INTERACT 3: Review of the Evidence for Intracerebral Hemorrhage (ICH) Treatment

The Third Intensive Care Bundle with Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT 3) trial was recently published in *Lancet*[1] showing significant improvement in 6-month outcomes for ICH patients that received an intracerebral hemorrhage (ICH) "care bundle" intervention consisting of blood pressure (BP) reduction, serum glucose control, fever control, and reversal of warfarin-related coagulopathy. INTERACT 3 used a stepped-wedge cluster randomized trial design. This design randomizes the timing of when different "clusters" or groups of hospitals will join the study. All clusters initially start out in the control arm of the study, with no change in how ICH patients have traditionally been managed at the hospital; during this time, investigators collect data on patient management processes, patient characteristics, and the study outcomes in the sample of enrolled patients receiving "usual care." By randomly selecting when clusters will start in the control phase in small sequences or groups, investigators may ensure proper trial conduct in a small number of participating sites before initiating additional sites that will also require study oversight. At a pre-determined timepoint, control sites then cross-over to begin using the intervention, in this case the ICH management bundle. The cross-over period to the intervention arm is similarly staggered to allow for oversight of smaller numbers of sites in each sequence. Ultimately, stepped-wedge cluster randomized trials allow an investigator to explore differences caused by an intervention in what are expected to be rather similar groups of patients enrolled before and after start of an intervention.

The INTERACT 3 study recruited hospitals from nine low-income and middle-income countries (Brazil, China, India, Mexico, Nigeria, Pakistan, Peru, Sri Lanka, and Vietnam), as well as one high-income country (Chile). To be eligible to participate, hospitals had to lack consistent relevant, disease-specific protocols for ICH patient management; additionally, participating sites had to agree to implement the ICH bundle to consecutive adult patients with computed tomography confirmed spontaneous ICH that presented within 6 hours of symptom onset. A total of 122 sites began enrolling in the study, however, 1 site was withdrawn from the study and all their patient data was eliminated due to failure to complete institutional review board/ethics approval processes (final number of sites: 121). Overall, 7036 patients were enrolled: 3221 ICH care bundle group and 3815 control/usual care group. Of these, data allowing for measurement of the primary outcome were available in 90% of the ICH care bundle group and 88% of the control group due to investigators failing to capture the required data at the time of follow-up; this happens most commonly due to an inability to "find" the subject at follow-up, in this case 6-months after release from hospital.

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The INTERACT 3 ICH care bundle consisted of intensive lowering of systolic blood pressure (SBP; target <140 mm Hg), strict glucose control (target = 6.1–7.8 mmol/L [110-140.5 mg/dL] in those without diabetes and 7.8–10.0 mmol/L [140.5-180 mg/dL] in those with diabetes), fever management (target = body temperature ≤37.5°C), and rapid reversal of warfarin-related anticoagulation (target = international normalized ratio [INR] <1.5); treatment had to be initiated to manage these parameters within 1 hour.

Subjects enrolled in the trial were 90% Chinese, with a mean age of 62 ± 13 years, 64% were men, and the presumed cause of ICH was hypertension in 94%, with 82% of bleeds located in the deep subcortex. Median hemorrhage size was 15 (IQR 7.8-30) mL, and overall admission mean SBP was 174.5 ± 28.3 mm Hg. Only 36% of patients had elevated blood glucose, and of these the overall mean serum glucose concentration was 8 mmol/L (144 mg/dL). Only 1.7% had an elevated body temperature, and only 1.2% had INR >1.4 at presentation. Because of this, the intervention used in the clinical trial was primarily limited to SBP lowering to below 140 mm Hg.

The proportion of patients receiving antihypertensive treatment in the first 24 hours was higher in the care bundle group (78.9%) compared to the usual care group (70.9%), however after this time it did not differ between groups. Mean SBP was 148.4 ± 21.5 mm Hg by 1 hour after treatment in the care bundle group and 154.7 ± 22.5 mm Hg in the usual care group; note that this is a mean difference of only 6.3 mm Hg at 1 hour from start of treatment. At 24 hours, the care bundle group had a mean SBP of 136.1 ± 16.5 mm Hg, while the usual care group had a mean SBP of 139.0 ± 17.2 mm Hg; the overall adjusted mean difference between groups at 24 hour was only -3.6 mm Hg (95% CI: -4.5 to -2.7; p<0·0001). Not surprisingly, care bundle patients achieved SBP ≤ 140 mm Hg faster (median 2.3 [IQR 0.8-8] hours) than usual care patients (median 4 [IQR 1.9-16] hours). Mean diastolic BP (DBP) was 86.2 ± 13.8 mm Hg at 1 hour in the care bundle group compared to 88.3 ± 14.2 mm Hg in the usual care group; at 24 hours, the care bundle group had mean DBP of 78.9 ± 11.5 mm Hg, compared to 80.4 ± 12.1 mm Hg in the usual care group with an overall adjusted mean difference at 24 h of -2.4 mm Hg (95% CI: -3.0 to -1.8; p<0.0001). Given how small these differences are in both SBP and DBP between groups, statistical significance was driven primarily by the extremely large patient sample.

Of patients with elevated serum glucose, more care bundle patients achieved control than in the usual care group (13.4% *vs.* 6.5%), but there were minimal differences in both adjusted mean serum glucose concentrations over 24 hours and time to achievement of glycemic control. There was no overall adjusted mean difference in fever control over 24 hours between the two groups, nor were there differences in anticoagulation reversal between groups. Additionally, data in the study appendices for differences in hematoma volume are limited by "clinician report" of hematoma size without unbiased, external adjudication; these data exclude about 800 cases at 24 hours yet show a reduction in volume in both groups which is highly unusual without a large volume of patients undergoing surgical hematoma removal, and they contain multiple outliers with a skewed distribution. Therefore, it is difficult to determine whether the care bundle affected hematoma volume. Ultimately, at 6 months patients in the care bundle group had better scores on the modified Rankin Score (mRS) compared to usual care patients (odds ratio 0.86 (95% CI: 0.76–0.97; p=0.015).

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External validity, also called generalizability, refers to how *widely applicable* study methods are across different practice settings, with highly generalizable methods capable of producing outcomes across various types of patients and practice settings. As a first step in considering generalizability, readers are encouraged to consider how closely their practice sites resemble those that participated in the study, including the standard of care for ICH patients that was in place at the study's practice sites *prior to* initiating the ICH care bundle. In this case, INTERACT 3 is clearly generalizable to ICH under-resourced practice sites in low- to middle-income countries. Secondly, readers should consider how similar their patient populations are to those patients enrolled in the study, in this case 90% Chinese patients with admission SBP means of approximately 170 mm Hg and hematoma volumes approximating 15 mL.

Internal validity considers the credibility of conclusions tied to a causal relationship, in this case whether the ICH care bundle alone could have produced the difference in mRS 6-month functional outcome. Readers should evaluate how great the differences are between the two groups in each component of the care bundle and how these differences could theoretically cause a shift in functional status, in particular the small differences in SBP.

Could it be that when under-resourced sites in low- and middle-income countries start to pay closer attention to ICH patients by closely monitoring a variety of parameters, that this vigilance is so effective that it has an additive effect capable of increasing the "potency" of the ICH care bundle? It is difficult to measure what are often considered "soft" parameters such as nursing and medical attention, and the degree of stroke team vigilance in overseeing care, yet these changes may cause a potent shift in functional status. Certainly, it is essential that stroke scientists continue to search for potent ICH interventions, but for well-resourced practice sites that are staffed with interprofessional stroke specialists, it's likely that many aspects of INTERACT 3's ICH care bundle are already in place, along with vigilant oversight and in some cases more sophisticated treatments such as early hematoma evacuation and use of agent-specific antidotes for anticoagulation reversal in patients on direct oral anticoagulants. So, while INTERACT 3 may be a big step for low- to middle-income under-resourced sites, much more still needs to be discovered and implemented to reduce the significant disability caused by this most severe form of stroke.

References

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