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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.

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 α 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.

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