 13: Whilst I understand that the authors are not able to provide definitive information regarding why administering ICH-1 or ICH-2 failed to improve the primary and secondary outcomes, the Discussion section would benefit from exploration of possible factors influencing the poor outcomes of using RBS within 6h of onset versus within 24 h onset. This would be especially helpful if it relates to specific herbs within either ICH-1 and ICH-2 and a critical analysis of why differences between ICH-1 and ICH-2 existed or did not exist.

Answer: We appreciate your novel viewpoint. But before we get started, let's clear up one point: the intervention ICH-1 contains the RBS herbal (Hirudo nipponica Whitman and Tabanus bivittatus Matsumura), and the intervention ICH-2 contains the same herbals with the ICH-1 but the RBS herbals. So RBS administration just refers to the intervention ICH-1.

In addition, it usually focuses on the research on the poor outcomes of using RBS within 6h of onset. We don’t know whether RBS treatment would be effective within 24hrs of onset from the evidence of the clinical study. This will be one of our concerns in our future research. Thanks for your enlightened comment. Thanks again for your valuable comments.

Response to reviewer 3:

Dear professor Cook ,

We appreciate your comments. These comments are all valuable and helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied the comments carefully and have made correction which we hope meet with your approval.

Comment 1: My major comment is that the safety results seem to be overstated. Specifically, the test for difference in the overall AE rate among the three groups yields a p-value of 0,022. While less than 0.05, this p-value is far from conclusive. Furthermore, comparisons of the two ICH groups do not individually yield statistically significant differences with placebo. It is not clear that there is any real difference between groups. Of course, in the absence of any evidence of benefit, it is unclear whether potential differences in AE rates are of interest.

Answer: We really appreciate the comment. But before we get started, let's clear up one point: since ICH-1 contains the RBS herbals (Hirudo nipponica Whitman and Tabanus bivittatus Matsumura), RBS treatment just refers to the intervention ICH-1 and the intervention ICH-2 (without RBS herbals) is also the control group in the study. The S3 table in the online-only Data Supplement shows the difference between the interventions ICH-1 and ICH-2.

we have carried out the paired comparisons among three groups, and the test for difference in the overall AE rate between group ICH-1 and group ICH-2 yields a p-value of 0.029. While the p-value is less than 0.05, we should adjust the level of a test. Maybe We should not jump to the firm conclusions based on the p-value, but anyway it shows us this trend. We have add the result of paired comparisons in the Result section. Thanks again for your careful attention to the details of our manuscript.

Comment 2: Similarly, while bleeding rates are numerically higher for the ICH-1 group, again it is unclear whether this is due to chance or an adverse effect of ICH-1, although it may be consistent with the RBS nature of ICH-1. Answer: It has been recognized that RBS herbal medicine, such as Hirudo nipponica Whitman, can exhibit an anticoagulation effect and increase bleeding risk (Breddin HK, Pathophysiol Haemost Thromb. 2002). While bleeding rates are just numerically higher for the ICH-1 group, it cannot be ruled out: it may be consistent with the RBS nature of ICH-1. Maybe it needs further study.

Comment 3: Page 10, around line 31, "The hematoma enlargement rate on days 10-14 (primary end point) and mortality between the three groups were compared using Fisher's exact test." How is Fisher's exact test used to compare 3 groups? It is generally only used for 2 group comparisons. Furthermore, The pairwise comparisons do not appear to be shown in any of the tables.

Answer: Fisher's exact test can be used to compare 3 groups, or more groups. Many packages provide the results of Fisher's exact test for 2 x 2 contingency tables but not for bigger contingency tables with more rows or columns. For Fisher's exact test of bigger contingency tables, we can use web pages providing such analyses. For example, the web page 'Social Science Statistics' (http://www.socscistatistics.com/tests/chisquare2/Default2.aspx) permits performance of Fisher exact test for up to 5 x 5 contingency tables(Kim HY, Restor Dent Endod. 2017).

The related reference:

1) Kim HY. Statistical notes for clinical researchers: Chi-squared test and Fisher's exact test. Restor Dent Endod. 2017. 42(2): 152-155.

Comment 4: Top of page 17, "There were 35 AEs reported by investigators, and 22 AEs may have been TAEs. All AEs occurred during the double-blinded treatment period (within 2 weeks)." If all AEs occured during the double-blind period, aren't they all TAEs? Do you mean that the 35 AE occurred in 22 patients? I.e., Table 2 reports 6, 3, and 13 AEs in the three groups, which I assume refers to patients with at least 1 AE. (If in fact this table refers to total

AEs, some of which occur in the same patient, then the p-value is wrong.) Answer: We are very sorry for our unclear expression as to some misunderstanding. There were altogether 35 AEs reported by investigators over the course of the study（from onset to 90 days), but only 22 AE occurred in 22 patients were classified TEAEs( treatment-emergent AEs) which were defined as AEs that first occurred or worsened (increased in severity) after the first dose of study drug .This table refers to total TEAEs and we just analyzed the TEAEs.

Comment 5: Page 17, starting near line 38 "There were no differences in the incidence or type of serious AEs leading to death". I think you probably mean that there were no statistically significant differences among groups (the are likely to be numerically different).

Answer: Yes. We mean that there were no statistically significant differences among groups. I have changed another expression in the manuscript for fear of misunderstanding. The changes were marked by using the track changes mode in the manuscript.

Comment 6: Page 19, starting near line 9, "Conversely, the incidence of AEs increased significantly." It is unclear what "increased" means. As previously noted, the incidence of TAEs in the ICH-1 group is not statistically significantly larger than placebo.

Answer: We are very sorry for our unclear expression as to some misunderstanding. In scientific view, we should draw the conclusion carefully.

We have slightly modified the expression in the manuscript as follows: Conversely, compared to the ICH-2, the incidence of TEAEs showed an increasing trend in the ICH-1 group (P= 0.029, ICH-1vs.

ICH-2)'. Comment 7: Figure 2: Given the small number of deaths, it's not clear if this figure is useful. Furthermore, the numbers in the caption don't seem to match the figure. E.g., from the figure, the ICH-2 group seems to have only one death around day 17, and the latest death day in the caption is day 9, whereas there appear to be at least 4 deaths beyond this time in the figure. Finally, the caption statest "A possible small benefit of treatment with ICH 1,ICH 2 was evident from 10 to 90 days after treatment." It is unclear what this means.

Please explain.

Answer: Thanks for your helpful comment. The censored patients are also showed in the figure 2. The numbers in the caption just represent the death count. We intended to convey that there was likely to be numerically different.

After careful consultation with statisticians, considering the small number of deaths, the figure does little to help in showing the differences among groups, and we decided to remove the figure 2. Thanks again for your valuable comments.

**VERSION 2 – REVIEW**

| | |
|---|---|
| **REVIEWER** | Dimitre Staykov<br>Hospital of the Brothers of St. John, Eisenstadt, Austria |
| **REVIEW RETURNED** | 21-Jan-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | The reviewer completed the checklist but made no further comments. |

| | |
|---|---|
| **REVIEWER** | Lily Lai<br>University of Southampton |
| **REVIEW RETURNED** | 02-Feb-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | Thank you for addressing my comments in my first review of this paper. This paper including the language has significantly improved since the first submission - well done.<br><br>There are a few final minor issues I'd like to pick up on regarding this revised manuscript:<br><br>Page 2: Incidence is singular, so the authors need to correct the incidence of hematoma enlargement from 'were' to 'was'<br><br>Although I thank the authors for clarifying that ICH-1 and ICH-2 formulae differ in RBS-containing herbs or not, this needs to be clarified in the abstract. For example, the abstract conclusion still refers to ICH-1 as 'RBS-herbal medicine' and it's not immediately clear to the reader that it is referring to ICH-1. The authors should state the facts - i.e. that ICH-1 did not exert significantly beneficial effects etc etc, and then make a comment that this difference in effects and AEs between ICH-1 and ICH-2 could be related to inclusion of RBS herbal medicines in ICH-1. As the manuscript stands, this is still not apparent to the reader. |

| | |
|---|---|
| | In page 4 the first bullet claims that there was one compound formula examined, when in fact there were two. Please correct in manuscript.<br><br>Page 4 Please insert '(AICH)' immediately after you have clarified the full terminology, not in the following sentence.<br><br>Page 7 please remove 'don't' and substitute with 'did not' and ensure that this edited section on informed consent is written in the same tense (past) as the rest of the 'Participants' paragraph.<br><br>Page 2 and Page 6 Your study objectives stated on these two pages are slightly different here which has led to some confusion when I have reviewed this paper again. The main text states that you are evaluating the safety and efficacy of RBS-containing herbal medicine but the abstract states only herbal medicine. This makes quite a big impact to the flow of the paper overall - please can the authors clarify and keep consistent throughout.<br><br>Page 8 Thank you for letting me know in your comments the responses to my questions re the herbs and method of manufacture. This information needs to be provided within your supplementary material which I can't see. Please include this here rather than only in response to my comments.<br><br>Page 9 'defined as the percentage of participants experienced hematoma enlargement' should be changed to 'defined as the percentage of participants who experienced hematoma enlargment'<br><br>Page 10 NIHSS and mRS scores are not explained in full in the Methods section - please specify in the Methods prior to reporting in Results.<br><br>The Discussion section is generally much clearer and much more self-critical. However, references to ICH-1 and 'RBS-group/RBS-herbs' are still used interchangeably when referring specifically to the interventions in the study. For clarity to the reader, I believe this needs to be made consistent, with ICH-1 referred to in the study intervention and RBS-herbs being referred to when discussing the broader impact of the results of the study in comparison to similar studies.<br><br>Discussion section - regarding the comment re '..suggest that RBS treatment for ICH patients within 6h of symptom onset is a safety concern. However, no data were available to suggest a mechanism for this effect.' - could the authors speculate by drawing on from wider literature in basic sciences and provide the reader with some possible reasons (even if the mechanisms were not investigated in this particular study)? |

| | |
|---|---|
| **REVIEWER** | Thomas Cook<br>University of Wisconsin-Madison, USA |
| **REVIEW RETURNED** | 10-Feb-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | The authors have adequately addressed my concerns. |

**VERSION 2 – AUTHOR RESPONSE**

Response to review 2:

Dear professor Lai,

Thanks for your valuable and helpful comments. We have revised our manuscript according to your clever and useful suggestion by using the track changes mode.

Comment 1:

1)Page 2: Incidence is singular, so the authors need to correct the incidence of hematoma enlargement from 'were' to ‘was’.

2) In page 4 the first bullet claims that there was one compound formula examined, when in fact there were two. Please correct in manuscript.

3) Page 4 Please insert '(AICH)' immediately after you have clarified the full terminology, not in the following sentence.

4) Page 7 please remove 'don't' and substitute with 'did not' and ensure that this edited section on informed consent is written in the same tense (past) as the rest of the 'Participants' paragraph.

5) Page 9 'defined as the percentage of participants experienced hematoma enlargement' should be changed to 'defined as the percentage of participants who experienced hematoma enlargement.

Answer: We have corrected these errors in writing by using the track changes mode. Thanks again.

Comment 2: Although I thank the authors for clarifying that ICH-1 and ICH-2 formulae differ in RBS-containing herbs or not, this needs to be clarified in the abstract. For example, the abstract conclusion still refers to ICH-1 as 'RBS-herbal medicine' and it's not immediately clear to the reader that it is referring to ICH-1. The authors should state the facts - i.e. that ICH-1 did not exert significantly beneficial effects etc etc, and then make a comment that this difference in effects and AEs between ICH-1 and ICH-2 could be related to inclusion of RBS herbal medicines in ICH-1. As the manuscript stands, this is still not apparent to the reader.

Answer: Thanks for your careful thought. We really agreed with your opinion and we have stated the conclusion in the manuscript as follows: Ultra-early administration of ICH-1formula for AICH patients did not exert significant beneficial effects on clinical outcomes but increased the risk of bleeding, which probably resulted from the inclusion of RBS herbal medicines in ICH-1.

Comment 3: Page 2 and Page 6 Your study objectives stated on these two pages are slightly different here which has led to some confusion when I have reviewed this paper again. The main text states that you are evaluating the safety and efficacy of RBS-containing herbal medicine but the abstract states only herbal medicine. This makes quite a big impact to the flow of the paper overall - please can the authors clarify and keep consistent throughout.

Answer: We have modified the statements and keep consistent throughout in the manuscript.

Comment 4: Page 8 Thank you for letting me know in your comments the responses to my questions re the herbs and method of manufacture. This information needs to be provided within your supplementary material which I can't see. Please include this here rather than only in response to my comments.

Answer: We have also supplemented the details in the supplemental material( shown in S4 Table in the online-only Data Supplement). Thanks again.

Comment 5: Page 10 NIHSS and mRS scores are not explained in full in the Methods section - please specify in the Methods prior to reporting in Results.

Answer: We have specified NIHSS and mRS in the Methods.

Comment 6: The Discussion section is generally much clearer and much more self-critical. However, references to ICH-1 and 'RBS-group/RBS-herbs' are still used interchangeably when referring specifically to the interventions in the study. For clarity to the reader, I believe this needs to be made consistent, with ICH-1 referred to in the study intervention and RBS-herbs being referred to when discussing the broader impact of the results of the study in comparison to similar studies.

Answer: We have modified the Discussion section according your opinion. We also consider this need to be made consistent, for fear that confuses the readers.

Comment 7: Discussion section - regarding the comment re '..suggest that RBS treatment for ICH patients within 6h of symptom onset is a safety concern. However, no data were available to suggest a mechanism for this effect.' - could the authors speculate by drawing on from wider literature in basic sciences and provide the reader with some possible.

Answer: We have supplement the possible mechanism for this effect in the manuscript.

**VERSION 3 - REVIEW**

| | |
|---|---|
| **REVIEWER** | Lily Lai<br>Unviersity of Southampton, United Kingdom |
| **REVIEW RETURNED** | 27-Mar-2019 |

| | |
|---|---|
| **GENERAL COMMENTS** | I would like to thank the authors for addressing the comments I made in the previous revision. I am satisfied that these have been considered fully and the necessary changes made to the manuscript. I have no further comments to add. |