Phase I Clinical Trial for Feasibility and Safety of Remote Ischemic Conditioning in Patients with Aneurysmal Subarachnoid Hemorrhage.

Mark Connolly; Joshua Robert Dusick MD; Paul M. Vespa MD, FCCM, FAAN; Nestor R. Gonzalez MD
University of California Los Angeles David Geffen School of Medicine

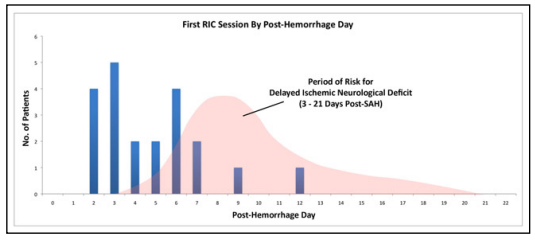
Introduction

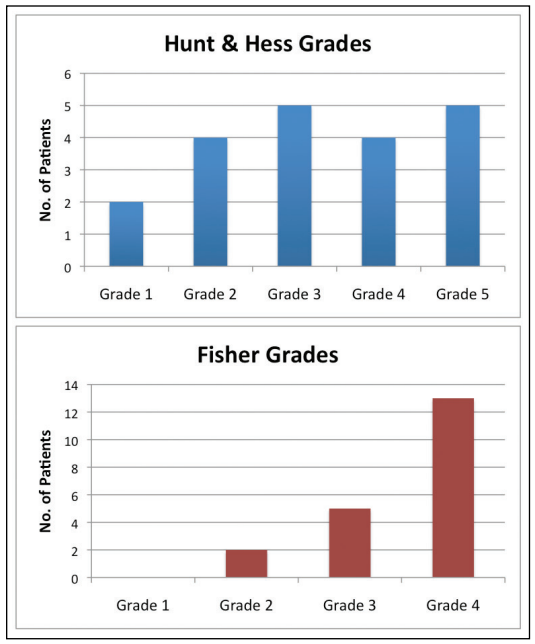
Remote ischemic conditioning (RIC) is a phenomenon by which brief periods of sublethal ischemia in one tissue confers protection from ischemic injury to distant tissues. Animal studies have demonstrated that ischemic conditioning is the most powerful neuroprotective strategy yet discovered. Application to human stroke has previously been limited by the fact that ischemia often occurs suddenly, without warning, and thus pre-conditioning can be logistically difficult or impossible to apply. However, in the setting of aneurysmal subarachnoid hemorrhage, delayed ischemic injury due to vasospasm often occurs several days *after* hemorrhage, providing a potential treatment window to initiate neuroprotection by RIC prior to the onset of ischemia. Furthermore, recent studies have shown that peri- or post-conditioning can also have profound protective effects against ischemic injury.

While early studies of RIC in humans have shown promising changes in terms of cerebral metabolic and hemodynamic effects, the safety and feasibility of RIC in humans must be assessed before applying it in larger efficacy trials in the treatment of stroke (1-4). We report a phase I trial of feasibility and safety of RIC in patients with aneurysmal subarachnoid hemorrhage (aSAH).

Methods

Individuals aged 18 to 80 who presented with acute aSAH, confirmed by CT, were eligible for enrollment following protection of the aneurysm. Exclusion criteria included intraparenchymal hematoma, past history of peripheral vascular, venous or nerve disease, or unprotected aneurysms. Subjects received 2-4 RIC sessions on non-consecutive days during their ICU hospitalization. A complete session was defined as 4 rounds of 5 minutes of lower limb ischemia followed by 5 minutes of reperfusion. If the patient had angiograms or femoral central venous catheters, the opposite leg was chosen for RIC. During treatment patients were closely monitored, including continuous ICP (if a ventriculostomy was in place), ECG, blood pressure and transcranial Doppler monitoring. An analog pain scale was used in conscious patients to assess tolerance of the procedure. Analgesic medications were offered to patients who experienced pain but wanted to continue the procedure. The leg used for RIC was closely monitored during the procedure (including pedal Doppler to confirm return of pulse following each inflation) and throughout their ICU hospitalization for any signs of complications, including ischemic injury and deep venous thrombosis. Primary end-points were tolerance to the procedure and any complication attributable to RIC. Sessions were considered to be not tolerated if the complete session could not be completed due to discomfort. Secondary end-points included cerebral infarction or hemorrhage.





Results

Twenty patients (70% female, mean age 52, Fisher 3.5, Hunt & Hess 3.3) were enrolled. Seventeen had evidence of vasospasm, detected by TCD and most confirmed by CTA or angiogram, during hospitalization. Of 76 RIC sessions performed, 75 were completed and tolerated. One session was incomplete due to poor cooperation secondary to delirium. No patients developed DVTs or other local complications related to the RIC procedure during their entire ICU hospitalization. No patients suffered cerebral infarction or hemorrhage throughout the duration of RIC sessions and through 72 hours after their last complete session. Three had infarctions, beyond 72 hous after the last RIC session, associated with ongoing vasospasm despite standard medical and endovascular treatment interventions.

Conclusions

In aSAH patients, RIC was successfully applied and well tolerated with no procedure-related complications. Moreover, no patient suffered ischemic stroke within 72 hours of a RIC session, consistent with our previous studies showing protective cerebral metabolic changes up to 48 hours after complete RIC sessions. These results suggest that application of RIC as a protective strategy is safe and feasible and may be associated with transient tolerance to ischemia during the treatment period. The efficacy of RIC as neuroprotection should be investigated in larger controlled trials.

References

1. Bilgin-Freiert A, et al. Muscle microdialysis to confirm sublethal ischemia in the induction of remote ischemic preconditioning. *Transl Stroke Res 3(2), 2012.*
2. Gonzalez NR, et al. Cerebral hemodynamic and metabolic effects of remote ischemic preconditioning in patients with subarachnoid hemorrhage. *Acta Neurocirugia Suppl* 115, 2013.
3. Koch S, Gonzalez N. Preconditioning the human brain: proving the principle in subarachnoid hemorrhage. *Stroke* 44(6), 2013.
4. Mayor F, et al. Effects of remote ischemic preconditioning on the coagulation profile of patients with aneurysmal subarachnoid hemorrhage: a case-control study. *Neurosurgery* (in press; 2013).