香港浸會大學李棕博士中醫藥圖書館

館藏與服務推廣通訊

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中醫藥臨床研究論文首次登上《The Lancet》引發關注

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引言

本通訊主要推廣中醫藥圖書館的到館新書、新購電子書、中醫藥相關教材、數據庫與平台、軟件與工具、特色館藏、圖書館的服務設施，以及重要的通知公告及其他信息服務等。

2024年11月12日，國際著名醫學期刊《The Lancet》在網上發表了一項關於中醫藥治療急性腦出血的多中心隨機、安慰劑雙盲對照臨床試驗結果，該項研究的題目為“Traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial”(中醫藥FYTF-919治療急性腦出血：一項多中心隨機、安慰劑對照的雙盲臨床研究)，這項研究將正式發表在2024年11月30日出版的《The Lancet》雜誌(Volume 404, Issue 10468)。這是《The Lancet》雜誌自1823年創刊200年來，首次刊登中醫藥多中心臨床研究，應該說具有里程碑式意義，然而這項大規模多中心的臨床研究結果卻顯示使用了20多年的國醫大師臨床經驗方竟然無效，研究結果立刻引起了大量的關注，不少媒體將此冠以“里程碑式”意義之外，又添上了“中醫藥無效”的標籤。隨著事件的發酵，很多官媒不但把當時高調宣傳的新聞稿件撤了下來，在醫藥行業也引發了廣泛的討論。《The Lancet》在發表本篇論文的同時，同步刊登了一篇評論，作者是四川大學華西醫院神經內科副教授吳思緲，該評論文章提到，該臨床試驗中的中風醒腦液被鑒定出30種化學成分，這些成分間可能存在藥代動力學或藥效學的協同作用，將使試驗結果的解讀變得複雜。

本期是通訊的第二十一期，主要向大家介紹這篇引起大家關注的《The Lancet》創刊200年來首次發表的中醫藥研究論文，轉載媒體的相關報道和網絡的一些代表性觀點。《The Lancet》相關的兩篇論文全文都附在本期通訊最後，以供大家參考。

香港浸會大學李棕博士中醫藥圖書館“館藏與服務推廣通訊(Library Collection and Services Promotion Newsletter)”旨在向中醫藥學院的老師和同學推廣中醫藥圖書館的館藏與服務，更好地為教學、臨床與科研提供支持。如果您對通訊的內容有任何的意見和建議，歡迎聯絡中醫藥圖書館，聯繫方式如下：

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《The Lancet》雜誌簡介

《The Lancet》中文翻译：《柳葉刀》或者《刺針》

《The Lancet》雜誌(中文翻譯為《柳葉刀》或者《刺針》)，是世界上最悠久及最受重視的同行評審醫學期刊之一，具有200年歷史，由英國外科醫生湯瑪斯·威克利（Thomas Wakley）創辦於1823年10月5日，他以外科用具「手術刀」（Lancet）的名稱來為這份刊物命名，而「Lancet」也有「尖頂穹窗」的意思，藉此寓意著期刊立志成為「照亮醫界的明窗」(to let in light)。

《柳葉刀》是全球頂尖綜合性醫學期刊，由愛思唯爾（Elsevier）公司出版發行，每週都會發表來自世界各地頂尖科學家的研究精粹，對全球醫學科學和臨床實踐具有啟發和推動意義，對衛生事業的發展有著無可比擬的影響。《柳葉刀》與另外三份國際醫學期刊《新英格蘭醫學雜誌》、《美國醫學會雜誌》、《英國醫學雜誌》成為公認的國際四大醫學期刊。

《柳葉刀》是全球頂尖的臨床、公共衛生和全球衛生知識的可信來源，最新影響因數為 98.4，在全球329本全科和內科學期刊中排名第一（2023 Journal Citation Reports®, Clarivate 2024），Scopus CiteScore 為 148.1，在全球636本全科醫學期刊中排名第一。

《柳葉刀》旗下共24本系列期刊，其中12本為金色開放獲取期刊，12本為混合型期刊，他們都制定了極高的發表標準，成為了科學研究發表的終點，也是提高科學研究全球影響力的重要平臺。

自創刊以來，《柳葉刀》一直努力推動科學的廣泛傳播，讓醫學服務社會、改變社會並積極影響人們的生活。迄今為止，《柳葉刀》已刊發一萬餘期，發表的論文對科學和人類健康做出了重要貢獻。當然，《柳葉刀》發表的個別文章也曾經引起廣泛的爭議。

中醫藥臨床研究論文首次登上《The Lancet》

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*部份內容來源於出版社網站及其他相關網站

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02

《The Lancet》雜誌自1823年創刊200年來首次刊登中醫藥多中心臨床研究

概述

急性自發性腦出血，是卒中類型中最嚴重的一種，導致三分之二的患者死亡或者殘疾，每年大約340萬人的生命健康因此受到威脅，給社會和家庭造成沉重負擔。儘管近年來醫學界在超急性期降壓、急性期組合性管理以及微創手術等方面取得了一定進展，但腦出血的有效治療手段仍然十分有限，亟須研發有效藥物改善患者結局。

2024年11月12日，國際著名醫學期刊《The Lancet》在網上發表了一項關於中醫藥治療急性腦出血的多中心隨機、安慰劑雙盲對照臨床試驗結果，該項研究的題目為《中醫藥FYTF-919治療急性腦出血：一項多中心隨機、安慰劑對照的雙盲臨床研究》(簡稱“CHAIN研究”)，這項研究將正式發表在2024年11月30日出版的《The Lancet》雜誌(Volume 404, Issue 10468)。

該研究由復旦大學的宋莉莉教授/Craig Anderson教授團隊和廣東省中醫院（廣州中醫藥大學第二附屬醫院，廣東省中醫藥科學院）郭建文教授團隊共同牽頭，研究旨在評估中藥中風醒腦方（紅參、三七、川芎、大黃）與安慰劑治療相比，能否改善急性腦出血患者的功能預後。中風醒腦液是源于國醫大師陳紹宏教授驗方製成的中藥複方製劑，臨床用於急性腦出血超過20年。此次研究歷經4年，全國共26個中心參與，是迄今為止全球最大規模的中醫藥治療急性腦出血的多中心、隨機、安慰劑對照臨床研究，為中醫藥雙盲試驗提供了嚴謹的臨床試驗設計範式。

這是《The Lancet》雜誌自1823年創刊200年來，首次刊登中醫藥多中心臨床研究，應該說具有里程碑式意義，然而這項大規模多中心的臨床研究結果卻顯示使用了20多年的國醫大師臨床經驗方竟然無效，研究結果立刻引起了大量的關注，不少媒體將此冠以“里程碑式”意義之外，又添上了“中醫藥無效”的標籤。隨著事件的發酵，很多官媒不但把當時高調宣傳的新聞稿件撤了下來，在醫藥行業也引發了廣泛的討論。


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ARTICLES · Volume 404, Issue 10468, P2187-2196, November 30, 2024

Traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial

Prof Jianwen Guo, PhD [a,b,c,x,*] · Xiaoying Chen, PhD [e,*] · Manli Wu, MD [c,*] · Dou Wang, MD [c,*] · Yang Zhao, PhD [f,*] · Qiang Li, MBiostat [e] · et al. Show more

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背景 Background

急性自發性腦出血是最嚴重的腦卒中類型，但有效治療手段十分匱乏，且局限在發病早期以減少血腫體積為目的。中藥FYTF-919（中風醒腦液）是一種由4種中草藥製成的口服製劑，在中醫理論上被認為具有促進血腫吸收和調節免疫的作用，在中國有多年應用於治療腦出血的臨床經驗。CHAIN研究旨在採用標準的隨機對照試驗方法評估FYTF-919在中重度腦出血患者中的臨床有效性和安全性。

There are few proven treatments for acute spontaneous intracerebral haemorrhage, and they all target reducing expansion of the haematoma. The traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao) in an oral solution is comprised of several Chinese herbs that are widely used to treat patients with intracerebral haemorrhage in China on the understanding that they enhance resorption of the haematoma and reduce neuroinflammation. We aimed to provide a reliable assessment of the safety and efficacy of FYTF-919 in patients with moderate to severe acute intracerebral haemorrhage.

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方法 Methods

CHAIN研究是一項在中國26家醫院開展的務實的、多中心、隨機、安慰劑對照、雙盲試驗。發病48小時內且經影像學證實的成年（≥18歲）自發性中重度腦出血患者（NIHSS≥8分或GCS 7-14分），按照1:1比例隨機分配至FYTF-919組或者安慰劑組。隨機分組採用區塊隨機（區塊大小為4或6），並按研究中心、神經功能缺損程度（NIHSS評分）和血腫位置進行分層。安慰劑和FYTF-919在外觀、氣味、味道和其他方面均能做到一致。患者在隨機後立即開始接收試驗藥物或者安慰劑的治療，每天3次，每次口服33ml（鼻飼患者改為每天4次，每次25ml），治療持續28天。主要研究終點是90天的utility-weighted mRS（UW-mRS，mRS是一個七級序數量表，範圍從 0[無症狀]到 6[死亡]，其中七個等級的效用權重分別為 0.97、0.88、0.74、0.55、0.20、-0.19 和 0.00，分數越高表示結果越好），主要分析使用廣泛線性模型並調整基線參數。我們對主要結局進行了多種校正和敏感性分析。主要結局在意向性治療人群中進行。此研究已在ClinicalTrials.gov註冊，註冊號為NCT05066620。

We did a pragmatic, multicentre, randomised, double-blind, placebo-controlled trial at 26 hospitals in China. We enrolled adults (age ⩾18 years) with a diagnosis of symptomatic spontaneous intracerebral haemorrhage (confirmed by brain imaging) within 48 h after the onset of symptoms (or last seen well), which resulted in moderate to severe neurological impairment defined by scores of at least 8 on the National Institute of Health Stroke Scale or between 7 and 14 inclusive on the Glasgow Coma Scale. Randomisation (1:1) was via a central internet-based system with a block grouping method stratified by provincial location of the hospital, severity of neurological impairment, and site of the haematoma in the brain. FYTF-919 and the placebo were masked through consistency in appearance, smell, taste, and other aspects. Participants were allocated to receive 33 mL (or 25 mL via a nasogastric tube if a participant's swallowing was impaired) of either oral liquid FYTF-919 or matching placebo administered at least 30 min after a meal every 8 h (or 6 h via nasogastric tube) over 24 h for 28 days. The primary efficacy outcome was the utility weighted modified Rankin Scale (a seven-level ordinal scale that ranges from 0 [no symptoms] to 6 [death], in which the utility weights of 0.97, 0.88, 0.74, 0.55, 0.20, –0.19, and 0.00 were assigned to the seven levels respectively, with higher scores indicating a better outcome according to the participants' perspective) at 90 days analysed in a general linear model with adjustment for baseline factors. We did several adjusted and sensitivity analyses. Primary analyses were assessed in the intention-to-treat population. This trial is registered at ClinicalTrials.gov, NCT05066620 and is complete.

*中文翻譯來源：柳葉刀 The Lancet 微信公眾號


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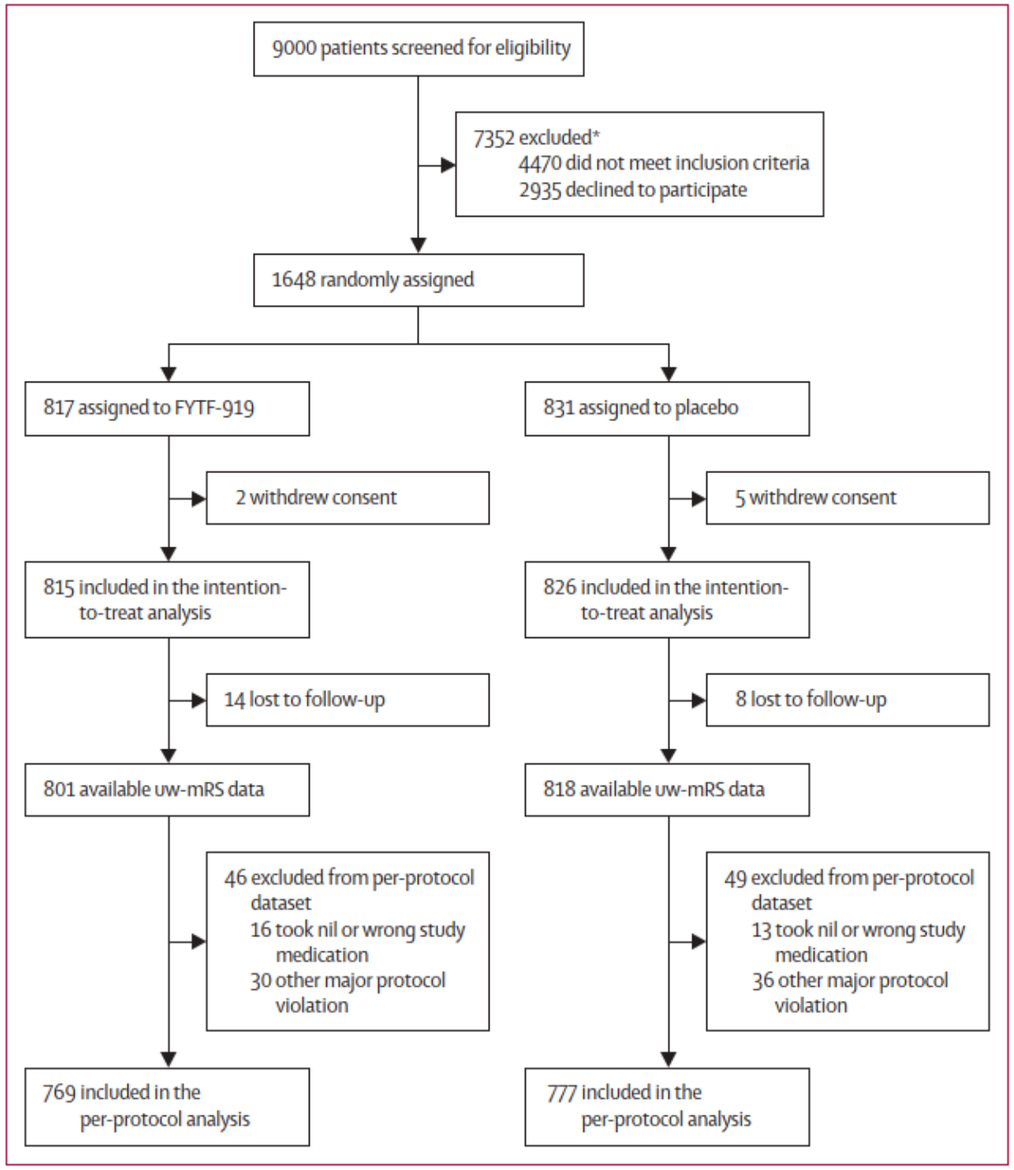

Figure 1: **Trial profile over 90 days**
uw-mRS=utility weighted modified Rankin Scale. *Data are not mutually exclusive.

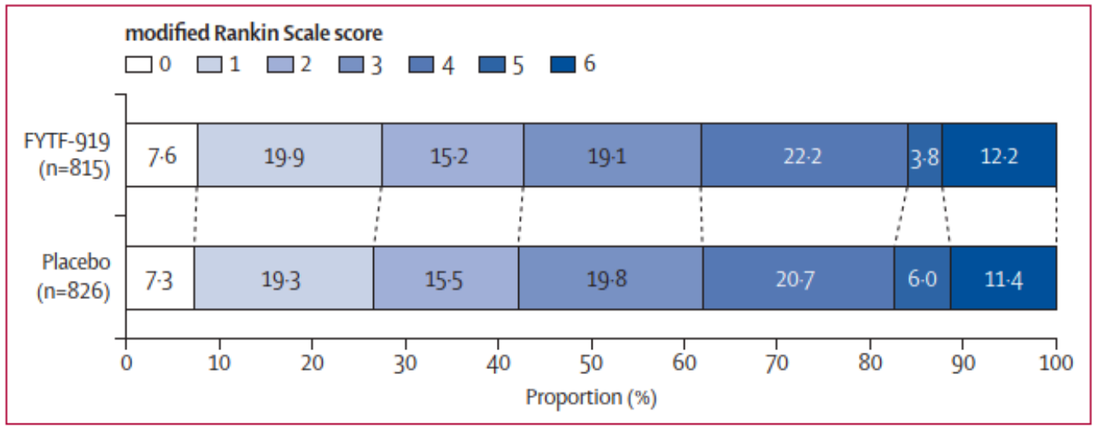

Figure 2: **Raw distribution of the modified Rankin Scale scores at 90 days by treatment group in the intention-to-treat population**
The figure shows the raw distribution of scores on the modified Rankin Scale at 90 days. Scores on the modified Rankin Scale range from 0 to 6. 0=no symptoms. 1=symptoms without clinically significant disability. 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability, and 6=death. In adjusted analysis of available data, the common odds ratio is 0·99 (95% CI 0·84 to 1·18; p=0·94) for poor outcome in the FYTF-919 group versus the placebo group.

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結果 Findings

2021年11月24日至2023年12月28日，CHAIN研究共篩選了9000名患者，納入1648例急性腦出血患者， 817例患者被隨機分配到了FYTF-919組，831例患者被隨機分配到了安慰劑組。FYTF-919組的2名患者和安慰劑組的5名患者在接受治療之前退出知情同意，因此1641名有主要結局資料的患者被納入意向性治療集，包含FYTF-919組的815例和安慰劑組的826例患者。1242（75.7%）的患者服用了超過80%的藥物，994名（60.6%）患者完全遵從方案，在28天內服用完所有藥物。FYTF-919組和安慰劑組的90天UW-mRS平均值都是0.44，兩組之間沒有顯著差異（difference 0.01, 95% confidence interval, -0.02 to 0.04; p=0.63）。各項敏感性分析結果均一致，兩組的嚴重不良事件也沒有顯著差異。

Between Nov 24, 2021, and Dec 28, 2023, of 9000 patients screened, 1648 were randomly assigned to treatment, 817 to the FYTF-919 group and 831 to the placebo group. Before receiving any treatment two patients in the FYTF-919 group and five patients in the placebo group immediately withdrew their consent leaving 1641 participants with available primary outcome data in the intention-to-treat population, 815 in the FYTF-919 group and 826 in the placebo group. 1242 (75.7%) participants consumed 80% or more of the study medication and 994 (60.6%) consumed all of it within 28 days. Mean utility weighted modified Rankin Scale scores at 90 days were 0.44 in the FYTF-919 group and 0·44 in the placebo group (difference 0.01, 95% CI −0.02 to 0.04; p=0.63). The neutral result was consistent in adjusted and sensitivity analyses. There was no significant difference in serious adverse events.

*中文翻譯來源：柳葉刀 The Lancet 微信公眾號


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結果 Findings

	n	FYTF-919 mean (SD)	n	Placebo mean (SD)	Mean difference (95% CI)	$p_{interaction}$
Sex						
Male	518	0·52 (0·35)	545	0·51 (0·36)	0·01 (–0·03 to 0·05)	0·95
Female	283	0·48 (0·36)	273	0·46 (0·36)	0·01 (–0·04 to 0·06)	
Age (years)						
18–64	440	0·55 (0·33)	489	0·56 (0·33)	–0·01 (–0·05 to 0·03)	0·11
≥65	361	0·44 (0·36)	329	0·40 (0·37)	0·04 (–0·00 to 0·09)	
Time to randomisation (h)						
0–12	335	0·49 (0·35)	331	0·53 (0·36)	–0·01 (–0·06 to 0·03)	0·25
≥12	466	0·51 (0·35)	487	0·47 (0·35)	0·02 (–0·02 to 0·06)	
NIHSS score						
0–14	365	0·67 (0·30)	373	0·66 (0·31)	0·01 (–0·04 to 0·05)	0·89
15–42	432	0·36 (0·33)	438	0·35 (0·34)	0·01 (–0·03 to 0·05)	
Haematoma volume (ml)						
<15	329	0·62 (0·33)	359	0·64 (0·32)	–0·03 (–0·07 to 0·02)	0·04
≥15	433	0·42 (0·34)	425	0·38 (0·34)	0·04 (–0·00 to 0·08)	
Haematoma location						
Cortical lobe	78	0·61 (0·36)	74	0·45 (0·44)	0·12 (0·02 to 0·22)	0·05
Deep	654	0·49 (0·34)	674	0·50 (0·35)	–0·01 (–0·04 to 0·03)	
Infratentorial	54	0·47 (0·39)	54	0·48 (0·35)	0·03 (–0·09 to 0·15)	

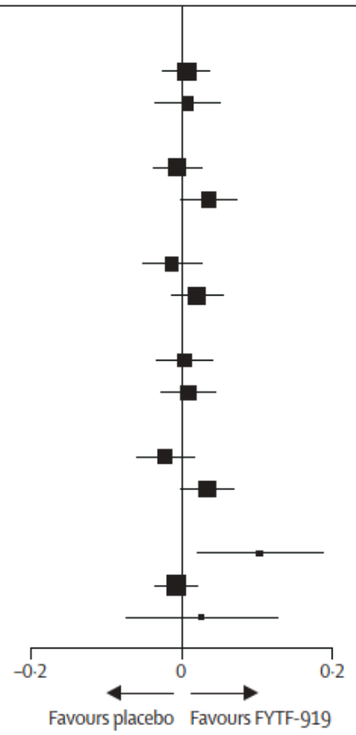

Figure 3: **Functional outcomes according to utility weighted modified Rankin Scale scores at 90 days in subgroups of patients in the primary adjusted model**
NIHSS=National Institutes of Health Stroke Scale.


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ARTICLES · Volume 404, Issue 10468, P2187-2196, November 30, 2024

Traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial

Prof Jianwen Guo, PhD [a,b,c,x,*] · Xiaoying Chen, PhD [e,*] · Manli Wu, MD [c,*] · Dou Wang, MD [c,*] · Yang Zhao, PhD [f,*] · Qiang Li, MBiostat [e] · et al. Show more

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中醫藥臨床研究論文首次登上《The Lancet》

論文鏈接

*中文翻譯來源：柳葉刀 The Lancet 微信公眾號

論文簡介：
中醫藥FYTF-919治療急性腦出血：一項多中心隨機、安慰劑對照的雙盲臨床研究

THE LANCET, Articles, Volume 404, Issue 10468, P2187-2196 November 30, 2024

郭建文,宋莉莉,Craig Anderson, 等

Traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial

解釋 Interpretation

這項大型的隨機、安慰劑對照、雙盲試驗顯示，中風醒腦方未能改善中重度腦出血患者的功能預後、生存率和生活品質。研究結果再次證明，需要進行方法嚴謹的隨機對照試驗來評估現有療法的有效性，包括已經在世界各地廣泛使用的傳統中藥。

This large, randomised, placebo-controlled, double-blind, clinical trial showed no effect of the traditional Chinese medicine herbal compound FYTF-919 on functional recovery, survival, and health-related quality of life in patients with moderate to severe intracerebral haemorrhage. The results reaffirm the need for methodologically rigorous, randomised controlled trials to evaluate the effectiveness of existing therapies, including traditional Chinese medicines that are already in widespread use throughout the world.


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研究團隊介紹

研究由復旦大學的宋莉莉教授/Craig Anderson教授團隊和廣東省中醫院（廣州中醫藥大學第二附屬醫院，廣東省中醫藥科學院）郭建文教授團隊共同牽頭完成。廣東省中醫院的郭建文教授、武曼麗、王豆博士和喬治全球健康研究院的陳曉英、趙洋博士為共同第一作者，復旦大學的宋莉莉教授、Craig Anderson教授和廣東省中醫院的郭建文教授為共同通訊作者。該研究受廣東省重點領域研發計畫嶺南中醫藥現代化項目（2020B1111100009資助）

中醫藥臨床研究論文首次登上《The Lancet》

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广东省中医院
广州中医药大学第二附属医院
广州中医药大学第二临床医学院
广东省中医药科学院
中国中医科学院广东分院

*中文翻譯來源：柳葉刀 The Lancet 微信公眾號

媒體報道：

廣東中醫再創紀錄！中醫藥治療腦出血研究成果登上《柳葉刀》

來源：羊城晚報·羊城派　作者：林清清　發表時間：2024-11-13 22:07

對於首登《柳葉刀》的過程，郭建文接受羊城晚報記者採訪時透露：“由於設計嚴謹、執行良好，資料的完整可靠和可溯源性，這次在《柳葉刀》的刊發審核過程也比較順利，僅用時一個多月就通過審核。”“此次登上國際頂刊的意義，不僅僅在於一項研究結果本身，而是兩種話語體系的對接，以及對未來中醫藥臨床試驗設計範式的影響。”郭建文表示，未來中藥的新藥研發上市流程，也有可能從中獲益。

對於研究所面臨的困難，郭建文介紹，研究之初，國際專家在交流溝通時就提出了兩大核心問題：安慰劑和中醫藥療效機制。中藥口服液安慰劑的製作，在國際層面上一直面臨困難，團隊通過與廣州本土的食品工業企業合作，用了近一年時間，突破了安慰劑的研發技術瓶頸；在中醫藥發揮療效的機制方面，國際專家已清晰理解中醫的辨證論治，就如同現代醫學的精准治療，找到了精准人群的精准靶點。“下一步，我們會針對優勢人群，開展進一步的療效確定性研究，並進行成果轉化，把這個處方開發成中藥新藥，為更大範圍內有需要的人群提供更多更好的選擇。”

*金羊網：https://health.ycwb.com/2024-11/13/content_53054598.htm


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來源：復旦大學，作者：汪蒙琪，發表時間：2024-11-13 11:30

據瞭解，該研究是迄今為止中藥領域針對腦出血治療所開展的最大規模的隨機對照臨床試驗，由復旦大學類腦智慧科學與技術研究院的宋莉莉教授與克雷格·安德森（Craig Anderson）教授團隊攜手廣東省中醫院的郭建文教授團隊共同完成。據宋莉莉介紹，此次研究涵蓋了中國12個省市的26家醫院，共納入了1648例急性腦出血患者。這一大規模的樣本，為研究結果的可靠性提供了基礎。宋莉莉說“我們用了一個完全國際標準化的試驗方法來評估中藥的療效。”

這項大規模隨機安慰劑對照雙盲試驗未能證明“中風醒腦方”能顯著改善中重度腦出血患者功能預後、生存率和生活品質，但證實了其安全性，兩組間不良反應無顯著差異。“儘管研究的總體結果為中性，但仍有一些積極信號讓我們感到樂觀。”克雷格·安德森表示，這項研究的創新之處在於，它不僅將高標準的國際化研究方法引入了中醫藥研究，還首次將患者的感知納入了康復情況評估體系。對於中醫藥，這位外籍醫學專家表達了開放、支持的態度，“西醫也有它的局限性，所以我們應當開放地尋找其他機會。中醫藥領域的知識、經驗和多樣化療法是非凡的。”他相信，傳統中醫藥療法將在卒中治療領域佔有一席之地。

“第一步是確立科學的方法，我認為目前的結果是符合預期的，並且我們看到它（“中風醒腦方”）可能在某個人群裡是有效的，未來可以在特定人群裡進一步進行驗證。”宋莉莉表示，基於目前的研究結果，團隊有望繼續推進二期研究。

據悉，此次研究還邀請了包括澳大利亞健康與醫學科學院院士格雷姆·漢基（Graeme Hankey）和英國愛丁堡大學教授魯斯塔姆·沙希·薩爾曼（Rustam Al-Shahi Salman）在內的多位國際知名專家學者擔任顧問，為研究提供了專業指導。這些頂尖學者的參與不僅提升了研究的國際水準，也促進了中西醫學之間的交流與對話。

*上觀：https://sghexport.shobserver.com/html/baijiahao/2024/11/13/1460082.html


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來源：復旦大學，作者：汪蒙琪，發表時間：2024-11-13 11:30

第十六屆世界卒中大會（World Stroke Conference, WSC 2024）於2024年10月23-26日在阿聯酋-阿布達比盛大召開，來自世界各地約3000名卒中領域專家齊聚一堂，進行廣泛的交流和溝通，以促進卒中領域的進一步發展。

據悉，該研究榮邀主會場演講，宋莉莉、克雷格·安德森和郭建文等團隊主要成員在會上介紹了此次研究成果，受到了各國專家學者的廣泛關注與讚譽。WSC副主席、歐洲卒中組織前主席維拉麗雅·卡索（Valeria Caso）認為該研究設計嚴謹、執行良好，通過高品質的研究顯示了中醫藥對較大的血腫患者具有前景的治療效果，給予重症腦出血患者更多生存和致殘恢復的希望。世界卒中組織（World Stroke Organization，WSO）主席傑亞·潘丹（Jeyaraj Pandian）教授盛讚該研究“用科學資料，促進傳統醫學走向世界”。

*上觀：https://sghexport.shobserver.com/html/baijiahao/2024/11/13/1460082.html


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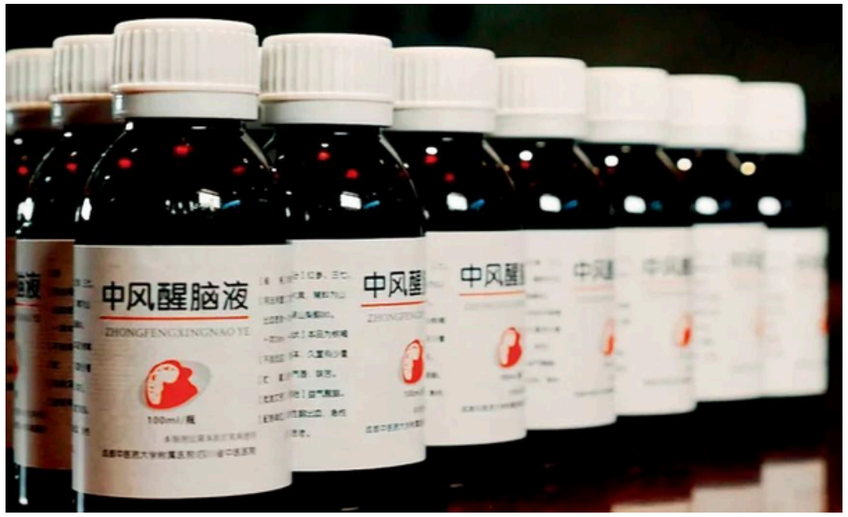
這款知名中藥，《柳葉刀》認為無效？

來源：中國新聞週刊，作者：牛荷，發表時間：2024-11-23 12:30



日前，國際醫學頂刊《柳葉刀》發表的一項研究，引發了醫學界的廣泛關注。這項研究旨在通過臨床試驗，評估中藥製劑中風醒腦液對急性腦出血患者的療效和安全性。這項試驗的結果顯示，與安慰劑組相比，沒發現中風醒腦液能改善中重度腦出血患者的生存率、生活品質等。

這是《柳葉刀》創刊兩百多年以來，首次發表中藥雙盲對照試驗。研究共納入1600多位患者，涉及中國26家醫院。全美中醫藥學會會長田海河告訴《中國新聞週刊》，看完這項研究，內心喜憂參半。“喜”的是，這項研究的樣本量較大，能發表在國際頂刊上；“憂”的是，這項研究的結果是否正確，還有待進一步驗證。

中風醒腦液是一種中藥製劑，由國醫大師、成都中醫藥大學附屬醫院主任醫師陳紹宏研製。該研究由復旦大學類腦智慧科學與技術研究院特聘研究員宋莉莉與克雷格·安德森團隊，以及廣東省中醫院副院長郭建文團隊共同完成。克雷格·安德森是著名臨床神經科學家、世界卒中組織副主席。

11月16日，《中國新聞週刊》致電成都中醫藥大學附屬醫院，工作人員表示，目前有需要的話，醫院仍可開出中風醒腦液。11月22日，克雷格·安德森在接受《中國新聞週刊》視頻採訪中談到，研究特意選擇中重度的腦出血患者作為受試者，因為初步資料表明，這種中藥可能通過抑制腦部炎症起作用。而大面積腦出血患者的炎症反應更強。“當然，現在回頭看，也可能藥物對小出血患者更有效，但我們當時並不知道。”他說。

*中國新聞週刊:https://mp.weixin.qq.com/s/_3vDAXnXTTIT-Twd0xPgHw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來源：中國新聞週刊，作者：牛荷，發表時間：2024-11-23 12:30

與安慰劑效果無明顯差異

據“廣東省中醫院”微信公眾號消息，11月13日，廣東省中醫院召開中醫藥治療腦出血臨床研究成果發佈會。郭建文在發佈會上提到，研究採用符合國際規範的臨床研究，用多中心、隨機、安慰劑雙盲對照設計，針對腦出血這一危及人類生命的重大疾病開展研究，為傳統醫學走向國際開創了範例，下一步將進行新藥開發研究，確證該藥物的療效，讓更多的腦出血患者用上中醫藥，獲得更多生存和康復的希望。

該研究受廣東省重點領域研發計畫嶺南中醫藥現代化項目資助，是中藥治腦出血的最大規模研究。研究已在ClinicalTrials.gov註冊，該網站是當前最具國際影響力的臨床試驗註冊機構之一。《中國新聞週刊》查詢該網站發現，該臨床試驗的“簡要概述”一欄寫道，該研究旨在確定中醫在更大樣本的中重度腦出血患者中的有效性和安全性，並為中醫臨床腦出血管理指南提供證據。

這項研究到底發現了什麼？研究顯示，2021年11月—2023年12月，研究人員從國內12個省份26家醫院的9000例患者中，篩選出1648例中度至重度的急性腦出血患者，年齡範圍為大於18歲。最終，1641名急性腦出血患者，依照病情、性別、年齡等，被隨機分配到試驗組和安慰劑組，接受為期28天的治療。這26家醫院，都屬於三級腦卒中醫院。患者都在發病的48小時內得到了救治，且出現中度至重度的神經功能損傷。患者的平均年齡為67.1歲，30.3%的患者接受過顱內減壓手術。

該研究中，患者平均在發病20小時後，開始服用中藥口服液或安慰劑。安慰劑的外觀、氣味、口感等方面與中風醒腦液基本一致。最終，75.7%的患者完成了80%的療程，60.6%的患者在28天內用完了藥物。

研究團隊重點觀察，患者接受治療90天后的表現。研究結果發現，兩組患者接受治療90天后，沒有顯著差異。對不同血腫量患者的藥效分析中，血腫較大的患者有獲益趨勢。但由於樣本量小，研究者認為這一發現尚無定論，需要在未來的試驗中加以驗證。

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來源：中國新聞週刊，作者：牛荷，發表時間：2024-11-23 12:30

此外，該試驗還驗證了這款中藥的安全性。結果顯示，用藥治療後的90天隨訪期間，兩組患者的不良事件和嚴重不良事件發生率，沒有顯著差異。不過，試驗組的腹瀉發生率是安慰劑組的近兩倍。對此，研究人員認為，這說明藥物含有活性成分，並在一定程度上支持“傳統中藥的主要作用是改善腸道微生物群，並調節胃腸道激素”的假說。

前述研究發表的同時，《柳葉刀》同步刊登了一篇評論，作者是四川大學華西醫院神經內科副教授吳思緲。該評論文章提到，該臨床試驗中，中風醒腦液被鑒定出30種化學成分。這些成分間可能存在藥代動力學或藥效學的協同作用，將使試驗結果的解讀變得複雜。

廣州中醫藥大學第一附屬醫院嶺南腫瘤研究所所長林麗珠對《中國新聞週刊》表示，雖然試驗結果顯示是陰性，但在她看來，臨床上這一藥物可能是有效果的。這項研究會讓大家認為，大部分中藥的臨床試驗結果，可能是無效的。

田海河的團隊長期關注中藥領域的臨床試驗研究，他談到了這項試驗的設計問題。田海河舉例，比如研究中納入的參與者年齡跨度過大、療效評估時間是否合適、評價標準是否可以反映有意義的功能改善等，這些都可能影響試驗結果。“這項研究的試驗設計以及結論的準確性，還有待進一步評估。”他說。

關於這項試驗設計引發的一些討論，克雷格·安德森談道，如果有機會重新設計研究，研究人員可能只納入65歲以上的患者，而不是≥18歲的患者。

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作為院內製劑應用20餘年

中風醒腦液在臨床已應用有20餘年，主要成分為紅參、三七、川芎、大黃，這些藥材被認為具有活血化瘀的功效。這款藥屬於成都中醫藥大學附屬醫院的院內製劑，也就是說，是醫療機構根據本單位臨床需要經批准而配製、自用的固定處方製劑，僅能在本單位或醫療機構間調劑使用。

成都中醫藥大學官網發佈的文章介紹，該藥物用於急性腦出血、急性腦梗死患者，飯後口服或鼻飼給藥。腦出血患者一次25毫升，一日4次；腦梗患者一次20毫升，一日4次。

據公開資料，中風醒腦液的研發者陳紹宏已從醫50餘年。2006年，他被省人民政府評為“四川省首屆十大名中醫”，2017年被人力資源社會保障部、原國家衛計委、國家中醫藥局評為首屆“全國名中醫”，2022年7月，被評為全國第四屆國醫大師。

這一複方製劑的雛形可追溯至1986年。據報導，當時，陳紹宏在接診一位元昏迷的急性腦出血患者時，開出一張11味藥材的處方，經過一個月治療後，患者治癒。基於這一處方，1988年，中風醒腦液的課題研究正式立項，並得到原國家科委、國家自然科學基金的資助。隨後的10年間，處方由最初的11味減到7味再到4味。據成都中醫藥大學附屬醫院牽頭的一項臨床研究資料，從1988年開始的10年時間裡，臨床研究結果表明，僅應用中風醒腦口服液，治療中、重型急性腦出血患者125例，總有效率為82.40%。項目驗收時，專家組認為，該研究“達到國內同類研究領先水準”。

2011年，成都中醫藥大學附屬醫院另一項關於中風醒腦液治療急性腦出血的臨床研究資料公佈。這項研究中，2005年11月—2009年10月，共213名病例被納入，最終對試驗組和對照組患者按性別、年齡、出血量、病情程度、伴發病等因素，進行比較分析。該研究的療效評定，以觀察用藥後28天為限。結果發現，試驗組的療效優於對照組。

據《中國醫藥報》報導，陳紹巨集團隊制定的出血性中風診療方案，2009年由國家中醫藥管理局組織在全國33家單位驗證，結果顯示，能明顯降低腦出血患者的病死率和致殘率。關於中風醒腦液治療急性腦出血機理，前述兩項研究均提到，動物實驗中，中風醒腦液能明顯降低顱內高壓、減輕腦水腫、促進血腫吸收，以及有益於腦出血損傷後腦血流供應、加速組織修復。

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華中科技大學同濟醫學院附屬協和醫院藥劑科主管藥師王哲告訴《中國新聞週刊》，事實上，目前臨床上尚無治療急性腦出血的特效藥物。急性腦出血主要的治療方法包括血壓和顱內壓的管理、癲癇發作的治療，以及相關併發症的預防與處理。

宋莉莉與克雷格·安德森團隊是國內專攻腦出血和腦梗死臨床研究的頂尖團隊。宋莉莉近期在採訪中談道，整個腦出血的研究領域，除了其團隊2023年的一個已發表的項目，至今還沒找到任何被驗證的、有效的腦出血治療方法，包括藥物和手術。

據《中國腦出血診治指南（2019）》（以下簡稱《指南》），腦出血的發病率為（12—15）/10萬人年，國內腦出血的比例更高，占腦卒中的18.8%—47.6%。腦出血發病兇險，僅有約20%的患者，在6個月後能夠恢復生活自理能力。《指南》指出，腦出血的治療以內科治療為主。如果病情危重，符合手術條件，可進行外科治療。

《指南》的藥物治療方面，除了止血藥物，還提到了中藥製劑。“有中藥製劑用於腦出血治療的臨床研究與分析，但因研究品質及研究樣本的局限性，尚需進行高品質、大樣本的隨機對照試驗予以進一步證實。”《指南》寫道。

北京大學第一醫院主任醫師孫永安告訴《中國新聞週刊》，中藥製劑並不是臨床上治療急性腦出血的核心用藥。對於情況嚴重的腦出血患者，需進行外科手術清除血腫，如果出血量很大，不及時手術，病人會面臨死亡風險。他進一步補充，引發患者腦出血的原因很多，最常見的是高血壓引發血管破裂，導致腦出血，這類患者首先要降壓。此外，一些患者也會因為出血形成血腫壓迫腦組織，出現水腫，因此減輕水腫也很重要。

中風醒腦液是臨床應用較長時間的院內製劑。2022年7月，四川省中醫藥管理局發文稱，中風醒腦液治療急性腦血管病患者，療效肯定，現已在全省調劑使用。張麟是一家三甲醫院藥劑科的副主任藥師，他告訴《中國新聞週刊》，院內製劑是市場藥物的一種補充。一種藥物想在市場上正常銷售使用，需要按正常新藥上市申報流程，這對醫院而言並不現實。院內製劑如果確有效果，往往通過轉讓的方式，將專利等所有權轉讓給藥品企業，實現更大範圍的銷售，但真正通過這種方式成為上市藥品的情況很少。

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近年來，相關政策對於院內製劑的監管日趨嚴格。林麗珠表示，現在對院內製劑的要求卡得很嚴格，比如，院內製劑的藥物成分含量不能超過《中國藥典》中的規定。因為《中國藥典》規定的劑量都很低，這種限制也會影響中藥製劑的藥效。

前述《柳葉刀》評論文章指出，由於中藥的生物學複雜性，一項試驗的結果，不一定能代表其他中風患者使用同類中藥的結果。全軍中醫藥研究所所長、解放軍總醫院肝病醫學部學術主任肖小河告訴《中國新聞週刊》，先前的臨床研究表明，原方在臨床上應該是有一定療效的。但在這項臨床研究中，中風醒腦液的劑型是口服液，這會導致藥物的有效成分含量比原方低很多，使療效大打折扣。通常，中藥大複方需要通過調減藥味數量和用量，才能製成口服液。如直接以湯劑形式，通過口服、鼻飼或灌腸等方式給藥，則載藥量多，藥效成分豐富，會產生更好的藥效作用。

在肖小河看來，該研究關注急性腦出血後症狀嚴重者，這類患者一般病情危急，預後較差。中風醒腦液用作急性腦出血的治療效果有限，這一藥物更多的優勢是用於降低高危人群的發病風險和致殘率，以及減少下次再發作的概率。

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中藥療效該如何評價?

“現在對中藥藥效的評估，目前普遍採用的是大型隨機對照試驗（RCT）的方法。”林麗珠表示。不過，中藥是否應依照國際認可的RCT方法驗證藥效，一直以來是業內熱議的焦點。今年10月，肖小河等發表在《中國中藥雜誌》的一篇研究提到，早在1996 年，美國國立衛生研究院曾指出，“RCT並不是唯一的評估方法,是否可作為補充和替代醫學評價的金標準值得商榷”。補充和替代醫學，包括中醫等治療辦法。

多名中醫藥領域專家告訴《中國新聞週刊》，通過RCT驗證藥效，是中藥走向國際的必經之路。“在這個過程中，會有許多藥物被淘汰，但也會有更多有效的藥物得以保留。”王哲說。

前述發表在《中國中藥雜誌》的研究提到，目前，國內中醫藥臨床療效評價專案迅速增長，部分中藥複方及針刺治療的療效通過高水準RCT得到了證實，如麻杏石甘湯與銀翹散加減改善甲型流感發熱、通心絡改善急性心肌梗死患者的臨床結局等，相關研究先後發表在《美國醫學會雜誌》等國際頂級醫學期刊。“做臨床試驗，無法避免陰性結果。”林麗珠表示，這次《柳葉刀》發佈的臨床試驗結果之所以引發爭議，其背後反映出的主要問題是：以西醫的標準來衡量中藥的療效，在現有條件下非常困難，因為目前還沒找到有效的中藥療效評價辦法。

在田海河看來，中藥有其自身的發展規律，已在人群中應用上千年，很多有效方劑在真實的臨床試驗中被證實有效，但為何在套用循證醫學的研究以後，就出現陰性結果？這裡無法回避的一個問題是：西方的循證醫學研究是否可以完全照搬套用在中醫研究上？他舉例，相較循證醫學設定的指標，中醫臨床治療中涉及的可變因素較多，比如出血量多少、出血的部位在哪裡、中藥劑型、年齡中位數、病人體質等。如果把這些指標再細化些，同樣的一款中藥，有可能得出完全不一樣的結論。

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Traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial

Prof Jianwen Guo, PhD [a,b,c,x,*] · Xiaoying Chen, PhD [e,*] · Manli Wu, MD [c,*] · Dou Wang, MD [c,*] · Yang Zhao, PhD [f,*] · Qiang Li, MBiostat [e] · et al. Show more

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媒體報道：

這款知名中藥，《柳葉刀》認為無效?

來源：中國新聞週刊，作者：牛荷，發表時間：2024-11-23 12:30

前述《中國中藥雜誌》研究提到，在藥物的有效性評價方面，以RCT為代表的標準化試驗，對於療效作用“簡單、直接、明快”的化學藥來說，適配性和適用性毋庸置疑。但是，中藥的藥效物質基礎具有多成分、低濃度且複雜易變等特點，其療效作用往往是通過多成分、多靶點、多通路的複雜網路，對人體進行整合調控而實現的，這對常規 RCT試驗觀察及療效評價來說，是重大挑戰。

陳嘉是一名常年從事藥學研究的資深專家。他告訴《中國新聞週刊》，整體而言，目前通過RCT驗證藥效的中藥，數量並不算多。因為RCT講究定量，中醫治療講究定性，這兩者很難實現完美融合。在他看來，現在中醫藥面臨的一個主要問題是，分散的臨床經驗和患者個人主觀感受，很難轉化成批量的客觀臨床資料。他舉例，中醫治療中，患者的生活品質、主觀真實感受等非定量指標，以及醫生觀察到患者的氣色、舌象、脈象等情況，都很難量化。

張麟分析，評價中藥藥效需要排除混雜因素，這是目前一些中醫藥學者選擇RCT的原因。不過，由於RCT本身有很多限定條件，外推至整個人群時難免會存在“失真”的問題。

如何找到更適合中藥療效評價標準的辦法，一直是醫學界未解決的問題。在林麗珠看來，RCT並不是最合適的中藥藥效評估辦法。因為這種臨床試驗，很難找准中藥發揮作用的精准治療切入點，以及療效的客觀評價標準。

今年7月，國家中醫藥管理局發佈了《中醫病證診斷與療效評價規範制修訂通則》中醫藥行業標準。在“療效評價”一欄，該檔規定，通過運用符合中醫藥特點的療效評價體系，評價中醫藥治療疾病的效果，包括症狀或體征的消失率/控制率、患者報告結局、具有普適性的生存品質或生活能力等量表，以及相關指標的改善情況。

林麗珠表示，現在大家還在探索。在這方面，可以考慮是否能參考一些慢性病治療藥物的療效評價標準。她表示，以中醫治療腫瘤的療效評價標準為例，現在研究中藥治療腫瘤患者的生存品質，主要通過量表測試、生活品質評估等這樣的軟指標，來評估中藥的藥效。

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來源：中國新聞週刊，作者：牛荷，發表時間：2024-11-25 13:31:59

日前，國際醫學頂刊《柳葉刀》發表的一項研究，在醫學界引發廣泛熱議。這項研究旨在通過臨床試驗，評估中藥製劑中風醒腦液對急性腦出血患者的療效和安全性。這項試驗的結果顯示，與安慰劑組相比，沒發現中風醒腦液能改善中重度腦出血患者的生存率、生活品質等。這是《柳葉刀》創刊兩百多年以來，首次發表中藥雙盲對照試驗。研究共納入1600多位患者，涉及中國26家醫院。該研究由復旦大學類腦智慧科學與技術研究院特聘研究員宋莉莉與克雷格·安德森(Craig Anderson)團隊，以及廣東省中醫院副院長郭建文團隊共同完成。克雷格·安德森是著名臨床神經科學家、世界卒中組織副主席，也是該研究的通訊作者之一，被《柳葉刀》稱為“卒中研究領跑者”。

如何看待試驗結果？受試者選擇中重度腦出血患者是否合適？對這項研究的一些批評看法如何看待？圍繞這些問題，11月22日，克雷格·安德森接受了《中國新聞週刊》視頻採訪。

*中國新聞週刊: https://www.inewsweek.cn/wh/2024-11-25/23773.shtml


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來源：中國新聞週刊，作者：牛荷，發表時間：2024-11-25 13:31:59

《中國新聞週刊》：你和你的團隊當初為何決定參與這項臨床研究？

克雷格·安德森：這項臨床試驗的研究方向，是廣東省中醫院的郭建文教授決定的。郭建文是這項研究的第一作者和通訊作者之一。在此之前，郭建文已經對這款中藥進行了初步研究，結果顯示非常有前景。這款中藥在臨床實踐中已有所應用，並且看起來有很大的潛力。於是，郭建文找到了我和我的團隊，邀請我們一同參與設計這項科學嚴謹的臨床試驗，進一步評估其療效。我們合作的目標是確保研究設計足夠嚴謹，從而能準確評估該藥物的潛在益處。

《中國新聞週刊》：根據研究結果，與安慰劑組相比，中風醒腦液並未改善患者的生存率、生活品質。你如何看待這一結果？

克雷格·安德森：腦出血是一種非常嚴重的卒中類型，致死率和致殘率都很高，在中國尤為常見。全球範圍內，大約1/5的卒中病例是腦出血。現有治療腦出血的方法非常有限，雖然可以做手術，但手術並不完美，且具有一定侵入性，可能會導致腦部腫脹等併發症。因此，中藥作為一種簡單且具有良好初步資料支援的治療方案，看起來很有吸引力。

儘管如此，研究結果沒有達到預期，這讓我感到有些驚訝和失望。但我仍相信我們設計了一項科學嚴謹的研究。結果顯示，整體患者群體中，這款藥物沒有展現出明顯的療效。不過，在某些亞組患者中，確實觀察到了一些積極的信號，尤其是在年長患者和出血較重的患者中。

《柳葉刀》的審稿非常嚴格，這項研究的摘要部分只關注主要研究結果，因此沒有提及特定患者特徵的治療差異。文章主體部分提到，中風醒腦液在一些亞組患者（年長患者和大面積出血患者）的治療中，有積極信號。這一點令人鼓舞。我們還分析了更多資料，雖然這些結果尚未發表，但從多個方面來看，這些積極信號是可信的，仍然值得關注。

這類現象在臨床試驗中並不少見，尤其是在腦出血這種複雜疾病的研究中。在臨床試驗中，我們通常評估的是群體效應，而不是單個患者的反應。因為不同年齡、性別、體質的患者對治療的反應會有所不同。我們不得不承認，雖然在整體患者群體中的結果是陰性的，但某些特定患者群體仍可能受益。我們希望能夠籌集更多資金，針對更具特異性的患者群體重複這項研究，以進一步驗證其療效。

*中國新聞週刊: https://www.inewsweek.cn/wh/2024-11-25/23773.shtml


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《中國新聞週刊》：你如何看待這項研究的價值和意義？

克雷格·安德森：所有的研究都會給我們帶來一些啟示，無論結果是積極的還是消極的。這項研究讓我們認識到，進行一項可靠的臨床試驗需要大量的患者樣本。我們無法僅依賴十幾例或幾百例患者，而是需要數千例患者的參與。幸運的是，我們能夠獲得醫生、患者和醫院的支持，順利完成患者的招募工作。

我們採用了非常可靠的方法來評估患者的健康狀況，並且使用了“雙盲”設計。這意味著，患者和醫生都無法知道自己接受的是活性藥物還是安慰劑。雙盲設計是確保結果可靠的一個關鍵因素，因為如果知道治療方案，患者和醫生的行為就可能發生變化，影響研究結果的公正性。研究發現，服用中風醒腦液的患者出現輕微的腹瀉症狀。如果醫生知道患者腹瀉，可能會影響他們對藥物療效的評估。

對此次研究的高品質設計和嚴謹性，我們非常自豪，這也是其能發表在《柳葉刀》上的原因。《柳葉刀》是世界頂級醫學期刊，只有最嚴謹的研究才能發表。

《中國新聞週刊》：本研究中，你的團隊主要負責哪些工作？遇到過哪些挑戰？

克雷格·安德森：我們與郭建文的團隊緊密合作。我們團隊的職責主要是支援郭教授團隊完成研究方案的設計、統計分析、資料品質監控，以及論文的撰寫。臨床試驗包括三個階段：設置階段、招募階段和結題階段。設置階段，我們需要籌集資金、制定方案並獲得倫理批准；招募階段，我們需要保持研究的高品質，確保患者參與並確保資料的準確性；結題階段則包括資料分析、統計和論文寫作等工作。這是一個艱苦的過程，所有的環節都需要細心完成。

研究過程中，我們也面臨了一些挑戰，尤其是在新冠疫情期間，醫院的資源被分散，患者的招募和藥物供應都受到影響。

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《中國新聞週刊》：你在參與研究之前是否預測到，這項臨床試驗會有陰性結果？關於這項研究的批評聲音，包括納入的參與者年齡跨度過大、療效評估時間是否合適、評價標準是否可以反映有意義的功能改善等，你如何看？

克雷格·安德森：關於這項研究，我們團隊從2019年就開始了相關討論。研究正式啟動前，需要完成檔準備、倫理審查、藥物生產以及協定簽訂等大量工作，整個過程煩瑣且耗時。

研究開始前，我們並未想到結果是藥物無效。研究的初衷總是為了找到積極的結果。如果我們一開始就認為結果會是負面的，就不會開展研究。研究的本質就是探索未知，有時結果會令人驚訝。這正是我們需要做研究的原因。

那些對這項研究的評論更多是個人意見。我們採用了非常靈敏的健康評估指標，既考慮了患者的功能性障礙，也考慮了患者的主觀感受。此外，90天的評估時間是卒中研究中常見的標準，而我們還在六個月的時間節點進行了跟蹤隨訪，結果保持一致。未來，如果有機會重新設計研究，我們可能會只納入65歲以上患者。但五年前，大家並不知道這些亞組可能表現出更強的療效信號。

《中國新聞週刊》：這一研究選擇了嚴重急性腦出血患者作為試驗對象，這類患者的病情危重、預後較差。對這類患者，中風醒腦液是否是合適的藥物？

克雷格·安德森：我們特意選擇了嚴重的腦出血患者，因為初步資料表明，這種中藥可能通過抑制腦部炎症起作用。而大面積腦出血患者的炎症反應更強，因此藥物可能更有效。然而，這些存在大量出血的患者的死亡率也更高，反過來說，可能無法顯示出效果。現在回頭看，也可能藥物對出血少的患者更有效，但我們當時並不知道，這正是我們開展研究的原因。

研究通常不會一次性提供所有答案，而是一個逐步積累資訊的過程。雖然對此的討論甚至批評是合理的，但我們的設計基於藥物可能的作用機制，這種機制更可能在嚴重患者中體現。

*中國新聞週刊: https://www.inewsweek.cn/wh/2024-11-25/23773.shtml


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來源：中國新聞週刊，作者：牛荷，發表時間：2024-11-25 13:31:59

《中國新聞週刊》：這項研究發表的同時，《柳葉刀》同步刊登了一篇評論。該評論文章提到，研究人員將中風醒腦液與治療腦出血的常規療法，如降壓藥和抗凝劑一起進行了測試。為何要做這樣的工作？

克雷格·安德森：這是一個非常重要的問題。患者必須在接受標準治療的基礎上，參加研究，這既是倫理要求，也是確保研究結果能夠被科學界廣泛接受的重要前提。中醫通常是作為補充治療，而不是替代治療，這種方式在這項研究中得到了體現。

我非常讚賞那些接受過西醫和中醫雙重培訓的醫生，他們能夠將兩者結合起來，提供更全面的治療方案。西醫對於一些症狀（如噁心、疲勞、頭暈）的治療效果有限，而中醫則能作為有力的補充。

對於中風醒腦液與降壓藥和抗凝藥聯合使用的試驗結果，我們未發現顯著的相互作用，且聯合使用是安全的。不過，想要明確哪種成分最有效，還需要進一步的研究。這方面的工作需要化學實驗專家提供指導和資料。

《中國新聞週刊》：該研究的通訊作者之一，你所在團隊的宋莉莉教授最近在採訪中提到，目前在腦出血研究領域，包括藥物和手術在內的治療方法尚未證明具有明確的療效。你如何看待現在的腦出血治療？

克雷格·安德森：宋教授的觀點是正確的。腦出血是一種非常具有挑戰性的疾病，因為患者病情危急，往往很難及時納入臨床試驗。此外，招募足夠的病例也很困難。目前治療腦出血，確實沒有任何被科學證實的絕對有效的治療方法。雖然現有的治療手段可能有用，但科學上尚未達成共識。例如，手術和藥物的研究已有許多，但我們仍無法確定最佳使用方法。最近兩年我們發現，快速控制高血壓可以改善患者的預後，這是一個重要的進展。

*中國新聞週刊: https://www.inewsweek.cn/wh/2024-11-25/23773.shtml


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《中國新聞週刊》：這次登上《柳葉刀》的研究引發了廣泛的討論，其中也包括對於中醫療效評價的討論，你如何看待？

克雷格·安德森：圍繞傳統中醫的爭議，在中國和世界範圍內都存在。支持者和反對者都有各自的立場。批評往往帶有情感色彩，而非完全基於科學事實。無論結果是積極的還是負面的，總會有人質疑，因此我們無法讓所有人滿意。

但是，這些爭論也是一種積極的信號，表明這項研究和中醫藥在全球範圍內引發了廣泛的關注和討論。這正是科研所需要的，挑戰現狀和不斷反思是推動科學進步的重要力量。中醫不僅是一種治療方法，它還是中國文化的一部分。從科學角度看，挑戰和爭議是好事，它們能激發討論和思考。一項成功的研究不僅在於結果，更在於它引發了怎樣的後續反應和思考。這項研究能引發如此廣泛的討論，證明它非常重要。

《中國新聞週刊》：有專家認為，隨機對照試驗（RCT）難以全面反映中醫的特點，可能不是評估中醫療效的最佳方法。你的看法是什麼？

克雷格·安德森：目前來看，所有其他方法都不如RCT被廣泛接受，所有其他方法，比如觀察性研究，都存在一定的局限性。

RCT被公認是醫學研究的金標準，這是全球共識。中藥通過RCT驗證藥效存在的爭議，在於是否採用了合適的療效評估標準。中醫的目標是提高整體健康水準、改善患者的生活品質，而這些目標在RCT設計中，很難具體量化。例如，中醫可能無法治癒肺癌，但可以改善患者的生活品質。這與西醫的研究目標不同，西醫通常針對具體病理，而中醫更加注重對患者身體的整體調理。你提到RCT難以全面反映中醫的特點的觀點有一定道理，但這並不意味著中醫不適合RCT。

如今，越來越多的中醫藥研究開始使用RCT方法，但這需要大量資金支援。目前，中醫藥的研究尚在探索階段，很多中藥依然被視為保健品。要想證明其療效，需要進行高品質的RCT研究。這是我的團隊首次嘗試進行中醫相關的臨床試驗。未來，我們會繼續在這一領域進行更多研究。

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《柳葉刀》中藥治療腦出血無效：臨床使用已超20年

來源：麥芽科研MaltSci，作者：曾老皮，發表時間：2024年11月28日 07:05

研究的爭議性結果：中醫藥的療效為何難以驗證

FYTF-919的隨機對照試驗是針對急性腦出血的傳統中醫藥研究中規模最大的試驗之一，但結果顯示其在改善患者功能恢復、生存率和生活品質方面與安慰劑無顯著差異。這一結果表明，儘管中醫藥在理論上強調“整體調理”和“多靶點作用”，其實際臨床療效可能並不如預期。究其原因，可能包括以下幾個方面：

- **組方機制的科學基礎不足**

中藥複方通常包含多種成分，其複雜性導致研究者難以明確其作用機制。例如，FYTF-919是否能夠通過減輕炎症反應或促進血腫吸收產生療效尚無充分證據支持。此外，其組方的配伍依據是否與現代藥理學原理契合，仍需進一步研究。

- **療效評估體系的局限性**

當前的隨機對照試驗通常採用西醫的量化指標（如mRS評分）評估療效，而中醫藥強調的“症狀改善”或“體質調節”可能無法完全體現在這些指標上。這一評價體系的不匹配或許是導致試驗結果不理想的原因之一。

- **個體化治療的挑戰**

中醫強調“辨證論治”，即根據患者個體情況制定治療方案。然而，大規模臨床試驗需要統一標準，這與中醫藥個體化治療的原則存在衝突。在試驗中，FYTF-919對所有患者均採用統一劑量，可能未能充分體現其個體化療效。

*麥芽科研MaltSci: https://mp.weixin.qq.com/s/1n_NjeoLJvddP2KFgAba0Q


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中醫藥現代化：平衡傳統與科學的路徑

儘管FYTF-919的試驗結果令人失望，但這一研究為中醫藥現代化進程提供了重要啟示：

- **加強基礎研究**

中藥複方的組方機制應以現代藥理學和分子生物學研究為基礎。通過明確主要活性成分的作用靶點和機制，可以提升中醫藥的科學性和國際認可度。

- **創新研究設計**

在臨床試驗中，應嘗試融入更多中醫藥特有的療效評估指標，例如結合患者主觀感受、生活品質改善等多維度數據。同時，可探索基於“精准醫學”理念的個體化中醫藥研究設計，解決傳統中醫藥與隨機對照試驗體系的矛盾。

- **跨學科合作**

未來，中醫藥的研究需要加強與神經科學、分子生物學等學科的合作。例如，通過腦成像技術監測中藥對神經修復的影響，可為中醫藥提供更直觀的證據支援。

- **科學與文化的融合傳播**

中醫藥的國際化不僅依賴於科學證據，還需要注重文化傳播。通過加強中醫藥文化與科學的結合，使國際醫學界更全面地理解中醫藥的理論與實踐意義。

*麥芽科研MaltSci: https://mp.weixin.qq.com/s/1n_NjeoLJvddP2KFgAba0Q


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來源：麥芽科研MaltSci，作者：曾老皮，發表時間：2024年11月28日 07:05

傳統中醫藥研究的現代化挑戰

FYTF-919的研究結果表明，在治療急性腦出血的領域，傳統中藥複方的療效和安全性尚需進一步驗證。然而，這並不意味著中醫藥在現代醫學中毫無價值。相反，這一結果促使研究者重新審視中醫藥的研究方法，並推動其向更科學化、國際化的方向發展。

該研究驗證了了使用大規模、多中心、隨機、安慰劑對照、雙盲臨床試驗評估中藥療效的可行性。未來，中醫藥研究需要以科學性為核心，逐步建立與現代醫學體系相容的標準化研究框架。同時，也需要堅守中醫藥的傳統智慧，在科學與傳統之間找到平衡，為全球患者提供更多可能的治療選擇。

通過這項研究，我們不僅看到中醫藥的挑戰，更感受到其潛力。期待在未來，更多基於中醫藥的現代研究能夠取得突破性進展，讓這一古老的醫學體系在全球範圍內煥發新的生命力。

*麥芽科研MaltSci: https://mp.weixin.qq.com/s/1n_NjeoLJvddP2KFgAba0Q

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國醫大師用了20多年的經驗方竟然無效？——如何看《柳葉刀》的中醫研究

來源：王虛步工作室，作者：王虛步，發表時間：2024年11月27日 20:00

再來談談值得商榷的地方

首先，一個方劑的否定，不要擴大為對整個中醫藥的否定。這方面是人們傾向性問題，更不免少數媒體的斷章截義，擴大化宣傳，不用太多解釋。

其次，該研究最大的不足在於，沒有按中醫的辨證分型來統計資料，也就是沒有按中醫的診斷結果來觀察研究療效。簡單地舉例，中醫八綱辨證，至少把病人根據表裡、虛實、寒熱分類，對應的一類，也就是八分之一（簡化起見）。假設該研究的對象，“中風醒腦方”只對其中一種證型有效，也就是八分之一有效。把八分之一的有效對象，混到百分之百的病人中，研究結果無效，也就很自然了。研究基本是按西醫的病名來納入研究對象的，用西醫的分類，來研究中醫的方劑，這是周星馳電影裡的“拿明朝的尚方寶劍，斬清朝的官”呀。而事實上，論文中也指出，對於某些特定分類，可能存在療效，有待進一步研究。

舉個西藥的著名例子：肺癌靶向藥，現在已經完全證實其對特定人群優異的療效，它的出現是有劃時代的意義的。可就是這樣一個劃時代的創新，在它開始研究時，卻差點被否定掉了。原因是當時大模本的雙盲對照研究結果，顯示最初的肺癌靶向藥是無效的。後來研究人員進一步細心研究，才發現該藥只對3%的那些有特定基因變異的肺癌患者有效。進一步針對這3%的人設計實驗，才得到了顯著性結果。所以，有必要的情況下，進一步特定人群研究，不同劑量的研究，原方的加減調整研究，都是有必要的。因為中醫學的理論在大方向是支持的。

其實，我想到的，論文的作者們估計早就想到了，但為什麼沒有設計呢？個人猜猜有兩個原因：一是按中醫分型又是很大的工作量，還需要多中心統一，不容易。更可能的是，中藥現在國際上慢慢接受認同了，按中醫分型，國際不一定認同呀，老外就沒有這一套。這一做法的直接結果是，文章就發表不了，因為不符合科學研究的標準嘛。

*王虛步工作室: https://mp.weixin.qq.com/s/wRJcY_6pqMta3xUAcWC2mA


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Traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial

Prof Jianwen Guo, PhD [a,b,c,x,*] · Xiaoying Chen, PhD [e,*] · Manli Wu, MD [c,*] · Dou Wang, MD [c,*] · Yang Zhao, PhD [f,*] · Qiang Li, MBiostat [e] · et al. Show more

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論文鏈接

Traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of acute intracerebral haemorrhage: a multicentre, randomised, placebo-controlled, double-blind, clinical trial

Jianwen Guo, Xiaoying Chen*, Manli Wu*, Dou Wang*, Yang Zhao*, Qiang Li, Guanghai Tang, Fengyuan Che, Zhangyong Xia, Zai Liang, Liu Shi, Qiuhua Jiang, Yajie Chen , Xiaoqiu Liu, Xinwen Ren, Menglu Ouyang, Borui Wang, Shoujiang You, Laurent Billot, Xia Wang, Zhenchuan Liu, Hongyan Jing, Wei Meng, Song Tian, Enzhi Liu, Yong Xiang, Xiaoping Tang, Tingting Xie, Wanzhen Cui, Yanwen Zheng, Jiamin Cao, Jingbei Zhang , Zehuai Wen, Tao Huang, Lixin Wang, Chao You, Suyue Pan, Yefeng Cai, Yun Lu, Graeme J Hankey, Rustam Al-Shahi Salman, Craig S Anderson†, Lili Song†, for the CHAIN investigators‡*

Summary

Background There are few proven treatments for acute spontaneous intracerebral haemorrhage, and they all target reducing expansion of the haematoma. The traditional Chinese medicine FYTF-919 (Zhongfeng Xingnao) in an oral solution is comprised of several Chinese herbs that are widely used to treat patients with intracerebral haemorrhage in China on the understanding that they enhance resorption of the haematoma and reduce neuroinflammation. We aimed to provide a reliable assessment of the safety and efficacy of FYTF-919 in patients with moderate to severe acute intracerebral haemorrhage.

Methods We did a pragmatic, multicentre, randomised, double-blind, placebo-controlled trial at 26 hospitals in China. We enrolled adults (age ≥18 years) with a diagnosis of symptomatic spontaneous intracerebral haemorrhage (confirmed by brain imaging) within 48 h after the onset of symptoms (or last seen well), which resulted in moderate to severe neurological impairment defined by scores of at least 8 on the National Institute of Health Stroke Scale or between 7 and 14 inclusive on the Glasgow Coma Scale. Randomisation (1:1) was via a central internet-based system with a block grouping method stratified by provincial location of the hospital, severity of neurological impairment, and site of the haematoma in the brain. FYTF-919 and the placebo were masked through consistency in appearance, smell, taste, and other aspects. Participants were allocated to receive 33 mL (or 25 mL via a nasogastric tube if a participant's swallowing was impaired) of either oral liquid FYTF-919 or matching placebo administered at least 30 min after a meal every 8 h (or 6 h via nasogastric tube) over 24 h for 28 days. The primary efficacy outcome was the utility weighted modified Rankin Scale (a seven-level ordinal scale that ranges from 0 [no symptoms] to 6 [death], in which the utility weights of 0·97, 0·88, 0·74, 0·55, 0·20, –0·19, and 0·00 were assigned to the seven levels respectively, with higher scores indicating a better outcome according to the participants' perspective) at 90 days analysed in a general linear model with adjustment for baseline factors. We did several adjusted and sensitivity analyses. Primary analyses were assessed in the intention-to-treat population. This trial is registered at ClinicalTrials.gov, NCT05066620 and is complete.

Findings Between Nov 24, 2021, and Dec 28, 2023, of 9000 patients screened, 1648 were randomly assigned to treatment, 817 to the FYTF-919 group and 831 to the placebo group. Before receiving any treatment two patients in the FYTF-919 group and five patients in the placebo group immediately withdrew their consent leaving 1641 participants with available primary outcome data in the intention-to-treat population, 815 in the FYTF-919 group and 826 in the placebo group. 1242 (75·7%) participants consumed 80% or more of the study medication and 994 (60·6%) consumed all of it within 28 days. Mean utility weighted modified Rankin Scale scores at 90 days were 0·44 in the FYTF-919 group and 0·44 in the placebo group (difference 0·01, 95% CI –0·02 to 0·04; p=0·63). The neutral result was consistent in adjusted and sensitivity analyses. There was no significant difference in serious adverse events.

Interpretation This large, randomised, placebo-controlled, double-blind, clinical trial showed no effect of the traditional Chinese medicine herbal compound FYTF-919 on functional recovery, survival, and health-related quality of life in patients with moderate to severe intracerebral haemorrhage. The results reaffirm the need for methodologically rigorous, randomised controlled trials to evaluate the effectiveness of existing therapies, including traditional Chinese medicines that are already in widespread use throughout the world.

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See **Comment** page 2135

*Contributed equally

†Contributed equally

‡A complete list of sites and trial investigators and coordinators in the Chinese Herbal medicine in patients with Acute INtracerebral haemorrhage is provided in the appendix (pp 4–6)

State Key Laboratory of Traditional Chinese Medicine Syndrome (Prof J Guo PhD, J Cao PhD, Prof Y Cai MD), **Research Team of Prevention and Treatment of Cerebral Hemorrhage Applying Chinese Medicine** (Prof J Guo), **The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; The Second Clinical Medical School, Guangzhou University of Chinese Medicine, Guangzhou, China** (Prof J Guo, M Wu MD, D Wang MD, W Cui PhD, Y Zheng MBBS, J Zhang MD, Prof Y Cai); **Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China** (Prof C S Anderson PhD, Prof L Song MD PhD); **The George Institute for Global Health, University of New South Wales, Sydney, NSW, Australia** (X Chen PhD, Q Li MBiostat, X Liu PhD, X Ren MPH, M Ouyang PhD, S You MD, Prof L Billot MRes, X Wang PhD, Prof C S Anderson, Prof L Song); **The George Institute for Global Health China, Beijing, China** (Y Zhao PhD, Y Chen MBiol,

B Wang MSc, Prof C S Anderson); **Liaoning Thrombus Treatment Centre of Integrated Chinese and Western Medicine, Shenyang, China** (G Tang MBBS, H Jing MD); **Department of Neurology** (Prof F Che PhD), **Department of Neurological Intensive Care Unit** (Z Liu MBBS), **Linyi People's Hospital, Linyi, China; Department of Neurology, The Second People's Hospital of Liaocheng, Liaocheng, China** (Prof Z Xia PhD); **Department of Neurology, Liaocheng People's Hospital, Liaocheng, China** (Prof Z Xia); **Liaocheng Hospital Affiliated to Shandong First Medical University, Liaocheng, China** (Prof Z Xia); **State Key Laboratory of Dampness Syndrome of Chinese Medicine, Shandong Sub-centre, Liaocheng, China** (Prof Z Xia); **Department of Stroke, Lianjiang People's Hospital, Lianjiang, China** (Z Liang MD); **Traditional Chinese Medicine, Hospital of Meishan, Meishan, China** (L Shi MBBS); **Department of Neurosurgery, Ganzhou People's Hospital, Ganzhou, China** (Prof Q Jiang MD); **Department of Neurology and Clinical Research Center of Neurological Disease, The Second Affiliated Hospital of Soochow University, Suzhou, China** (S You); **Neurosurgery Department, Panjin Central Hospital, Panjin, China** (Prof W Meng MD); **Neurology Department, The First Affiliated Hospital of Shaoyang University, Shaoyang, China** (S Tian MD); **Department of Neurosurgery, Fushun Central Hospital, Fushun, China** (Prof E Liu MD); **Neurology Department, People's Hospital of Anshun City, Guizhou Province, Anshun, China** (Y Xiang MBBS); **The Affiliated Hospital of North Sichuan Medical College, Nanchong, China** (Prof X Tang PhD); **General Medicine, The Affiliated Hospital of Changchun University of Traditional Chinese Medicine, Changchun, China** (T Xie PhD); **Department of Neurology** (Prof J Guo, Prof Y Cai), **Key Unit of Methodology in Clinical Research** (Prof Z Wen PhD), **Department of Neurosurgery** (Prof T Huang PhD), **Department of Neurocritical Care** (Prof L Wang PhD),

Research in context

Evidence before this study

We searched PubMed (from 1970), Web of Science (from 1970), and Embase (from 1947), and the Chinese National Knowledge Infrastructure, WanFang database, VIP Chinese SciTech Periodical Database and China Biological Medicine Database on July 1, 2024, for publications with relevant text words in the title or abstract in English and Chinese that included "intracerebral haemorrhage", "haemorrhagic stroke", or "cerebral haemorrhage" and "traditional Chinese medicine" or "herbal medicine". Studies were eligible for inclusion if they were randomised and assessed the effect of traditional Chinese medicine on a clinical outcome. We identified only three randomised trials, including two small single-centre and one multicentre trial, published in English, which reported uncertain effects of traditional Chinese medicine on mortality and functional outcome. Only one other ongoing trial (ChiCTR2100043796) besides the CHAIN study was identified through a search of registered trials at ClinicalTrials.gov and the Chinese Trial Clinical Registry. There were hundreds of randomised trials published in Chinese, but most of them were single centre, had a small sample size (including less than 100 patients), and were of poor quality.

After adding the terms "Zhongfeng Xingnao" or "FYTF-919" to the above search, we identified nine randomised trials published in Chinese involving a total of 1448 participants. Two of these trials were double-blind, placebo-controlled trials. We did a systematic review and meta-analysis on the basis of these nine trials. The results showed that compared with conventional medicine alone, FYTF-919 as an adjunct treatment could reduce mortality (relative risk 0·54, 95% CI 0·40–0·74) in patients with intracerebral haemorrhage. However, the evidence was considered weak because of small sample sizes, single-centre designs, and methodological limitations (such as the use of surrogate or non-standard outcome measures).

Added value of this study

The CHAIN study is one of the largest randomised controlled trial to date of a traditional Chinese medicine in any type of acute stroke. The primary result did not show a significant difference in mean utility weighted modified Rankin Scale scores at 90 days in the FYTF-919 group compared with the placebo group. The neutral results were consistent in sensitivity analyses of the primary outcome and across all secondary clinical outcomes. There was significant heterogeneity of the effect in the predefined subgroups of patients by size and location of the haematoma but this may be due to chance through small numbers and multiple testing. FYTF-919 is deemed safe as there was no significant difference in serious adverse events between the two groups.

Implications of all the available evidence

These results provide conclusive evidence of the lack of effect of FYTF-919, a traditional Chinese medicine which hitherto has been used throughout China for the treatment of acute intracerebral haemorrhage on the basis of weak evidence of it reducing mortality. The study has shown that it is feasible to do a large, methodologically rigorous, randomised controlled trial to evaluate a traditional Chinese medicine that is already in widespread use in China. It can serve as a paradigm for further evaluations of these medicines which are increasingly used throughout the world.

Introduction

Despite substantial recent advances in the medical and surgical management of acute intracerebral haemorrhage,[1] this condition remains the most serious and least treatable form of stroke, causing considerable global disease burden.[2] Intracerebral haemorrhage accounts for approximately 10% of strokes in high-income countries but rates are much higher in low-income and middle-income countries where populations have a high prevalence of hypertension. Sex-related biological and social factors may also influence the pathophysiology, response to treatments, and prognosis for recovery from intracerebral haemorrhage.[3–5] Most interventions for intracerebral haemorrhage target reducing the size of the haematoma through the early control of elevated blood pressure, surgical decompression, and reversal of anticoagulation therapy.[1] However, these interventions need to be administered early after the onset of symptoms and may not directly modify the neuro-inflammatory response to haemoglobin breakdown products (iron and thrombin) in the brain, which manifests as perihaematomal oedema on brain imaging.[6–9]

Herbs have long been used in contemporary health care in China to remove so-called blood stasis in patients with intracerebral haemorrhage.[10] There is now a considerable body of animal and early phase clinical data to support the use of various Chinese herbs to promote reabsorption of the haematoma, reduce perihaematomal oedema, and enhance the immune system in intracerebral haemorrhage.[11–14] One particular herbal compound, FYTF-919 (or Zhongfeng Xingnao oral prescription), is composed primarily of four Chinese herbs used for the treatment of intracranial haemorrhage in China. FYTF-919 has a range of potential anti-inflammatory and immunological effects,[15–20] and as a liquid preparation for oral administration, it aligns well with how traditional Chinese medicine is commonly used and is suitable for use in patients who are disabled or unconscious. Although a systematic review and meta-analysis of nine randomised trials of 1448 participants suggests that FYTF-919 can enhance the clearance of haematoma, reduce mortality, and improve recovery after ICH, this evidence is generally of low

methodological quality, mainly in relation to deviations from the intended intervention and bias in measurement of the outcome (Xi Wu, et al, personal communication; further details are provided in the appendix pp 183–233). Moreover, a multicentre, double-blind, placebo-controlled trial involving 324 participants suggests that FYTF-919 might be harmful, when administered within 6 h after the onset of intracerebral haemorrhage.[10] We therefore designed the Chinese herbal medicine in patients with acute intracerebral haemorrhage (CHAIN) study to establish the efficacy and safety of FYTF-919 in patients with acute intracerebral haemorrhage. We purposefully restricted the inclusion criteria to patients with at least a moderate degree of neurological impairment as they have the greater potential to benefit from this treatment than those with less impairment by virtue of having larger volumes of haematoma and perihaematomal oedema.

Methods

Study design and participants

CHAIN was an investigator-initiated, pragmatic, multicentre, prospective, randomised, double-blind, placebo-controlled trial done at 27 tertiary-level hospitals with comprehensive stroke services in China (appendix pp 5–6). The aim was to assess the safety and efficacy of FYTF-919 in patients with moderate to severe acute primary intracerebral haemorrhage. The protocol and statistical analysis plan have been published elsewhere,[21,22] and are available in the appendix (pp 234–312). A data safety and monitoring board oversaw the trial (appendix pp 31–33).

Adults (aged ≥18 years) were included with a diagnosis of spontaneous intracerebral haemorrhage that was confirmed by brain imaging within 48 h after the onset of symptoms or last seen well; and with a moderate to severe level of neurological impairment, defined by having a score of at least 8 on the National Institutes of Health Stroke Scale (NIHSS range 0–42, with higher scores indicating greater severity) or 7–14 inclusive on the Glasgow Coma Scale (range 3–5, with lower scores indicating greater loss of consciousness). Key exclusion criteria included being unlikely to benefit from the treatment (eg, advanced dementia or high likelihood of early death), as judged by the responsible treating clinician; having another medical illness that would interfere with the outcome assessments or follow-up (eg, known significant pre-stroke disability, with estimated scores 3–5 on the modified Rankin scale, advanced cancer, or use of haemodialysis); having a definite indication or contraindication to the use of FYTF-919; being a pregnant or lactating woman; or participation in another trial. Details of the inclusion and exclusion criteria are provided in the appendix (p 13).

The study complied with the Declaration of Helsinki and was approved by the ethics committee of each participating site and appropriate regulatory agencies. All participants, or their approved surrogate for those who were too unwell, provided written informed consent. We followed the CONSORT extension reporting guidelines for Chinese herbal medicine formulations.[23] This trial is registered at ClinicalTrials.gov, NCT05066620.

Randomisation and masking

After confirmation of eligibility, patients were randomly assigned (1:1) to either FYTF-919 or matching placebo via a central internet-based system with a variable 4 by 6 block grouping method stratified by the location of the hospital (provincial region), severity of neurological impairment (scores <15 *vs* ≥15 on the NIHSS), and location of the haematoma in the brain (deep basal ganglia, thalamus) *vs* lobar *vs* infratentorial [cerebellum, brain stem, or ventricle]). Eligible patients were assigned to either FYTF-919 or matching placebo.

FYTF-919 (Zhongfeng Xingnao oral prescription) was developed by the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine in accordance with the Chinese standards for good manufacture practice of medical products, and this hospital (investi-

Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China; Department of Neurosurgery, West China Hospital, Sichuan University, Chengdu, China (Prof C You MD); **Department of Neurology, Nanfang Hospital, Southern Medical University, Guangzhou, China** (Prof S Pan PhD); **Guangdong Provincial Key Laboratory of Research on Emergency in Traditional Chinese Medicine, Guangzhou, China** (Prof Y Cai); **Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou, China** (Prof Y Cai PhD); **Emergency Department, Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu, China** (Prof Y Lu PhD); **Centre for Neuromuscular and Neurological Diseases, Medical School, The University of Western Australia, Perth, WA,**

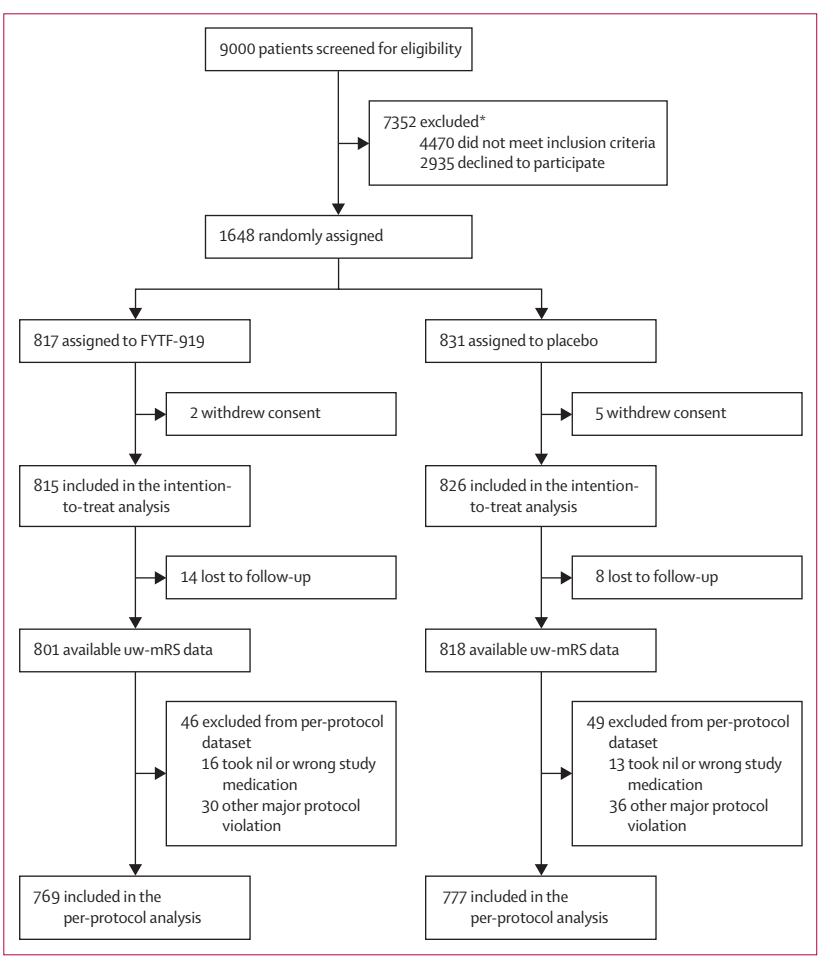

Figure 1: **Trial profile over 90 days**
uw-mRS=utility weighted modified Rankin Scale. *Data are not mutually exclusive.

Australia (Prof G J Hankey MD); **Perron Institute for Neurological and Translational Science, Perth, WA, Australia** (Prof G J Hankey); **Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK** (Prof R Al-Shahi Salman PhD); **Edinburgh Clinical Trials Unit, Usher Institute, University of Edinburgh, Edinburgh, UK** (Prof R Al-Shahi Salman); **Neurology Department, Royal**

gator Shaohong Chen) owns the invention patent (Chinese patent ZLO 18 023262.0) from 2005. It is a plant-based compound composed mainly of renshen (*Panax ginseng*), dahuang (Radix et Rhizoma Rhei), Sanqi (*Radix notoginseng*), and chuanxiong (Rhizoma *Ligustici chuanxiong*), which are combined with sorbic acid and polysorbate 80 as auxiliary materials and prepared as a brown–yellow liquid in a standard 100 mL vial. The dose and method of delivery is determined by a patient's level of consciousness and ability to swallow.

The placebo was developed by Guangdong Huixiangyuan Biotechnology, as a plant-flavoured solution without any pharmacological activity. It was composed of a soybean peptide with a black sugar syrup, combined with an edible essence and maltodextrin, and salt and monosodium glutamate, as auxiliary materials. According to the safety guarantee from the manufacturer, manual consistency testing showed that the placebo had good consistency with FYTF-919 in appearance, smell, taste, and other aspects. Our own independent designated testing also confirmed successful masking of the placebo and FYTF-919 through consistency in appearance, smell, taste, and other aspects (details are outlined in the appendix pp 14–25).

	FYTF-919 (n=815)	Placebo (n=826)
Mean age, years	62·2 (12·0)	61·3 (11·9)
Sex		
Male	528 (64·8%)	551 (66·7%)
Female	287 (35·2%)	275 (33·3%)
Ethnicity		
Han Chinese	790 (96·9%)	797 (96·5%)
Other	25 (3·1%)	29 (3·5%)
Medical history		
Hypertension	539/813 (66·3%)	572/823 (69·5%)
Coronary artery disease	43 (5·3%)	30 (3·6%)
Diabetes	69 (8·5%)	73 (8·8%)
Pre-stroke level of function on the modified Rankin Scale*		
0	738/814 (90·7%)	747 (90·4%)
1	47/814 (5·8%)	43 (5·2%)
2	29/814 (3·6%)	36 (4·4%)
Current smoker	211 (25·9%)	225 (27·3%)
Current alcohol consumption	206/814 (25·3%)	216/825 (26·2%)
Use of aspirin or other antiplatelet agent	35 (4·3%)	29 (3·5%)
Use of anticoagulation	1 (0·1%)	3 (0·4%)
Mean systolic blood pressure, mm Hg	172 (29)	172 (29)
Mean diastolic blood pressure, mm Hg	98 (19)	99 (20)
Median severity of neurological deficit on the NIHSS†	15 (10–21)	15 (10–20)
Median level of consciousness by scores on the Glasgow Coma Scale‡	12 (10–14)	12 (10–14)
Features of the intracerebral haemorrhage on CT imaging§		
Haematoma location‖		
Cerebral lobe	79/799 (9·9%)	74/810 (9·1%)
Basal ganglia or thalamus	664/799 (83·1%)	682/810 (84·2%)
Cerebellum or brainstem	56/799 (7·0%)	54/810 (6·7%)
Median haematoma volume, mL	18 (8–35)	17 (8–30)
Presence of intraventricular haemorrhage	359/809 (44·4%)	332/821 (40·4%)
Median time from the onset of symptoms to presentation, h	3·0 (2·0–5·7)	3·0 (1·9–5·2)
Median time from onset of symptoms to randomisation, h	15·1 (7·3–26·1)	15·5 (7·4–25·5)

Data are n (%), mean (SD) or median (IQR). NIHSS=National Institutes of Health Stroke Scale. *Scores on the modified Rankin Scale of functional recovery range from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence. The modified Rankin Scale score before stroke onset was assessed by the treating physician with the use of information obtained from patients (if possible) or their family members. Only patients with a modified Rankin Scale score of 0 to 2 were included in the trial. †Scores on the NIHSS range from 0 to 42, with higher scores indicating more severe neurological deficits. ‡Scores on the Glasgow Coma Scale range from 15 (normal) to 3 (deep coma). §Reported by clinician investigators. ‖Includes 15 cases of isolated intraventricular haemorrhage, 10/799 (1·3%) in the FYTF-919 group and 5/810 (0·6%) in the placebo group.

Table 1: **Baseline characteristics of study participants**

Participants who were awake and able to swallow received warm FYTF-919 (or placebo) orally, at a dose of 33 mL at least 30 min after a meal, every 8 h per day. For those with dysphagia, insufficient oral intake, unconsciousness, or who were in a critical condition, a lower dose of 25 mL was administered usually via a nasogastic tube, four times (every 6 h) per day. Treatment started immediately after randomisation and continued until 28 days. The dose regime for FYTF-919 was chosen on the basis of a systematic review showing an association with optimal efficacy (appendix pp 183–233). Participants were required to return all bottles of the study medication at the 28-day assessment visit. Full details of FYTF-919 and the placebo are outlined in appendix (pp 14–25).

Procedures

Treatment was not modified or discontinued unless a participant (or surrogate) chose to withdraw their consent to participate; a serious adverse event occurred which, in the opinion of the investigator, was related to the trial protocol; or the investigator felt it was in the participant's best interest. Cessation of treatment did not usually lead to emergency unmasking.

All participants were initially managed in a neurointensive care unit or similar monitored facility, and their subsequent management was in accordance with guideline recommendations. Follow-up data were collected in all participants except those who withdrew their consent for the release of such information. Follow-up evaluations were undertaken at 1, 7, 14, 28, 90, and 180 days, either by telephone or in person, by trained certified medical staff. The trial was overseen by a steering committee and all serious adverse events were reviewed with an independent data and safety monitoring board. Project management staff did the quality control activities necessary for conduct of the trial in accordance with the protocol, applicable guidelines, and regulations. A masked independent clinical events committee checked the data for completeness, accuracy, and logic, and adjudicated all serious adverse events to prespecified endpoint definitions on review of reports. Details of the assessment schedule and definitions are listed in the study protocol (appendix pp 234–70) and appendix (pp 33–34).

Outcomes

The primary outcome was the utility weighted mRS score at 90 days.[24] The mRS is a standard global 7-level measure of disability, in which scores of 0–1 indicate a favourable outcome without or with symptoms but no disability, scores of 2–5 indicate increasing amounts of disability (and dependency), and a score of 6 indicates death. We assigned utility weights to the seven levels of 0·97, 0·88, 0·74, 0·55, 0·20, –0·19, and 0·0, respectively, with higher scores indicating a better outcome according to participants' perspective. These weights were derived from a large database of predominantly Chinese patients with intracerebral haemorrhage,[24] as opposed to the use of standard non-Chinese weights in trials of acute ischaemic stroke.[25] Secondary efficacy outcomes were utility weighted scores on the mRS at 180 days, an

	Number of patients			Group values		Estimated mean difference or odds ratio (95% CI)	p value*
	FYTF-919	Placebo	Total	FYTF-919	Placebo		
Primary outcome—uw-mRS*							
Primary model	782	795	1577	0·44	0·44	0·01 (–0·02 to 0·04)	0·63
Sensitivity 1*	782	795	1577	0·46	0·46	0·01 (–0·03 to 0·04)	0·80
Sensitivity 2†	699	708	1397	0·56	0·56	0·01 (–0·03 to 0·04)	0·78
Sensitivity 3‡	782	795	1577	0·46	0·46	0·01 (–0·03 to 0·04)	0·80
Adjusted model§	781	795	1576	0·42	0·41	0·02 (–0·02 to 0·04)	0·33
Secondary outcome							
Ordinal mRS for poor outcome¶	782	795	1577	..	..	0·99 (0·84 to 1·18)	0·94
Death or disability (mRS 4–6)	782	795	1577	38·1	37·9	1·00 (0·80 to 1·25)	0·99
Death	795	802	1597	11·8	11·3	1·11 (0·81 to 1·52)	0·53
Disability (mRS 4–5)	782	795	1577	26·1	26·4	0·94 (0·74 to 1·19)	0·58
Barthel index	689	707	1396	71·1	69·9	1·18 (–1·58 to 3·93)	0·40
EQ-5D-5L utility score‖	591	607	1198	0·59	0·60	–0·76 (–2·95 to 1·43)	0·50
Pneumonia	745	755	1500	3·9	3·8	0·99 (0·58 to 1·71)	0·98
Hospital discharge by day 28	738	754	1492	81·0	81·0	..	..
Safety							
Serious adverse events**							
Number reported	507	541	..	..	..	..	0·44
Number of patients	338 (41·5%)	358 (43·3%)	..	..	..	..	..
Related to treatment††	9/507 (1·8%)	5/541 (0·9%)	..	..	..	..	..
Adverse events							
Number reported	1761	1751	..	..	..	..	0·70
Number of patients	650 (79·8%)	665 (80·5%)	..	..	..	..	..
Related to treatment††	116/1761 (6·6%)	76/1751 (4·3%)	..	..	..	..	..
Adverse events of special interest‡‡							
Number reported	116	81	..	..	..	..	0·01
Number of patients	111 (13·6%)	78 (9·4%)	..	..	..	..	..
Related to treatment††	58/116 (50·0%)	28/81 (34·6%)	..	..	..	..	..

EQ-5D-5L=5-level EuroQoL5-dimension self-report questionnaire. mRS=modified Rankin Scale. uw-mRS=utility weighted modified Rankin Scale. *uw-mRS was calculated as adding weight to mRS values for functional outcome. Scores on mRS range from 0 (no symptoms) to 6 (death). A score of 2 or less indicates functional independence. The utility weights of 0·97, 0·88, 0·74, 0·55, 0·20, –0·19, and 0·0 were assigned to each of the 7 mRS scores. †Use of scores on the EQ-5D-5L for participants at day 90 to impute utility values for participants with missing utility scores at day 90. ‡Use of available EQ-5D-5L utility scores at day 90 to derive utility weights for participants with non-missing EQ-5D-5L data. ‡In participants with missing EQ-5D-5L utility scores at day 90 but these were available at 180 days, the later were used to impute utility values at day 90. §Values are adjusted for adding the following covariates to the main linear model: age (continuous), premorbid scores on the mRS (categorical), sex (male *vs* female), time to randomisation (<12 h *vs* ≥12 h). ¶The common odds was estimated in an ordinal logistic regression model. The test for proportional odds across mRS scores was p=0·38. The distribution of mRS scores 0, 1, 2, 3, 4, 5, and 6 was 7·5%, 19·7%, 15·3%, 19·3%, 22·4%, 3·7%, and 12·0% in the FYTF-919 group and 7·4%, 19·2%, 15·5%, 20·0%, 20·9%, 5·5%, and 11·4% in the placebo group. ‖The EQ-5D-5L covers 5 domains of health–related quality of life: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each domain has three graded levels of response: no problems, moderate problems, or extreme problems. Scores from these levels are combined to provide an overall health utility score that was calculated with population norms from the UK. **Any serious adverse event defined by standard criteria includes any of the following events that might or might not be considered related to the treatment that results in death, is life–threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in medical or surgical intervention to prevent permanent impairment to body structure or function. Refers to the number of reported serious adverse events; a patient could have more than one event. Values refer to the number of patients with a reported serious adverse event. ††Local investigator considered the event to be definitely or possibly related to the study medication. ‡‡Reported by the local investigators including haematoma enlargement (>6 mL or >33%), new intracranial haematoma, and diarrhoea.

Table 2: **Primary and secondary efficacy and safety outcomes at 90 days in the intention-to-treat population**

Prince Alfred Hospital, Sydney, NSW, Australia (Prof C S Anderson)**; Key Laboratory of Computational Neuroscience and Brain-Inspired Intelligence (Fudan University), Ministry of Education, Shanghai, China** (Prof C S Anderson, Prof L Song)

Correspondence to:
Prof Lili Song, Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Zhangjiang Campus, Pudong New Area, Shanghai 201203, China
lili_song@fudan.edu.cn

or

Prof Jianwen Guo, Guangdong Provincial Hospital of Chinese Medicine, Yuexiu District, Guangzhou, Guangdong 510120, China
jianwen_guo@qq.com

or

Prof Craig S Anderson, Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai Zhangjiang Campus, Pudong New Area, Shanghai 201203, China
canderson@fudan.edu.cn

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original analysis of the mRS at 28, 90, and 180 days, and dichotomous analysis of scores on the mRS at 28, 90, and 180 days: 4 to 6 (disability or death) versus 0 to 3 (independence). Other outcomes were death or neurological deterioration according to the distribution of scores on the NIHSS at 24 h and 7 days; death within 90 days; and health-related quality of life on the 5-level EuroQoL 5-dimension self-report questionnaire (EQ-5D-5L) at 28, 90, and 180 days; basic activities of daily living according to the Barthel Index at 28, 90, and 180 days; investigator-reported haematoma volumes at 24 h, 7 days, and 14 days (or hospital discharge, if sooner); hospital discharge by day 28; and stroke-associated pneumonia according to the clinical pulmonary infection score.[26] All serious adverse events and adverse events of special interest that were presumed to be related to FYTF-919, including diarrhoea and abnormal biochemistry, were recorded through to study completion.

Statistical analysis

We estimated that a sample of 1504 patients would provide 90% power (α=0·05) to detect an improvement in mean utility weighted mRS scores of 20% or greater between the FYTF-919 group and placebo group (ie, 0·65 *vs* 0·59, mean difference 0·06; SD=0·32), assuming equal amounts of group participation, 6% non-adherence, to the protocol (ie, drop-in–drop-out), and 10% lost to follow-up at 90 days. This calculation was based on data from the second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2), in which the mean utility weighted mRS score was 0·59 in the less intensive blood pressure usual care control group.[27]

The principal analysis was done on the intention-to-treat population of all randomly assigned patients who provided consent for use of their data, regardless of whether they received the study treatment according to the protocol. The main analysis used a general linear model with utility weighted mRS scores at day 90 as the dependent variable. Treatment allocation was included as a fixed effect along with site, baseline NIHSS scores, and haematoma location. The effect of the intervention is presented as a mean difference and 95% CI, with the placebo group as the reference. Three sensitivity analyses were done by means of different approaches to imputing utility weights in those participants with missing utility scores. A per-protocol analysis excluded participants with a major protocol violation of not meeting the inclusion or exclusion criteria, consumption of contraindicated Chinese medicines, and a deviation from the protocol for consumption of the study medication.

Adjusted analyses were also done by adding the following covariates as fixed effects to the main linear model: age (continuous), premorbid scores on the mRS (categorical), sex (male *vs* female), time to randomisation (<12 *vs* ≥12 h). Sensitivity analysis of the primary and secondary outcomes at 28, 90, and 180 days was done with the primary and adjusted models. Heterogeneity of the treatment effect on the primary endpoint was assessed in the six prespecified subgroups of age (<65 *vs* ≥65 years), sex (male *vs* female), or time to randomisation (<12 h *vs* ≥12 h), baseline NIHSS score (<15 *vs* ≥15), baseline haematoma volume (<15 *vs* ≥15 mL), and haematoma location (cortical *vs* basal ganglia–thalamic *vs* cerebellar–brainstem–ventricular). The analysis for each subgroup was done by adding the subgroup variable as well as its interaction with the intervention as fixed effects to the main linear model. Within each subgroup, summary measures were raw mean (SD) within each treatment group. Shift in the seven levels of the mRS was analysed by ordinal logistic regression with tests regarding whether the proportional odds assumption was violated. Secondary categorical outcomes were analysed by a logistic regression model. Analyses of the brain imaging parameters of haematoma and perihaematomal oedema volumes are ongoing and will be available in a later publication. All analyses were done by use of SAS Enterprise Guide 8.3, SAS version 9.4. A data safety and monitoring board oversaw the trial (appendix pp 31–33).

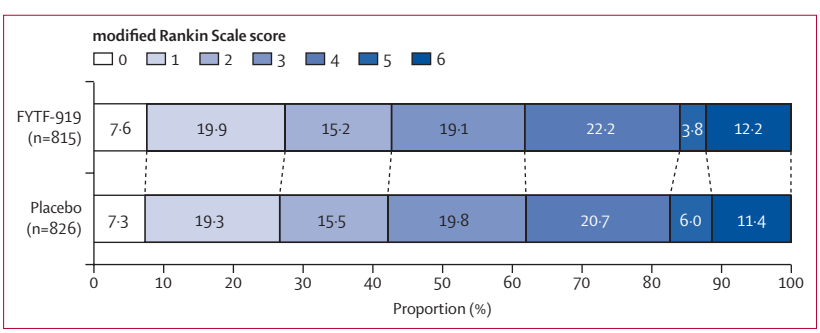

Figure 2: **Raw distribution of the modified Rankin Scale scores at 90 days by treatment group in the intention-to-treat population**

The figure shows the raw distribution of scores on the modified Rankin Scale at 90 days. Scores on the modified Rankin Scale range from 0 to 6. 0=no symptoms. 1=symptoms without clinically significant disability. 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability, and 6=death. In adjusted analysis of available data, the common odds ratio is 0·99 (95% CI 0·84 to 1·18; p=0·94) for poor outcome in the FYTF-919 group versus the placebo group.

Role of the funding source

The sponsors and funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Nov 24, 2021, to Dec 28, 2023, of 9000 patients screened, 1648 were randomly assigned at 26 tertiary-level hospitals with comprehensive stroke services in China. One activated hospital did not recruit any patients. Because seven patients withdrew their consent immediately after random assignment without receiving any study treatment, 1641 patients were included in the

modified intention-to-treat analysis: 815 were assigned to the FYTF-919 group and 826 to the placebo group (figure 1, appendix p 36). 14 participants in the FYTF-919 group and eight participants in the placebo group were lost to follow-up at 90 days, and 46 and 49 participants in each group, respectively, with prespecified protocol violations who were excluded from the per-protocol analyses of outcomes at 90 days (appendix pp 29–30, p 37). Only 1 participant was lost to follow-up in the FYTF-919 group between 90 days and 180 days (appendix p 178).

The two groups were balanced with respect to baseline demographic, clinical, and treatment characteristics, overall (table 1, and appendix 2 pp 38–39) and by age and sex (appendix pp 40–69). The mean age was 67·1 years (12·0) and 34·2% were female. The site of the haemorrhage was in the basal ganglia or thalamus in 1346 (83·7%), the median baseline NIHSS score was 15 (IQR 10–20; appendix p 179), and 30·3% had received early decompressive surgery. The median time from onset to randomisation was 15·3 h (IQR 7·4–25·8), when the mean systolic blood pressure was 172 (SD 29) mm Hg.

The medium time from the onset of symptoms to receipt of the first dose of study medication was 20·0 h (IQR 11·4–30·5) and the medication was taken in nearly equal proportion orally and by nasogastric tube (appendix p 70). The median duration of medication was 29 days (27–29) and the median number of bottles completed was 28 (24–28). Overall, 1242 (75·7%) participants consumed 80% or more of the study medication (1235 [82·4%] surviving participants) and 994 (60·6%) completely adhered to the dosing schedule to consume all the study medication by 28 days (appendix p 70). There were no significant differences in the clinical management of participants over 28 days; 424 (52·0%) participants in the FYTF-919 group and 416 (50·4%) in the placebo group received neurosurgical intervention during the study period (appendix pp 71–74). Details of the clinical assessments and investigator-reported brain imaging features are outlined in the appendix (pp 75–80).

Mean utility weighted mRS scores at 90 days were 0·44 in the FYTF-919 group and 0·44 in the placebo group (difference 0·01, 95% CI, –0·02 to 0·04; p=0·63; table 2 and appendix pp 81–83, figure 2). The neutral result was consistent in adjusted and per-protocol analysis (table 2 and appendix pp 84–113) and in analysis of the primary outcome at 180 days (appendix pp 84–85, 114). There was significant heterogeneity in the treatment effect on the primary outcome for the prespecified subgroups of the volume and location of the haematoma (figure 3). However, apart from the location of haematoma on the treatment effect at 180 days, there was no heterogeneity of the treatment effect in post-hoc analysis using a classification of these subgroups into tertiles and in the use of surgery at 90 days and 180 days (appendix pp 180–82).

There was no significant between-group difference between the FYTF-919 group and the placebo group across any of the secondary outcomes (table 2 and appendix pp 84–85 during 90 days of follow-up). The results were consistent in per-protocol analysis (appendix pp 103–13).

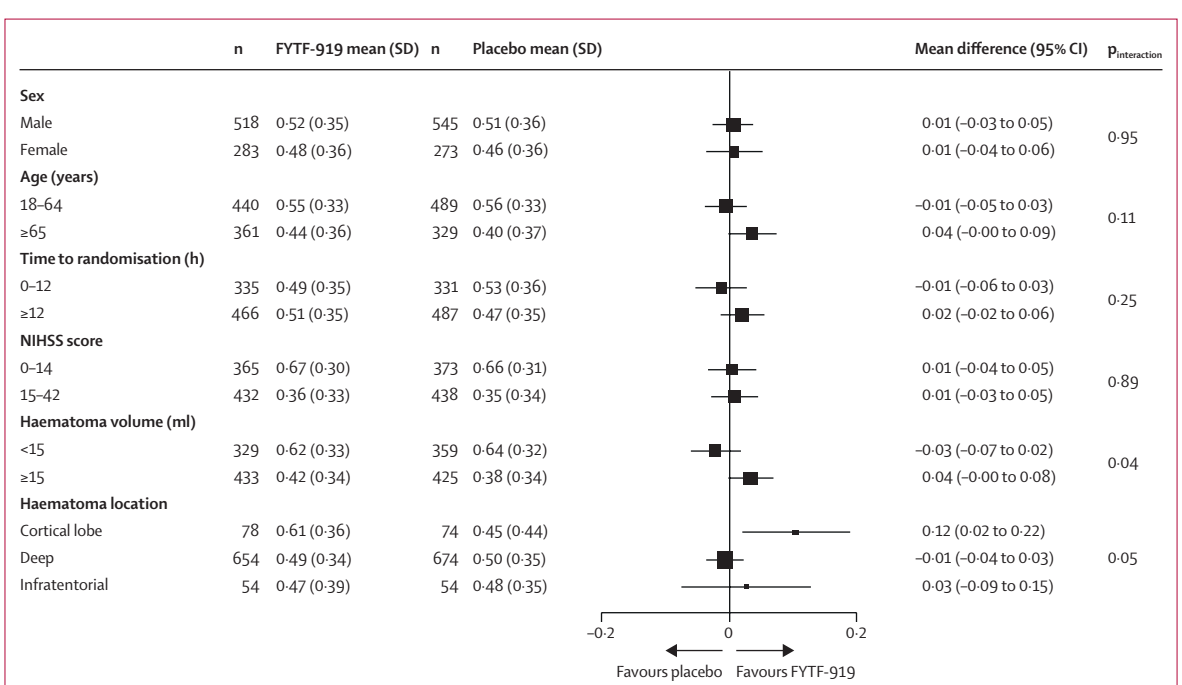

Figure 3: **Functional outcomes according to utility weighted modified Rankin Scale scores at 90 days in subgroups of patients in the primary adjusted model**
NIHSS=National Institutes of Health Stroke Scale.

Details regarding the causes of death are provided in the appendix (pp 115, 131–39).

Overall, there were no significant differences between the FYTF-919 group and the placebo group in adverse events (79·8% *vs* 80·5%) or serious adverse events (41·5% *vs* 43·3% during 90 days of follow-up). Among the events of special interest, diarrhoea occurred in 10·6% of the FYTF-919 group and 6·5% of the placebo group. A complete list of adverse events is provided in the appendix (pp 116–30, 140–76).

Discussion

In this multicentre, randomised, double-blind, placebo-controlled, clinical trial, the traditional Chinese medical herbal compound FYTF-919 did not affect the utility weighted mRS at 90 days in patients with moderate to severe acute intracerebral haemorrhage. In addition, there were no between-group differences in any of the secondary clinical measures (including death) or serious adverse events.

Herbal formulas have been used to treat people in China for thousands of years. Traditional Chinese medicine continues to be an integral part of mainstream health care in China, now organised alongside the conventional biomedical approaches of western medicine. Elsewhere in the world, Chinese herbal medicines are widely used as complementary or alternative medicine to maintain wellness without the need for professional advice or disclosure, and despite scarce supporting evidence of efficacy.[28] Despite some favourable results, the poor methodological quality of existing clinical trials has created ambiguity about the effects of traditional Chinese medicine.[29,30] Recently, however, two large double-blind, placebo-controlled, clinical trials of traditional Chinese medicine herbal compounds have shown beneficial effects in cardiology: Tongxinluo for the treatment of 3797 patients with acute myocardial infarction[31] and Qiliqiangxin for the treatment of 3110 patients with heart failure with reduced ejection fraction.[32] Yet, even when quality control issues, such as sample size, concealment of allocation, masking, and patient selection, have been appropriately addressed, issues persist over the interpretation of results in relation to the study context and variable quality of the component ingredients.[33] A variety of Chinese herbal medicines have been tested in patients with acute ischaemic stroke, but apart from one large clinical trial of MLC601 (NeuroAiD), a combination of nine herbal and five animal components in capsule form to enhance recovery,[34] these have generally been small and of low quality.[35]

We were motivated to undertake the CHAIN study because of the paucity of treatments for intracerebral haemorrhage, which causes more loss of productive life from death or disability globally than the more common ischaemic stroke.[2] Intracerebral haemorrhage causes the initial (primary) brain injury from mass effect and physical disruption of the haematoma.[1] The release of iron and thrombin as haemoglobin degradation products from the haemolysis of red blood cells within the haematoma are major contributors to secondary neuronal injury after intracerebral haemorrhage.[7–9] These products cause various processes that include apoptosis, oxidative stress, inflammation, and autophagy, which further disrupt the blood–brain barrier and lead to parenchymal cell swelling manifest on brain imaging as perihaematomal oedema. Initially, these processes have the potential to increase intracranial pressure and lead to herniation and death, and later to compromise the speed and degree of recovery of physical function and wellbeing.[36]

Our study has several strengths. It was designed with a large sample size to minimise random error and ensure we were able to establish a reliable assessment of the effects of FYTF-919 in a potential patient-responder group with a high likelihood of developing secondary neuroinflammatory injury and perihaematomal oedema. The use of utility weighted mRS scores as the primary outcome measure was purposely chosen to provide efficiency gains in statistical power and as a more appropriate assessment of functional recovery in those with severe disability, many of whom would undergo neurosurgery.[24,25] There was no systematic bias due to imbalance in the baseline characteristics of patients between the randomised groups, and no apparent unmasking of the study medication that could be recognised either through specific testing or differences in the management of participants or their adherence to procedures. Participants were managed with a high degree of background interventions and supportive care appropriate for a critical illness, and they achieved a high degree of adherence to the study medication.

The nearly two-fold increase in diarrhoea reported in the FYTF-919 group confirms that it contained active ingredients and provides some support to the hypothesis that a major therapeutic effect of traditional Chinese medicine is to improve gut microbiota and regulation of gastrointestinal hormones.[37] Although subgroup analysis indicates a treatment effect of FYTF-919 in participants with superficial and larger haematomas (volumes of 15 mL or greater), these findings are not reliable due to the small numbers of participants with superficial cortical haematomas and the absence of an association when haematoma volumes were reclassified into tertiles.

Our study has some limitations. Although the patients were recruited from several provinces in China and had similar characteristics to participants in the third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3), which used a stepped wedge cluster randomised design,[38] the generalisability of these findings outside of China is unknown. In China, patients have different demographic and clinical characteristics and patterns of intracerebral haemorrhage than patients in other high-income countries. Moreover, the high rates of active

management, including the use of neurosurgery, intensive care, and certain medical treatments, is not the usual standard of care in many countries and might have compromised the sensitivity in detecting an effect of FYTF-919. Although further data on the temporal changes in the volumes of perihaematomal oedema in participants will be reported in the future, this may not be a reliable surrogate measure of neuroinflammation.[9]

In conclusion, our study has shown that in patients with primary intracerebral haemorrhage that led to a moderate to severe amount of neurological impairment within 48 h after the onset of symptoms, use of the traditional Chinese herbal compound FYTF-919 had no effect on utility weighted modified Rankin scores or any other clinical outcome. This randomised controlled trial provides a paradigm for the assessment of other traditional Chinese medical herbal compounds for the treatment of acute stroke in China, and elsewhere in the world where the use of complementary and alternative medicines are increasing.

Contributors

JG, CSA, and LS designed the study. LS, XC, YCh provided quality control oversight. XL and XR did the statistical analysis and reports. QL wrote the statistical analysis plan with input from CSA and LS. CSA wrote the first draft of the manuscript. All the other authors reviewed and commented on the final draft of the manuscript. The first authors QL, XL, and XR, and the corresponding authors had full access to verify all the study data, and they had final responsibility for the decision to submit the paper for publication. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JG received grants from The Department of Science and Technology of Guangdong Province, and Guangzhou Municipal Science and Technology Bureau. GJH is a member of of the data safety monitoring board (DSMB) of the Triple Therapy Prevention of Recurrent Intracerebral Disease Events Trial (TRIDENT) of which CSA is the principal investigator, and is an Associate Editor of *Circulation*. CSA has received grants from the National Health and Medical Research Council (NHMRC) of Australia, the Medical Research Council and Medical Research Foundation of the UK, and Penumbra and Takeda China. He also reports receiving advisory committee fees from AstraZeneca, is President-elect of the World Stroke Organization, editor-in-chief of *Cerebrovascular Diseases*, and associate editor of the *International Journal of Stroke*. He is a member of the DSMB for the PROTECT-MT, MAGIC-MT, and DIST trials. LS has received grants from Takeda China and Unionstrong Technology, and is a member of the DSMB for the PROTECT-MT and STROKE-ICAS trials. All other authors declare no competing interests.

Data sharing

Individual de-identified participant data used in these analyses can be shared by request from any qualified investigator following approval of a protocol and signed data access agreement via a corresponding author.

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haematopoiesis, the backbone of beti-cel therapy rests on the myeloablative conditioning regimen used in allogenic HSCT. The development of haematological malignancies after lentiglobin gene therapy in other studies means that longer-term follow-up is warranted to ensure safety in these participants and those who will be receiving beti-cel as standard of care.[8]

For such a therapy to gain widespread adoption, it must overcome several obstacles. First, to make the risk–benefit ratio more acceptable to patients, toxicities—including infertility—from the myeloablative conditioning regimen need to be overcome. Antibody-based conditioning regimens, already in development, could offer such possibilities.[9] In addition, the logistics of beti-cel therapy restrict widespread access. The need for specialised manufacturing centres, the cost of the gene therapy itself, the necessary infrastructure required to collect the HSPC via apheresis, storage and transport, the pharmacokinetic-adjusted myeloablative conditioning regimen, and the management of associated complications impose enormous challenges to low-income and low-middle-income countries, where the majority of patients with β-thalassaemia reside. In vivo gene therapy would be a major step forward to increased access.[10]

It has been 65 years since the discovery of the structure of haemoglobin. Kwiatkowski and colleagues' publication[5] marks another step towards treatment for a devastating monogenic disease. But, for this therapy to truly change lives, more work will need to be done to improve accessibility, safety, and cost.

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*Kevin H M Kuo, Stéphanie Forté
kevin.kuo@utoronto.ca

Division of Haematology, University of Toronto, Toronto, ON M5G 1L7, Canada (KHMK); Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada (KHMK); Division of Haematology and Medical Oncology, Department of Medicine, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada (SF); Department of Medicine, University of Montreal, Montreal, Canada (SF)

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Integrative medicine for the treatment of stroke

Intracerebral haemorrhage is a devastating and less treatable type of stroke.[1] Globally, intracerebral haemorrhage constitutes approximately one-third of all incident strokes and nearly half of the disability-adjusted life-years attributed to stroke.[2] Burden of intracerebral haemorrhage is more prominent in low-income to middle-income countries, where unidentified and uncontrolled hypertension is an outstanding risk factor. Intracerebral haemorrhage accounts for 24% of incident stroke cases in China, and in some regions of central China it accounts for 60% of all strokes.[3] Treatment for intracerebral haemorrhage is an integrative approach with multidisciplinary collaboration, where existing interventions are mainly targeted at limiting haematoma through lowering of blood pressure, reversal of anti-coagulation and antiplatelet treatment, and surgical evacuation.[4] Clinicians and researchers have made persistent efforts to investigate pathophysiological mechanisms and to explore treatment for protecting tissue from secondary injury after intracerebral haemorrhage.[5]

Herbal medicine with presumed antithrombotic, anti-inflammatory, and neuroprotective properties has been used for the treatment of stroke for thousands of years in China and many other countries.[6] In *The Lancet*, Jianwen Guo and colleagues' Chinese herbal medicine in patients with acute intracerebral haemorrhage


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(CHAIN) trial evaluated the efficacy and safety of a traditional Chinese medicine herbal compound FYTF-919 (Zhongfeng Xingnao oral prescription) for the treatment of intracerebral haemorrhage.[7] The study randomly assigned 1648 patients with moderate to severe spontaneous intracerebral haemorrhage within 48 h after symptom onset, to receive either oral liquid FYTF-919 or placebo 33 mL every 8 h (or 25 mL every 6 h via nasogastric tube) over 24 h for 28 days. In the modified intention-to-treat analysis of 1641 patients (mean age 67·1 years, 34·2% women, 96·7% Han Chinese), FYTF-919 showed no effect compared with placebo on the primary outcome of utility-weighted modified Rankin Scale scores at 90 days, nor on survival, health-related quality of life, or serious adverse events. Despite the neutral results, the study proved the feasibility of evaluating traditional Chinese medicine by a large-scale, multicentre, randomised, placebo-controlled, double-blind, clinical trial. It ensured successful masking by providing placebo with good consistency with FYTF-919 in appearance, smell, and taste. In addition, this study used the utility-weighted modified Rankin Scale scores derived from a predominantly Chinese population as the primary outcome, which reflected the health perception and wellbeing of patients and provided greater statistical power in assessing treatment effect over traditional modified Rankin scale scores.[8]

Traditional Chinese medicine prescriptions often consist of a mixture of ingredients. FYTF-919 is mainly composed of four herbs, including renshen (*Panax ginseng*), dahuang (Radix et Rhizoma Rhei), sanqi (*Radix notoginseng*), and chuanxiong (Rhizoma *Ligustici Chuanxiong*). These herbs are believed to have properties of promoting blood circulation and removing blood stasis.[7] Chemical analysis by ultra-high performance liquid chromatography and mass spectrometry identified 30 chemical profiles of FYTF-919 compound. There is presumed possible pharmacokinetic or pharmacodynamic synergism of these ingredients, which would complicate the interpretation of trial findings. Furthermore, FYTF-919 was tested along with conventional treatment for intracerebral haemorrhage such as antihypertensive agents and reversal of anticoagulation. In this integrative medicine approach, there is potential interaction of these ingredients with chemical medications. Isolation and testing of active compounds of FYTF-919 would help to better understand the translational gap. To ensure the replicability and generalisability, the CONSORT guidelines encourage a detailed description of the dosage regimen with names of isolated active ingredients and quantified chemical constituents in herbal medicine.[9] Following the successful drug development of isolating aspirin from the bark of willow and extracting artemisinin from leaves of *Artemisia annua* (qinghao), future trials with a rigorous design to evaluate the active components of herbal medicine might provide more convincing evidence for the treatment of stroke.

In contrast to a previous trial in which herbs with properties to remove blood stasis increased the risk of bleeding after intracerebral haemorrhage,[10] the CHAIN trial proved the safety of FYTF-919 in patients with acute intracerebral haemorrhage but no efficacy on clinical outcomes. The CHAIN trial enrolled patients with moderate to severe intracerebral haemorrhage, who were assumed to have a high likelihood of secondary neuroinflammatory injury and perihaematomal oedema and thus a potentially responsive group to FYTF-919. This was based on a hypothesis that perihaematomal oedema was attributed to neuroinflammation. However, markers of neuroinflammation or perihaematomal oedema were not reported in the primary report, and whether perihaematomal oedema is associated with neuroinflammation is expected to be explored. The subgroup analysis on heterogeneity in the effect of FYTF-919 between patients with different volumes of haematoma implied a trend of benefit towards patients with larger haematomas. This finding was inconclusive owing to small sample size and needs to be validated in future trials. FYTF-919 is used in practice in China for the treatment of both ischaemic (ChiMCTR2100004506) and haemorrhagic stroke, which are two distinct pathological entities sharing a similar clinical syndrome. Intracerebral haemorrhage has different but overlapping risk factors to ischaemic stroke; both may include neuroinflammation as a secondary injury.[11] Treatment such as blood pressure lowering applies to both conditions but requires different initiating time and treatment targets.[12] Similarly, herbal medicine targeting neuroinflammation might not benefit both conditions or might require different regimens. Owing to the biological complexity of herbal medicine, results from one trial do not necessarily support nor refute the use of herbs with the same pharmacological properties for other groups of stroke patients.

Integrative medicine combines evidence-based conventional medicine with evidence-based complementary medicine to provide appropriate health care for individuals. The CHAIN trial integrated the evaluation of traditional Chinese medicine into the evidence-based research framework. The study set a methodological paradigm for evaluation of traditional Chinese medicine with a generally rigorous trial design. Future efforts at isolating and testing the active ingredients of FYTF-919 and other herbal medicine might further improve the evidence for the treatment of stroke.

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Simiao Wu
simiao.wu@hotmail.com

Department of Neurology, West China Hospital, Sichuan University, Chengdu 610041, China; Center of Cerebrovascular Diseases, West China Hospital, Sichuan University, Chengdu 610041, China

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Addressing transnational exploitation and armed conflict in the response to mpox

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Since the current outbreak of mpox clade I began in eastern DR Congo in 2023, there has been a rapid increase in cases, primarily in DR Congo, and spread of the monkeypox virus to other countries in Africa.[1–3] While 85% of mpox deaths in DR Congo since 2022 have occurred in children younger than 15 years,[2] a new clade Ib strain, which is apparently more transmissible than other strains, is causing infections linked to heterosexual intimate or sexual contact.[4] Since the August, 2024 declaration by the Africa Centres for Disease Control and Prevention (Africa CDC) of a Continental Public Health Emergency and by WHO of a Public Health Emergency of International Concern, comprehensive global, regional, and national strategies to respond to clade Ib mpox in eastern DR Congo and clades I and II across Africa are under way.[3,5] High-income countries are pledging technical assistance and donations of mpox vaccines from their vast stockpiles, although donations need to be increased as do efforts to ensure vaccine equity.[6,7] The Africa CDC and governments of affected countries have moved quickly to update response plans, mobilise funds to invest in disease surveillance, diagnostics, and health-care infrastructures, and secure additional vaccine doses.[6–8]

Approaches narrowly focused on stemming the mpox outbreaks in eastern DR Congo, however, will not be sufficient if they do not also address the ongoing conflict, exploitation in licit and illicit mining, conflict-related sexual violence, worsening poverty, and displacement of people in some of the affected countries in Africa. These accelerating human rights and humanitarian crises fuel the spread of mpox and hinder control efforts. With people from multiple countries converging in eastern DR Congo, cross-border transmission is affecting already fragile health-care systems and exacerbating risks of mpox and potentially other infectious disease outbreaks.