



The third intensive care bundle with blood pressure reduction in acute cerebral haemorrhage trial (INTERACT3): an interactional, stepped wedge, cluster randomized controlled trial

Samuel Wilson¹ · Dar Dowlatshahi² · Jeffrey J. Perry¹

Received: 10 November 2023 / Accepted: 20 December 2023 / Published online: 1 February 2024

© The Author(s), under exclusive licence to Canadian Association of Emergency Physicians (CAEP)/ Association Canadienne de Médecine d'Urgence (ACMU) 2024

Keywords Emergency medicine · Cerebral haemorrhage · Care bundle · Journal club

Mots clés Médecine d'urgence · Hémorragie cérébrale · Trousse de soins · Journal Club

Full Citation: Ma et al. The third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT3): an international, stepped wedge cluster randomized controlled trial. *The Lancet* 2023 May 24

Abstract Link: [https://doi.org/10.1016/S0140-6736\(23\)00806-1](https://doi.org/10.1016/S0140-6736(23)00806-1)

Article Type: Therapy

Ratings: *Methods*—4/5, *Usefulness*—3/5

hyperglycemia, pyrexia and anticoagulation improves outcomes for patients with ICH.

Methods

Design

Pragmatic, international, multicenter, blinded endpoint, stepped wedge cluster randomized controlled trial.

Setting

One hundred forty-four hospitals from nine low- or middle-income countries (Brazil, China, India, Mexico, Nigeria, Pakistan, Peru, Sri Lanka, Viet Nam) and one high-income country (Chile).

Subjects

Eligible sites either had no or inconsistent protocols for managing ICH. They needed to enrol consecutive adult (age > 17 years) patients presenting within 6 h after the onset of ICH and have a local champion for implementation.

Intervention

Stepped wedge implementation of a care bundle: early lowering of systolic blood pressure, glucose control, antipyresis < 37.5 and reversal of warfarin, to pre-determined targets within 1 h of treatment, to be maintained for 7 days. Hospital sites were randomly assigned into three sequences (with four time periods) with a balanced number of enrolments across sequences and periods.

Introduction

Background

Goal-directed care bundles improve outcomes for patients in ischaemic stroke; no bundles exist for acute intracerebral haemorrhage (ICH).

Objectives

Evaluate whether implementing a goal-directed care bundle incorporating early management of hypertension,

✉ Samuel Wilson
sawilson@toh.ca

¹ Department of Emergency Medicine, University of Ottawa, Ottawa, ON, Canada

² Department of Medicine, University of Ottawa, Ottawa, ON, Canada

Comparator

Usual care.

Outcomes

The primary outcome was functional recovery measured at 6 months using modified Rankin scale (mRS). Secondary outcomes were multiple dichotomous and continuous analyses of mRS, National Institutes of Health Stroke Score (NIHSS), health-related quality of life (EuroQoL Group 5-Dimension Self-Report), and one residence vs other, at various time points.

Results

In this study, 121 hospitals were included in a modified intention-to-treat analysis of 7036 patients, with primary outcome data available in 6255 (2892 assigned to bundle care and 3363 assigned to usual care). 4.3% of patients treated with the care bundle were in the emergency department. The likelihood of a poor functional outcome was lower in the care bundle group (common OR 0.86; 95% CI 0.76–0.97; $p=0.015$). The favourable shift in mRS in the care bundle group was generally consistent across a range of sensitivity analyses adjusting for countries and patient variables (Table 1). Patients in the care bundle group had fewer serious adverse events than those in the usual care group (16.0 vs 20.1%; $p=0.0098$).

Appraisal

Strengths

- Large sample size across ten countries
- First phase 3 multicenter randomized controlled trial to show a positive outcome for acute treatment of ICH
- Patient-centred outcomes

Limitations

- Only one of ten included countries were high-income countries, raising generalizability concerns to the Canadian context.
- ICU admission was 5% higher in the care bundle group, a notable bias as access to continuous observation has pre-established benefit in ICH.
- Only warfarin anticoagulation reversal included. Many patients from high-income countries will be on direct oral anticoagulant (DOAC).

Context

In 2013, the INTERACT2 study demonstrating that lowering elevated blood pressure in acute intracranial haemorrhage improves rates of death or major disability: the keystone of early treatment [1]. In 2021, after advent of care bundles for ischaemic stroke, a post hoc analysis of INTERACT2 was performed to confirm associations between elevated blood pressure, hyperglycemia, fever, and anticoagulant use, with spontaneous ICH [2, 3].

Stroke neurologist, Dr. Dar Dowlatshahi, feels the benefit shown in INTERACT3 is small, but important, as blood pressure control reduces bleeding without eliminating it, analogous to turning down a tap without shutting it off. He highlighted increasing need for bundled care in stroke care, as it has become increasingly obvious that whilst blood pressure control is necessary to reduce hematoma expansion, it may not be sufficient where other key factors such as coagulation status are not controlled. These results are in keeping with pre-existing Canadian best practise guidelines and the recommendation of the American Heart Association.

Bottom line

Hospitals should incorporate a goal-directed care bundle approach into the management of acute spontaneous ICH, including early management of blood pressure, fever, hyperglycemia, and early reversal of anticoagulation. This trial reinforces the role of the Canadian ED physician in early management until specialized stroke care is available.

Author contributions SW, DD, and JJP drafted the manuscript. All the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Data availability The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Declarations

Conflict of interest None.

References

1. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, Hata J. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. *N Engl J Med*. 2013;368(25):2355–65.
2. Middleton S, McElduff P, Ward J, Grimshaw JM, Dale S, D'Este C, Drury P, Griffiths R, Cheung NW, Quinn C, Evans M. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *The Lancet*. 2011;378(9804):1699–706.
3. Song L, Wang X, Ouyang M, Sun L, Chen X, Arima H, Sandset EC, Delcourt C, Wang J, Chen G, Robinson T. Associations of an abnormal physiological score with outcomes in acute intracerebral hemorrhage: INTERACT2 study. *Stroke*. 2021;52(2):722–5.