Tranexamic acid to improve functional status in adults with spontaneous intracerebral haemorrhage: the TICH-2 RCT

Nikola Sprigg,^{1,2*} Katie Flaherty,¹ Jason P Appleton,¹ Rustam Al-Shahi Salman,³ Daniel Bereczki,⁴ Maia Beridze,⁵ Alfonso Ciccone,⁶ Ronan Collins,⁷ Robert A Dineen,^{8,9} Lelia Duley,¹⁰ Juan José Egea-Guerrero,¹¹ Timothy J England,¹² Michal Karlinski,¹³ Kailash Krishnan,^{1,2} Ann Charlotte Laska,¹⁴ Zhe Kang Law,^{1,2,15} Christian Ovesen,¹⁶ Serefnur Ozturk,¹⁷ Stuart J Pocock,¹⁸ Ian Roberts,¹⁹ Thompson G Robinson,²⁰ Christine Roffe,²¹ Nils Peters,²² Polly Scutt,¹ Jegan Thanabalan,²³ David Werring,^{24,25} David Whynes,²⁶ Lisa Woodhouse¹ and Philip M Bath^{1,2} for the TICH-2 Investigators

¹Stroke Trials Unit, Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK

²Stroke, Nottingham University Hospitals NHS Trust, Nottingham, UK

³Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

⁴Department of Neurology, Semmelweis University, Budapest, Hungary

⁵The First University Clinic of Tbilisi State Medical University, Tbilisi, Georgia

⁶Neurology Unit, Azienda Socio Sanitaria Territoriale di Mantova, Mantua, Italy

⁷Stroke Service, Adelaide and Meath Hospital, Tallaght, Ireland

⁸Radiological Sciences, Division of Clinical Neuroscience, University of Nottingham, Nottingham, UK

⁹NIHR Nottingham Biomedical Research Centre, Nottingham, UK

¹⁰Nottingham Clinical Trials Unit, University of Nottingham, Nottingham, UK

¹¹UGC de Medicina Intensiva, Hospital Universitario Virgen del Rocío, IBiS/CSIC/ Universidad de Sevilla, Seville, Spain

¹²Vascular Medicine, Division of Medical Sciences & GEM, University of Nottingham, Derby, UK

¹³Second Department of Neurology, Institute of Psychiatry and Neurology, Warsaw, Poland

¹⁴Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden

- ¹⁵Department of Medicine, National University of Malaysia, Kuala Lumpur, Malaysia
- ¹⁶Bispebjerg and Frederiksberg Hospital, University of Copenhagen, Department of Neurology, Copenhagen, Denmark
- ¹⁷Department of Neurology, Selcuk University Medical Faculty, Konya, Turkey
- ¹⁸Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, UK
- ¹⁹Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, UK
 ²⁰Department of Cardiovascular Sciences and NIHR Leicester Biomedical Research Centre, University of Leicester, Leicester, UK
- ²¹Stroke Research, Faculty of Medicine and Health Sciences, Keele University, Keele, UK
- ²²Department of Neurology and Stroke Center, University Hospital Basel, Basel, Switzerland
- ²³Division of Neurosurgery, Department of Surgery, National University of Malaysia, Kuala Lumpur, Malaysia
- ²⁴Stroke Research Centre, University College London Queen Square Institute of Neurology, Faculty of Brain Sciences of University College London, University College London, London, UK
- ²⁵National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, London, UK
- ²⁶School of Economics, University of Nottingham, Nottingham, UK

Declared competing interests of authors: Rustam Al-Shahi Salman is a member of the Efficacy and Mechanism Evaluation Funding Board panel. Lelia Duley reports grants from the Nottingham Clinical Trials Unit during the conduct of the study. Christian Ovesen reports grants from the Velux Foundation (Søborg, Denmark), the Hojmosegaard Grant/Danish Medical Association (Copenhagen, Denmark), the Axel Muusfeldt's Foundation (Albertslund, Denmark), the University of Copenhagen (Copenhagen Denmark) and non-financial support from Merck Sharp & Dohme (MSD; Kenilworth, NJ, USA) outside the submitted work. Robert A Dineen reports grants from the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project number 11/129/109) during the conduct of the study. Timothy J England reports grants from the NIHR HTA programme during the conduct of the study. Thompson G Robinson reports grants from the University of Leicester. Christine Roffe has been a member of the HTA General Board since 2017. David Werring reports personal fees from Bayer AG (Leverkusen, Germany) outside the submitted work. Philip M Bath reports grants from the British Heart Foundation and the NIHR HTA programme during the conduct of the study, others from Platelet Solutions Ltd (Nottingham, UK) and personal fees from Diamedica (UK) Ltd (Bratton Fleming, UK), Nestlé SA (Vevey, Switzerland), Phagenesis Ltd (Manchester, UK), ReNeuron Group plc (Bridgend, UK), Athersys Inc. (Cleveland, OH, USA) and Covidien (Dublin, Ireland) outside the submitted work.

Published July 2019 DOI: 10.3310/hta23350

^{*}Corresponding author Nikola.sprigg@nottingham.ac.uk

Plain English summary

The TICH-2 RCT

Health Technology Assessment 2019; Vol. 23: No. 35 DOI: 10.3310/hta23350

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Plain English summary

Background

Stroke caused by bleeding in the brain [i.e. an intracerebral haemorrhage (ICH)] is a medical emergency. Around one-third of such strokes are complicated by continuing bleeding, which usually occurs within the first few hours after trauma and childbirth, and is associated with death or severe disability. Tranexamic acid is a drug that is seen to reduce death from bleeding after trauma and childbirth.

Methods

The study enrolled adults within 8 hours of an ICH into this large randomised trial. Half of the participants were given an injection of tranexamic acid and the other half placebo (in the form of salt water). The main aim of the trial was to measure changes in recovery by a telephone questionnaire on how much the person was able to do or needed help with 90 days after the stroke (i.e. functional status). Other measures included amount of brain bleeding, complications after stroke (serious adverse events), drug side effects and death within 7 days of stroke.

Results

A total of 2325 participants from 124 hospitals in 12 countries were enrolled between 2013 and 2017.

Participants treated with tranexamic acid had no significant difference in functional status 90 days after stroke. There were small but significant reductions in brain bleeding, death in the first 7 days and complications after stroke, and tranexamic acid was safe with no increased side effects.

Conclusion

Treatment with tranexamic acid did not result in a significant improvement in recovery at 90 days (i.e. functional status), despite small reductions in the number of early deaths, amount of brain bleeding and the number of complications. Larger trials are needed to confirm if these small benefits observed after treatment with tranexamic acid can significantly improve functional status after stroke due to bleeding in the brain (ICH).

HTA/HTA TAR

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.819

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the Health Technology Assessment journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 11/129/109. The contractual start date was in March 2013. The draft report began editorial review in September 2018 and was accepted for publication in March 2019. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

© Queen's Printer and Controller of HMSO 2019. This work was produced by Sprigg et al. under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

NIHR Journals Library Editor-in-Chief

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

NIHR Journals Library Editors

Professor John Powell Chair of HTA and EME Editorial Board and Editor-in-Chief of HTA and EME journals. Consultant Clinical Adviser, National Institute for Health and Care Excellence (NICE), UK, and Honorary Professor, University of Manchester, and Senior Clinical Researcher and Associate Professor, Nuffield Department of Primary Care Health Sciences, University of Oxford, UK

Professor Andrée Le May Chair of NIHR Journals Library Editorial Group (HS&DR, PGfAR, PHR journals) and Editor-in-Chief of HS&DR, PGfAR, PHR journals

Professor Matthias Beck Professor of Management, Cork University Business School, Department of Management and Marketing, University College Cork, Ireland

Dr Tessa Crilly Director, Crystal Blue Consulting Ltd, UK

Dr Eugenia Cronin Senior Scientific Advisor, Wessex Institute, UK

Dr Peter Davidson Consultant Advisor, Wessex Institute, University of Southampton, UK

Ms Tara Lamont Director, NIHR Dissemination Centre, UK

Dr Catriona McDaid Senior Research Fellow, York Trials Unit, Department of Health Sciences, University of York, UK

Professor William McGuire Professor of Child Health, Hull York Medical School, University of York, UK

Professor Geoffrey Meads Professor of Wellbeing Research, University of Winchester, UK

Professor John Norrie Chair in Medical Statistics, University of Edinburgh, UK

Professor James Raftery Professor of Health Technology Assessment, Wessex Institute, Faculty of Medicine, University of Southampton, UK

Dr Rob Riemsma Reviews Manager, Kleijnen Systematic Reviews Ltd, UK

Professor Helen Roberts Professor of Child Health Research, UCL Great Ormond Street Institute of Child Health, UK

Professor Jonathan Ross Professor of Sexual Health and HIV, University Hospital Birmingham, UK

Professor Helen Snooks Professor of Health Services Research, Institute of Life Science, College of Medicine, Swansea University, UK

Professor Ken Stein Professor of Public Health, University of Exeter Medical School, UK

Professor Jim Thornton Professor of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, University of Nottingham, UK

Professor Martin Underwood Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, UK

Please visit the website for a list of editors: www.journalslibrary.nihr.ac.uk/about/editors

Editorial contact: journals.library@nihr.ac.uk