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Susanne Muehlschlegel

University of Massachusetts Medical School

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Dantrolene for the Prevention and Treatment of Cerebral Vasospasm After Subarachnoid Hemorrhage – a Randomized Placebo-Controlled Trial to assess Safety, Tolerability and Feasibility

Susanne Muehlschlegel, MD, MPH^{1,2,3}; Raphael Carandang, MD^{1,3}; Wiley Hall, MD^{1,3}; Nishi Kini, MPH⁴; Saef Izzy, MD¹; I. Martijn VanDerBom, PhD⁵; Thomas F. Flood, BA⁵; Matthew Gounis, PhD⁵; John Weaver, MD⁶; Bruce Barton, PhD⁴

Departments of ¹Neurology (Neurocritical Care), ²Anesthesia/Critical Care, ³Surgery, ⁴Quantitative Health Sciences, ⁵Radiology and ⁶Neurosurgery, University of Massachusetts Medical School, Worcester, MA

Contact information

Susanne Muehlschlegel, MD, MPH

Departments of Neurology (Neurocritical Care), Anesthesia/Critical Care and Surgery

University of Massachusetts Medical School

55 Lake Ave. North, S5, Worcester, MA 01655

Phone:(508) 856-4684; Fax:(508) 856-6778

Email:susanne.muehlschlegel@umassmemorial.org

Introduction:

Dantrolene is neuroprotective in animal models and may attenuate cerebral vasospasm (cVSP) after aneurysmal subarachnoid hemorrhage (aSAH) in humans. We evaluated safety/tolerability and feasibility of intravenous dantrolene (IV-D) after aSAH.

Methods:

In this single-center, randomized, double blind, placebo-controlled trial, 31 patients with acute aSAH were randomized to IV-D 1.25 mg IV every 6 hours x 7 days (n=16) or placebo (n=15). Primary endpoint was incidence of hyponatremia (sNa \leq 134 mmol/L) and liver toxicity (% patients with ALT, AST and AlkPhos $>$ 5x upper limit of normal). Secondary safety endpoints included tolerability, systemic hypotension and intracranial hypertension. Efficacy was explored by clinical, transcranial Doppler (TCD) or angiographic cVSP occurrence, delayed cerebral ischemia (DCI) and 3-month modified-Rankin-Scale, Glasgow Outcome Scale and Barthel Index. Statistical analysis was performed using non-parametric tests, generalized estimating equations and mixed models.

Results:

Between IV-D vs. placebo, no differences were observed in the primary outcome (hyponatremia: 44% vs. 67% [$p=0.29$]; liver toxicity 6% vs. 0% [$p=1.0$]). Numerically more AEs and SAEs were seen in the IV-D group, but did not reach statistical significance (16 vs. 5 AEs, of which 5 vs. 2 were severe; RR 2.2; 95% CI 0.7-6.7; $p=0.16$). Three IV-D vs. two placebo patients reached stop criteria: one IV-D patient developed liver toxicity; two patients in each group developed brain edema requiring osmotherapy. No differences in angiographic, TCD, clinical cVSP, DCI, or 3-month functional outcomes were seen. Quantitative angiogram analysis revealed a trend towards increased vessel diameters in the IV-D group after the 7-day infusion-period ($p=0.05$).

Conclusions:

In this small trial, IV-Dantrolene after aSAH was feasible, tolerable and safe, but was underpowered to show efficacy or outcome differences.

Clinical Trial Registration Information: <http://clinicaltrials.gov> NCT01024972

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