Letter to the Editor

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Letter by Chang et al Regarding Article, "Minocycline in Acute Cerebral Hemorrhage: An Early Phase Randomized Trial"

To the Editor:

We read with great interest the article, "Minocycline in Acute Cerebral Hemorrhage: An Early Phase Randomized Trial," by Fouda et al[1] published in *Stroke*. Although its efficacy in improving clinical outcome after ischemic stroke is unclear,[2,3] minocycline's safety profile in ischemic stroke is well established. However, until now, its safety profile and clinical efficacy in intracerebral hemorrhage (ICH) remained unclear.

The search for neuroprotectants in ICH that improve clinical outcome is particularly important in the current landscape because recent trials targeting hematoma expansion have failed to show clinical benefit. Minocycline has been shown to be an MMP-9 (matrix metalloproteinase-9) inhibitor. This allows for a potential mechanism where MMP-9 inhibition can result in preserved blood–brain barrier and decreased perihematomal edema in neurological pathology.

We think our recent randomized, placebo-controlled, double-blinded pilot trial, "Minocycline and Matrix Metalloproteinase Inhibition in Acute Intracerebral Hemorrhage: A Pilot Study,"[4] complements the findings of Fouda et al. Both studies showed convincingly that minocycline use in ICH could be safely delivered. However, several differences between the methodologies offer unique insights. First, dosage and route of entry (intravenous versus oral) was different. In the study by Fouda et al, a standard dose of intravenous 400 mg was given followed by an oral dose for 4 days, which the authors believed averaged out to ≈4 mg/kg. In contrast, we followed a previously described dose of 10 mg/kg given intravenously (maximum 700 mg per day) for 5 days. Our average dosing regimen was 7.7 mg/kg, showing that patients with ICH can tolerate an even larger dose intravenously.

Second, although both studies reported no significant change in MMP-9 levels, this may not represent a complete picture. We report several interesting trends that show that minocycline may actually reduce serum MMP-9 levels. When looking at our results, although absolute values evaluating MMP-9 levels at day 3 show no difference, a trend is noted at day 5 for MMP-9 levels (472 [±235] ng/mL for placebo versus 282 [±158] ng/mL; P=0.052). The analysis is complicated because of the lack of a standard physiological level of MMP-9 in human beings, uncertainty associated with predicted elevations in brain injury, and temporal uncertainty associated with physiological and pathological MMP-9 increases after neurological injury.[5] Therefore, analyzing MMP-9 level differences may actually be more reliable. When we looked at MMP-9 differences between our set time points (admission, day 3, and day 5), we found the most significant MMP-9 differences occurred between days 3 and 5.

Although both studies were underpowered to evaluate for clinical efficacy, they lay the foundation for future trials. Given the current climate, the pursuit of therapies that mitigate secondary mechanisms of injury in ICH may be the next viable target.

Disclosures

None.

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