DEM Journal Club

Article Appraisal

Article: Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial
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Background and Study Objective(s):
Non-traumatic intracerebral haemorrhage (ICH) is responsible for about 20% of overall stroke diagnoses, yet accounts for 50% of stroke mortality (Sprigg et al., 2018). To date, the only intervention associated with improved functional outcomes is early intensive blood pressure management (Anderson et al., 2013). Tranexamic acid (TXA) is a low cost anti-fibrinolytic that was demonstrated to significantly reduce mortality in the setting of trauma in the CRASH-2 trial. This mortality benefit was demonstrated without an increase in vascular occlusive events provided this intervention was administered within 3 hours of injury (Roberts et al, 2013). Evidence for the use of TXA in the setting of spontaneous ICH is lacking. Previous small randomized controlled trials have failed to show benefit or harm and/or have failed to report safety outcomes (Arumugam et al., 2015; Sprigg et al., 2018).

TICH-2 tested the hypothesis that intravenous TXA was superior to placebo by measuring the change in modified Rankin Scale (mRS) at day 90 as a marker of functional outcome.

Study Design:
TICH-2 was an international double-blind, randomized, placebo-controlled, phase 3 trial. 124 hospitals in 12 countries were involved in the study. Patients presenting within 8 hours of acute symptom onset with spontaneous ICH were included. Patients with ICH secondary to anticoagulation, trauma, thrombosis, known structural abnormality, or short life expectancy prior to ICH were excluded. Randomization was completed centrally via a secure website and intervention and placebo drugs were made to look identical to protect randomization and blinding. Patients in the intervention arm received a 1 gram bolus of TXA over 10 minutes then 1 gram infusion of TXA over the subsequent 8 hours. Patients in the control placebo arm received saline given in the exact same fashion.

The primary outcome of functional status at 90 days was measured by the modified Rankin Scale (mRS) via a phone based interview. If patients could not be reached by phone, a paper copy of interview questions was sent and collected by mail. Secondary outcomes included: neurological impairment at day 7 or discharge (NIHSS); health-related quality of life (EQ-5D); activities of daily living (Barthel index); cognition (TICS-M); mood (ZDS); costs (length of hospital stay and discharge destination); and radiological efficacy (24h change in hematoma volume and hematoma location). Safety outcomes measured up to day 90 included: death; venous thromboembolism; ischaemic events (stroke, TIA, MI, ACS, peripheral artery disease); and seizures.

Results:

2325 patients were enrolled and 1161 were randomized to TXA (1150 received intervention; 1152 analysed at day 90 with an ITT analysis) and 1164 were randomized to placebo (1157 received; 1155 analysed at day 90 with an ITT analysis). Greater than 80% of patients included where from the UK.

Median time from stroke onset to randomization was 3.6 hours, with 36% of patients recruited within the first 3 hours after onset of injury.

No significant difference existed between the groups in the primary outcome of functional status at 90 days as measured by the mRS after adjustment for stratification and minimisation criteria, with an adjusted odds ratio of 0.88 (CI 0.76 to 1.03, p=0.11).

For secondary outcomes, the TXA group demonstrated a significant decrease in hematoma size (3.72mL vs 4.90 mL for placebo.) Although there was a significant reduction in death at day 7 (TXA 9%, Placebo 11%; OR 0.73; 95% CI 0.53 - 0.99, p = 0.0406) there was no difference in 90 day mortality between the two groups (TXA 22% vs Placebo 21%; HR 0.92; 95% CI 0.77 – 1.10; p = 0.37). There was no statistically significant difference in safety outcomes or costs.

Validity of Results:

Strengths of this trial include appropriate sample size, randomization strategy, multinational recruitment, allocation concealment methods, and clinically relevant outcome.

Limitations included the broad inclusion criteria (including severe strokes that may not have been salvageable) and the timing of intervention. The heterogeneous population that may obscure impact of TXA on a given subtype of patients.TXA was generally administered around 4 hours, yet previous evidence indicates that administration only within 3 hours is beneficial. (Roberts, et al., 2013). Finally, the proxy outcome of reduction in hematoma volume is clinically difficult to interpret.

Generalizability of Results:

This study investigated an intervention broadly available and utilized in Canada and is therefore relevant to current clinical practise. The inclusion criteria were broad, which led to a heterogeneous population including many severe strokes, representing a population that is similar to what we see clinically.

Although an international study, 82.2% of the patients were enrolled in the UK and the rest of the patients came from other 11 countries; the ethnicity was described as 85% white, which may not necessarily be applicable across all BC.

The Bottom Line:
TXA for spontaneous undifferentiated ICH cannot be recommended at this time, although there may be benefit with regards to hematoma expansion and early mortality. ICH patients may benefit from more rapid administration of TXA.

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