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Withdrawal of active treatment after intracerebral haemorrhage in the INTERACT2 study

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Abstract

Background: in the second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2), a minority of patients received withdrawal of active treatment (WAT). We wished to determine the characteristics of these patients, and the relation of this decision-making to subsequent management and final outcome.
Methods: the INTERACT2 cohort of acute intracerebral haemorrhage (ICH) patients had a decision of WAT within 7 days after hospital admission recorded. Multivariable logistic regression was used to identify the determinants of WAT and poor outcome at 90 days, defined by modified Rankin scale (mRS) scores 3–6.
Results: of 2,779 participants with available data, WAT occurred in 121 (4%) and this was significantly associated with increasing age, greater neurological severity, larger haematoma volume, intraventricular extension and randomisation to intensive BP lowering. Compared to other patients, those with WAT had greater mortality (81/121 [67%] versus 205/2624 [8%]; $P < 0.001$) and survivors were more likely to be severely disabled (mRS score 4–5, 19/39 [49%] versus 695/2419 [29%]; $P = 0.006$).
Conclusions: WAT was undertaken in patients with recognised predictors of poor prognosis, who subsequently were more likely to die or be left with severe disability. Improved understanding of specific factors determining WAT in ICH patients might improve care delivery and outcomes.
Clinical Trial Registration: the INTERACT2 study is registered with ClinicalTrials.gov (NCT00716079).

Keywords: *Intracerebral haemorrhage, withdrawal of care, withdrawal of treatment, outcome, prognosis, older people*

Introduction

In the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) [1], patients with spontaneous intracerebral haemorrhage (ICH) were randomised to early intensive blood pressure (BP) lowering or guideline-recommended BP treatment. In this study, a

higher proportion of patients randomised to early intensive BP lowering had withdrawal of active treatment (WAT) documented within several days after hospital admission, as compared to those who received guideline-recommended BP treatment. This was the only aspect of clinical management that differed significantly between the randomised groups, the reasons are unclear but it may reflect between-group differences in the degree of BP lowering treatment offered to 'poor prognosis' patients. Although WAT occurred in only a minority of INTERACT2 participants, studies have identified premature decisions over withdrawal of care are an independent predictor of poor outcome after ICH [2–4]. Thus, we wished to define the clinical characteristics of the patients who received WAT, and determine the influence of this factor on management and subsequent outcomes.

Methods

Participants and design

INTERACT2 was an international, multicentre, open, blinded-endpoint assessed, randomised controlled trial, the details of which are outlined elsewhere [1, 5]. Briefly, 2,839 acute spontaneous ICH patients with elevated systolic BP were included from 144 hospitals in 21 countries in a randomised evaluation of intensive versus guideline-based BP management. Any WAT decision in the first 7 days after hospital admission was recorded, without the exact time or reason of implementation. Baseline demographic, clinical characteristics and management procedures were recorded in all participants. An assessor blind to acute treatment evaluated functional outcomes at 90 days post-randomisation. All participating centres' ethics committees approved the study and informed consent was obtained from all patients or relevant surrogates.

Data analysis

Chi-squared, Wilcoxon rank-sum or *t*-tests were used as appropriate. A multivariate model adjusted for demographic, medical history, admission clinical and imaging features, and 7-day treatments, was created to identify determinants of WAT and mortality; model variables consistent with those reported in previous INTERACT2 analyses [1], but briefly include patient demographics (Model 1), stroke severity factors (Model 2) and management factors (Model 3). Data are presented with odds ratios (OR) and 95% confidence intervals (CIs). A standard two-sided P value < 0.05 was considered significant. SAS version 9.3 (SAS institute, Cary, NC, USA) was used.

Results

Of 2,779 patients with available data, WAT was decided in 121 (4%). Table 1 indicates these patients received less intravenous mannitol, but more intensive BP lowering, intubation, surgical intervention and haemostatic therapy. Chile had the highest rate of WAT (8/29, 28%), followed by Italy (6/47, 13%), the UK (8/69, 12%) and Australia (7/71, 10%) (see Appendix 1, Supplementary data, available at *Age and Ageing* online). Multivariate regression analysis shows that WAT was independently associated with increasing age (OR 1.05, 95% CI 1.03–1.07), high admission National Institute of Health Stroke Scale (NIHSS) score (OR 2.32, 95% CI 1.44–3.72), greater haematoma volume (OR 1.02, 95% CI 1.01–1.03), intraventricular extension (OR 2.05, 95% CI 1.32–3.19) and randomisation to intensive BP lowering (OR 2.20, 95% CI 1.39–3.48) (Table 1).

With respect to prognosis, 81/121 (67%) of WAT patients died within 90 days, as compared to 205/2624 (8%) of non-WAT patients ($P < 0.001$); WAT being independently associated with 90-day mortality in adjusted multivariate regression (OR 16.54, 95% CI 9.69–28.25) (Table 2). WAT patients died earlier (median 4 [IQR 2–7] versus 12 [IQR 6–28] days; $P < 0.001$) and had shorter lengths of hospital stay (median 4 [IQR 2–8] days versus 21 [IQR 13–35] days; $P < 0.001$) than non-WAT patients. Following hospital discharge, there were no between-group differences in mortality (21/81 [18%] versus 38/205 [19%], respectively).

Thirty-nine WAT patients survived to 90 days (see Appendix 2, Supplementary data, available at *Age and Ageing* online); they were more likely to have severe disability, defined by modified Rankin scale (mRS) score 4–5 (19/39 [49%] versus 695/2419 [29%], respectively; $P = 0.006$). No significant differences were found in the characteristics of WAT patients who survived with mRS 4–5 compared to 0–3, or in the treatments they received during the first 7 days.

Discussion

In this *post hoc* analysis of the INTERACT2 study, a WAT decision in ICH patients resulted in increased likelihood of poor outcome, with WAT being associated with increasing age, worse initial NIHSS score, greater baseline haematoma volume and the presence of intraventricular haemorrhage, in keeping with previous studies [2, 6]. Nonetheless, patients with these poor prognostic factors received more in-hospital interventions, including surgery, intubation and intensive BP lowering. It is likely, therefore, that the decision to WAT was a consequence of failure to improve clinically and of death being considered inevitable [7].

Ageing is a recognised independent predictor of poor outcome in ICH patients and has been associated with withdrawal of care in patients with subarachnoid haemorrhage [8], although scarce research has been conducted on limiting care or medications and its impact in frail older adults or patients approaching end of life [9].

Not surprisingly, WAT was an independent predictor of death [10]; with such a 'self-fulfilling prophecy' occurring within days [3, 10] and without an association with out-of-hospital death. Importantly, one-third of INTERACT2 participants with a WAT decision were alive at the end of follow-up, which is higher than reported previously [3] and may reflect the trial cohort having less severe disease and fewer comorbid conditions. Most WAT survivors were Chinese (71.8%), which may represent cultural differences

Table 1. Patients characteristics by WAT—multivariate regression

Characteristics	Withdrawal of treatment				
	No (n = 2658)	Yes (n = 121)	P value	aOR (95% CI)	P value
Demographic					
Age years	63.2 (12.7)	70.9 (14.4)	<0.0001	1.05 (1.03–1.07)	<0.0001
Female	989 (37.2)	50 (41.3)	0.360	1.44 (0.93–2.25)	0.106
Chinese ethnicity	1822 (68.6)	63 (52.1)	0.0001	0.90 (0.54–1.49)	0.677
Medical history					
Acute coronary and other cardiac disease	271 (10.2)	25 (20.7)	0.0003	1.44 (0.81–2.55)	0.214
Diabetes mellitus	289 (10.9)	11 (9.2)	0.555		
Prior ICH	211 (7.9)	11 (9.2)	0.628		
Admission glycemia >6.5 mmol/L	1197 (47.9)	65 (60.8)	0.009	1.14 (0.73–1.78)	0.573
Medications					
Antihypertensive therapy	1196 (45.0)	62 (51.7)	0.152		
Oral anticoagulant or antiplatelet therapy	300 (11.3)	28 (23.1)	<0.0001	0.97 (0.49–1.92)	0.932
Lipid lowering therapy	180 (6.8)	18 (15.0)	0.0006	1.40 (0.68–2.87)	0.359
Clinical features					
NIHSS score ≥15	706 (26.6)	71 (58.7)	<0.0001	2.32 (1.44–3.72)	0.0005
GCS <13	638 (24.0)	56 (46.3)	<0.0001		
CT findings					
Haematoma volume at baseline mL	10.6 (5.6–18.7)	16.8 (7.9–42.4)	<0.0001	1.02 (1.01–1.03)	0.0001
Infratentorial ICH (brain stem and cerebellum)	161 (6.1)	6 (5.0)	0.619		
Intraventricular extension	660 (26.9)	58 (51.8)	<0.0001	2.05 (1.32–3.19)	0.0015
Treatment (*during first 7 days*)					
Randomised to intensive BP lowering	1304 (49.1)	75 (62.0)	0.005	2.20 (1.39–3.48)	0.001
Intubation	168 (6.3)	21 (17.4)	<0.0001	1.75 (0.90–3.38)	0.098
Admission to an ICU	1016 (38.2)	45 (37.2)	0.819		
IV mannitol	1657 (62.3)	62 (51.2)	0.014		
Any surgical intervention	141 (5.3)	13 (10.7)	0.011	1.39 (0.65–2.96)	0.398
DVT prophylaxis	584 (22.0)	26 (21.5)	0.900		
Haemostatic therapy	86 (3.2)	11 (9.1)	0.0006	1.30 (0.56–3.02)	0.539

Data are n (%), mean (SD) or median (IQR). CT, computerised tomography; GCS, Glasgow coma scale; ICU, intensive care unit; DVT, deep venous thrombosis; aOR, adjusted odds ratio. Multivariate analysis model includes all significant baseline characteristics and management factors during first 7 days.

Table 2. Unadjusted and adjusted multivariate models of early WAT and risk of mortality

	90 days mortality Unadjusted OR (95% CI)	90 days mortality Adjusted Model 1 OR (95% CI)	90 days mortality Adjusted Model 2 OR (95% CI)	90 days mortality Adjusted Model 3 OR (95% CI)
WAT	24.72 (16.44–37.16)	21.45 (13.96–32.94)	15.70 (9.32–26.45)	16.54 (9.69–28.25)
Age		1.05 (1.04–1.06)	1.05 (1.04–1.07)	1.05 (1.04–1.07)
Gender		0.77 (0.58–1.03)	0.68 (0.49–0.94)	0.69 (0.49–0.96)
Ethnicity		1.01 (0.74–1.38)	1.07 (0.75–1.52)	1.18 (0.72–1.96)
GCS			0.85 (0.80–0.90)	0.86 (0.81–0.92)
ICH volume			1.03 (1.02–1.04)	1.03 (1.02–1.04)
Infratentorial haemorrhage			0.94 (0.46–1.91)	0.84 (0.41–1.74)
IVH			1.39 (1.01–1.92)	1.36 (0.98–1.88)
Admission glycemia >6.5			1.35 (0.98–1.86)	1.35 (0.98–1.88)
Intensive BP lowering				0.87 (0.64–1.19)
ICU				1.52 (1.09–2.11)
Mannitol				1.10 (0.71–1.72)
Any surgery				1.19 (0.68–2.10)
Haemostatic therapy				0.86 (0.54–1.37)
DVT prophylaxis				2.71 (1.47–4.99)

Referent category for male was female. Referent category for Non-Caucasian/European was Caucasian/European. For continuous variables, OR presented is per unit increase. CT, computerised tomography; GCS, Glasgow coma scale; ICU, intensive care unit; DVT, deep venous thrombosis. Adjusted 1: age, gender, ethnicity. Adjusted 2: Model 1 plus initial GCS (modelled continuously), ICH volume (modelled continuously), IVH, infratentorial haemorrhage, admission glycemia >6.5. Adjusted 3: Model 2 plus intensive BP lowering, ICU, mannitol, any surgery, haemostatic therapy, DVT prophylaxis.

concerning how WAT decisions are applied and/or how patients are treated. Yet, these survivors remain severely disabled (50% with mRS scores 4–5), suggesting further study is required to better understand the quality of life of these patients and whether an earlier WAT decision could have influenced this outcome.

Strengths and limitations

Whilst this was a study of WAT in a wide range of ICH patients from a variety of healthcare settings and cultures, we acknowledge an important limitation of selection, treatment and reporting bias in an open clinical trial cohort that excluded patients with poor prognosis. In addition, we acknowledge the small sample size of the WAT cohort, and the lack of information on reasoning and timing of the WAT decision, and its operationalisation. Therefore, generalisation to an unselected clinical population should be treated by caution, and ideally requires confirmation in a larger patient cohort. Furthermore, cultural interpretation of WAT is likely to vary and differ from that related to withdrawal of care.

Implications and conclusions

A WAT decision in ICH patients with known poor prognostic predictors at admission was associated with higher mortality and increased rates of severely disabled survivors, despite being in receipt of more intensive early in-hospital management. Future studies are required to improve our understanding of outcome predictors in ICH patients, and their application to everyday clinical practice to reduce the burden of disability, and associated health and social care costs.

Key points

- Acute ICH is associated with significant risk of death and disability, and often associated with premature decisions to withdraw care.
- In the INTERACT trial of intensive versus guideline BP lowering in acute ICH, a WAT decision was associated with increasing age and markers of stroke severity.
- Patients in whom active treatment was withdrawn were more likely to die or survive with significant disability.

Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Conflicts of interest

C.S.A. has received travel reimbursement and honorarium from Takeda China; D.B.Z., funding from the National Institutes of Health (R01NS091112, K23AG038731); J.C., research grants from Servier, through University of Sydney, and honoraria and travel support; and T.R., consultancy payments from Bayer, Boehringer Ingelheim, Daiichi Sankyo, and his institution has received grant funding from the National Institute of Health Research, British Heart Foundation, Stroke Association, and the Engineering and Physical Sciences Research Council. Other authors declare no conflict of interest.

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