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Original Article

Randomized trial to assess safety and clinical efficacy of intensive blood pressure reduction in acute spontaneous intracerebral haemorrhage

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ABSTRACT

Background: Haematoma expansion due to raised blood pressure in spontaneous intracerebral haemorrhage may determine outcome. The aim of this study was to determine safety and efficacy of lowering blood pressure in acute spontaneous intracerebral haemorrhage. **Methods:** This open label, multicentric trial randomized patients ≥ 18 years with spontaneous intracerebral haemorrhage with no secondary cause within 72 h of onset to tight BP control arm where treatment was initiated if mean arterial pressure (MAP) was ≥ 115 mm of Hg and conventional BP control arm where treatment was initiated if MAP was ≥ 130 mm of Hg. The MAP was maintained in the respective arm for another 72 h after which both arms had MAP below 115 mm of Hg. Primary outcome was modified Rankin Scale at 90 days. **Results:** 118 patients, 59 in each arm were included. Follow up was available for all. Baseline characteristics were similar. At 90 days there was no significant difference between median mRS between the two arms. Odds Ratio for “poor outcome” (mRS 3–6) in the tight control arm (safety of the intervention) against “good outcome” (mRS 0–2) was not significant (OR 0.70 [95% CI 0.34–1.47] $p = 0.35$). Efficacy of the intervention in the form of Odds Ratio for “good outcome” in the tight control arm was not significant (OR 1.43 [95% CI 0.68–2.99], $p = 0.35$).

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Conclusion: In patients with spontaneous intracerebral haemorrhage who present within 72 h of the onset of symptoms, MAP can be safely lowered if it crosses 115 mm of Hg but it does not improve clinical outcome.

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Introduction

Stroke is one of the leading causes of morbidity and mortality all over the world.¹ It can cause a loss of 43.7 million DALYs (disability-adjusted life years) every year.² Of all the subtypes of stroke, spontaneous intracerebral haemorrhage is the most dramatic, and though it is responsible for only 15–20% of all cases of stroke, it accounts for a disproportionately high mortality and morbidity.^{3,4} Thirty-day case fatality rates in most studies range from 25% to 50%.^{5,6} Expansion of haematoma occurs in about 30–40% of patients and is one of the most important determinants of mortality and morbidity.⁷ Raised blood pressure during the acute phase has been found to be a risk factor of haematoma expansion.⁸ Currently there is no approved treatment of proven benefit in decreasing morbidity and mortality after intracerebral haemorrhage (ICH). In the absence of any definite treatment modality, various pharmacological and non-pharmacological treatment strategies have been tried in ICH, with variable success. Rapid control of blood pressure with the aim of preventing haematoma expansion is one such strategy.⁹ However, control of raised blood pressure in the early phase of ICH may be a double edged situation with poor control contributing to haematoma expansion and excessively aggressive control leading to poor perfusion of the surrounding brain parenchyma with resultant worsening of pre-existent deficits. Guidelines for managing raised blood pressure in ICH at the time of conception and execution of this study recommended that treatment should be initiated only if the mean arterial pressure (MAP) crosses 130 mmHg.¹⁰ This aim of study was to study the efficacy and safety of intensive blood pressure lowering strategy as compared to conventional management of blood pressure during the first 72 h in patient with spontaneous ICH.

Materials and methods

This study was an open label, 1:1, intention to treat, randomized controlled trial, not blinded during assessment and conducted at three tertiary care centres of Armed Forces Medical Services in India from June 2012 to August 2014 with one of them being the coordinating centre. Patients were included in the study if they were more than 18 years of age, had spontaneous intracerebral haemorrhage as confirmed by a non-contrast computerized tomography (NCCT) of the brain and who presented within 72 h of onset of symptoms. Exclusion criteria included patients who had Glasgow Coma

Scale (GCS) 3 at admission, proof or suspicion at admission (or later after randomization) that the cause of ICH was either trauma, aneurysm, arterio-venous malformations, cavernous angioma, dural arteriovenous fistula, capillary telingectasia, coagulopathy, amyloid angiopathy, vasculitis, drug induced, neoplasm, cerebral venous thrombosis, haemorrhage into an infarct or any other cause. To calculate sample size, hospital admission records for the previous two years at all three institutes were screened for the diagnosis of spontaneous intracerebral haemorrhage. There were 200 patients identified. An online sample size calculator was used to obtain a sample size of 126 keeping the type I (α) error at 0.05, type II (β) error at 0.2, mean difference in mRS between the two group as at least 0.5 with SD of 1. Patients were randomized within an hour of admission to either of the two treatment arms consisting of a “conventional arm” where the patient was treated if the MAP was ≥ 130 mm Hg and “a tight control of BP arm” where the treatment was initiated if the MAP was ≥ 115 mm Hg. Randomization was done centrally for all three centres by the first author from the coordinating centre using computer generated block randomization model. Block size of 4 was chosen. All patients were admitted to the intensive care unit (ICU) initially where MAP was measured using a standard multi parameter monitor with non-invasive blood pressure (NIBP) measurement facilities. Along with the systolic and diastolic BP, MAP was also displayed on the screen of the monitor. Although the monitors were from different manufacturers in the three centres the parameters measured were same. All patients underwent a CT scan at admission to document the location and size of bleed, to check for any signs of raised ICP, and to look for presence of intraventricular extension. Haemogram, serum biochemistry, coagulation profile, chest radiography, ultrasonography of the abdomen, and ECG was done for all patients.

Over the next 72 h after randomization MAP was measured every 30 min. Depending on the arm to which the patients were randomized, blood pressure lowering medications were initiated if needed. The choice of blood pressure lowering medication was left to the discretion of the treating neurologist. The treating clinicians could start parenteral, oral or oral along with parenteral anti-hypertensive drugs. The drugs could include any of the standard drugs used to treat hypertension like calcium channel blockers, β blockers, ACE inhibitors, angiotensin II receptor blockers, α blockers, and centrally acting $\alpha 2$ agonists. The aim was to maintain MAP below the limits for that arm. Clinicians were permitted to initiate other standard therapy for patients if indicated. These included therapies for raised intracranial pressure, seizures, infections, prophylaxis for ulcer and deep venous thrombosis.

After 72 h, all patients included in the study were treated if needed to bring their MAP below 115 mm of Hg by appropriate drugs. All patients were followed up at 90 days after randomization, either by OPD visits or telephonically, and outcome was assessed using modified Rankin Scale (0 = no symptoms; 1 = mild symptoms but no disability, able to carry out all usual activities; 2 = mild disability, but able to look after self without assistance; 3 = moderate disability, able to walk without help but requires some assistance for daily needs; 4 = moderately severe disability; unable to walk without help, requires assistance for own bodily needs; 5 = severe disability; bedridden, requiring constant nursing care, incontinent; 6 = dead). This assessment was done by a neurologist who was not blinded to the treatment given.

Informed written consent was taken from patient or next-of-kin in case patient was not in a state to give consent. The study protocol was approved by the institutional ethics committee. Funds for the research project (4131/2011) were obtained through Armed Forces Medical Research Committee. Data extraction pro forma was filled for all patients and analysis was done using SPSS software version 20. For baseline comparison of patients, chi-square (χ^2) test was used for categorical variables, which included ICH score, GCS, and presence of midline shift, and intraventricular extension of haemorrhage. Continuous variables were compared using the Student t test, and included age, MAP at admission, and volume of bleed. Student t test was also used to compare MAP

after 72 h between the two groups. Outcome at 90 days was compared using the χ^2 test.

Results

A total of 163 patients were screened in the two year period, out of which 118 were included in the study with 59 patients being randomized in each arm. Details are shown in the Consort diagram (Fig. 1). No patient required to be excluded after randomization. Baseline characteristics were comparable between the two groups with no statistical difference (Table 1). Follow up was 100% with no cases being lost to follow up. MAP was maintained at <130 mm Hg for conventional BP control group, and below 115 mm Hg for tight control group for 72 h. At the end of 72 h, MAP was significantly different in both the arms suggesting that the blood pressure lowering strategy was successful in the tight control arm in all three centres (Table 2). Primary outcome of difference in modified Rankin scale at 90 days between two groups is shown in Table 3. There was no significant difference in median mRS. We also compared the number of patients with good outcome (mRS 0–2), poor outcome (mRS 3–5) and death between the two groups and found no statistically significant difference (Table 4). There was no statistical difference in odds of poor outcome (mRS 3–5) in the intervention arm as compared to convention arm (OR 0.70 [95% CI 0.34–1.47] $p = 0.35$).

Fig. 1 – Consort diagram.

Table 1 – Baseline characteristics.

Variable	Conventional BP control group (n = 59)	Tight BP control group (n = 59)	p value
Mean age (years $\pm$ SD)	62.8 ($\pm$ 8.9)	65.1 ($\pm$ 9.2)	0.41
Sex (no of males)	46	39	0.15
Mean duration of symptoms before randomization (h $\pm$ SD)	11.1 ($\pm$ 13.6)	11.1 ($\pm$ 14.1)	0.49
Mean MAP at randomization (mmHg $\pm$ SD)	133.7 ($\pm$ 12.9)	131.5 ($\pm$ 11.2)	0.49
Mean systolic BP at randomization (mmHg $\pm$ SD)	178.5 ($\pm$ 23.9)	175.1 ($\pm$ 17.4)	0.51
Mean diastolic BP at randomization (mmHg $\pm$ SD)	111.7 ($\pm$ 11.9)	109.8 ($\pm$ 9.8)	0.48
Mean volume of bleed (ml $\pm$ SD)	41.3 ($\pm$ 19.2)	47.3 ($\pm$ 20.0)	0.29
ICH score at admission (median)	2	2	0.93
GCS at admission (median)	11	11	0.13
No of patients with IVH (%)	24 (40.7)	23 (38.9)	0.85
No of patients with midline shift (%)	38 (64.4)	37 (62.7)	0.85

Table 2 – Comparison of MAP after 72 h in the two groups.

	Conventional BP control group	Tight BP control group	p value
MAP after 72 h (mm of Hg $\pm$ SD)	120.2 ($\pm$ 11.2)	110.1 ($\pm$ 6.9)	0.03

Table 3 – Comparison of median mRS between the two groups at 90 days.

	Conventional BP control group	Tight BP control group	p value
Median mRS (IQR) ^a	3 (1–6)	3 (1–6)	0.69

^a IQR = interquartile range.

Table 4 – Comparison of outcome at 90 days based on mRS sub groups.

mRS sub group	No of patients (%)		p value (Chi-square test)
	Conventional BP control (n = 59)	Tight BP control (n = 59)	
Good outcome (0–2)	21 (35.6)	26 (44.1)	0.61
Poor outcome (3–5)	24 (40.7)	22 (37.3)	
Death (6)	14 (23.7)	11 (18.6)	

Discussion

At the time of conception and subsequent execution of our study AHA/ASA guidelines of 2010 suggested lowering of blood pressure only if the MAP crossed 130 mm of Hg.¹⁰ This was due to the fear that if blood pressure is lowered below a poorly defined critical level it may precipitate ischemia around the haematoma due to the disturbed auto regulation. However, a more solid body of evidence suggested that haematoma growth is linked to raised blood pressure and its rapid control may be beneficial.^{8,9} We designed our study with the aim of finding out the safety and efficacy of lowering the blood pressure below that mentioned in guidelines. Our study has demonstrated that in patients with acute spontaneous intracerebral haemorrhage who present within 72 h of the onset of symptoms, blood pressure can be safely lowered if the MAP crosses 115 mm of Hg. The outcome at 90 days in the form of mRS in this group of patients is no different when compared to a control group of patients whose BP is lowered only if MAP crosses 130 mm of Hg, the conventional level mentioned in

standard guidelines at the time of conception and execution of this study.¹⁰

Our findings are similar to four other previous trials with clinical primary outcomes (Table 5). These trials have shown that blood pressure reduction in acute intracerebral haemorrhage is safe. However, this does not translate into clinical benefit in the form of an improved mRS. The only trial which showed marginal benefit in subgroup analysis of data of mRS was INTERACT 2.¹³ The ordinal analysis of mRS for functional outcome showed marginal although significantly lower modified Rankin scores with intensive treatment (odds ratio for greater disability, 0.87; 95% CI, 0.77 to 1.00; $p = 0.04$). This was probably due to the large numbers in the trial. Two meta-analysis have been conducted. The first one by Ma et al. showed that the pooled OR of mortality and unfavourable outcome after ICH in intensive blood pressure control group when compared with less intensive blood pressure targets group was 0.99 (95% CI 0.81–1.23) and 0.90 (95% CI 0.78–1.03) respectively. The pooled OR was 0.97 (95% CI 0.80–1.18) for neurological deterioration and 0.83 (95% CI 0.61–1.11) for haematoma expansion. There was no difference in other

Table 5 – Similar trials with primarily clinical outcome (as ours).

Trial	ATACH ¹¹	SAMURAI ¹²	INTERACT2 ¹³	ATACH2 ¹⁴
Year of publication	2010	2012	2013	2016
Design of study	RCT	Observational with no control group	RCT	RCT
No of patients	60	211	2839	1000
Target BP	Sequential systolic BP reduction	Systolic BP 120–160 mm of Hg	Systolic BP < 140 mm of Hg	Systolic BP 110–139 mm of Hg
Primary Outcome	Haematoma growth, perihematoma oedema increase and 3 month poor mRS (4–6)	GCS fall ≤ than 2 points or NIHSS increase ≥ 4 points in 24 h	90 day mRS	Death or disability
Conclusion	No significant relationship between systolic BP reduction and primary outcome but no adverse effect either.	Using nicardipine systolic BP could be lowered to ≤160 mmHg, this was well tolerated	Systolic BP could be safely lowered to ≤140 mm of Hg but this did not significantly reduce death or severe disability. However, an ordinal analysis of mRS showed improved functional outcome	Systolic BP could be safely lowered without increase in disability or death but no improvement in clinical outcome

adverse events between two groups.¹⁵ The second meta-analysis by Pan et al. also showed similar results.¹⁶ They included 1427 patients with the primary outcome being serious adverse events. Odds ratios (ORs) of primary outcome was 0.96 (95% confidence interval [CI]: 0.82–1.13, $p = 0.61$). They concluded that aggressive blood pressure reduction was safe. Based on these trials the AHA/ASA revised their guidelines in 2015 and now recommends that ICH patients presenting with systolic BP between 150 and 220 mm Hg can have their systolic BP lowered to 140 mm Hg, this is safe and can be effective for improving functional outcome.¹⁷ However, the more recent ATACH2 was terminated prematurely due to lack of clinical benefit.¹⁴ The trial concluded that patients with ICH were treated to reduce their blood pressure to systolic of 110–140 mm of Hg but it did not result in a lower rate of death or disability when compared to reduction of systolic blood pressure to 140–179 mm of Hg.

Although our findings of safety of reduction and lack of efficacy are similar to other trials there are small differences in methodology which contribute to its strength. Firstly, we chose MAP as a marker of blood pressure because it is a product of both systolic and diastolic blood pressure. Secondly, to make it more pragmatic and wider applicability of results we included patients up to 72 h of onset of symptoms as it is only a small percentage of patients in our country who can reach a medical set up for diagnosis of ICH by a CT scan in the first few hours. We are however aware that blood pressure reduction undertaken to reduce haematoma expansion is likely to be most effective in the first few hours as that is the period when haematoma expansion occurs. This was the basis of treating early in the INTERACT 2 and ATACH2 trials.^{13,14} Lastly, we left it to the discretion of the treating clinician to lower the blood pressure either by oral or parenteral methods, the target being more important rather than the means to achieve it.

The main limitations of our study are that it was open label and not blinded in assessment. We also fell short of the sample size due to time limitations. A study with larger sample size in future may demonstrate efficacy.

In conclusion, our open label, open assessment, randomized control trial has demonstrated that in patients with spontaneous acute intracerebral haemorrhage who present within 72 h of onset of symptoms the MAP can be lowered to less than 115 mm of Hg without increasing the odds of a poor clinical outcome at 90 days. This has wide spread practice implications for clinicians managing this common but devastating emergency.

Conflicts of interest

The authors have none to declare.

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