Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials

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Brain edema occurs in up to 10% of large, cortical infarcts, specifically in malignant, middle cerebral artery (MCA) infarcts. The prognosis in these cases is poor, with a case fatality rate of ~80% and no effective medical treatment. However, at the time of this study, non-randomized trials had suggested a mortality benefit of decompressive surgery (hemicraniectomy and duraplasty) for malignant MCA infarcts. In addition, the effect of hemi-craniectomy on functional outcome had also been studied in three randomized trials, namely the DECIMAL, DESTINY, and HAMLET trials. DESTINY and DECIMAL had shown a mortality benefit of surgery (both were terminated early due to evidence for this mortality benefit) and HAMLET was on-going at the time of this study. However, none had sufficient data, alone, to reliably estimate the effect of surgery on functional outcome. As such, the goal of this study was to pool the data from these three larger-scale trials, in order to generate sufficient data to assess the functional outcomes following decompressive surgery in patients with malignant MCA infarcts.

Experimental design and statistical analysis: This pooled analysis combined individual patient data from DESTINY, DECIMAL, and HAMLET, all of which were multi-center, randomized, controlled clinical trials. At the time of this study, outcome data from each trial (other than mortality rates) were unknown. Inclusion criteria into the original trials were generally similar across all three, and for the purpose of this pooled analysis included the following: age 18-60yrs old, presence of an MCA infarct, NIHSS > 15, decreased LOC, infarct size of > 145cm^2 or $\geq$ 50% of the MCA territory, and trial inclusion within 45h of stroke onset. Exclusion criteria is noted below.[1] In all three trials, eligible patients had been randomized to receive either decompressive surgery (duraplasty, bone flap, and later cranioplasty) or conservative treatment. In the surgical group, anti-edema therapy was usually not necessary; in the conservative treatment group, the best available medical management was provided. Outcome measurements between the 3 trials were similar as well, namely functional outcome via mRS scores. In this pooled analysis, the primary outcome measure was mRS score at 1yr, dichotomized to favorable (0-4) vs. unfavorable (5 to death). Statistically, the distributions of mRS scores between the two treatment groups were compared via Mann Whitney U testing. Absolute risk reduction (ARRs), odds ratios (ORs), and 95% CIs were also calculated for the specified outcomes in each trial and then pooled for the combined analysis. Additional subgroup analyses were conducted according to age, timing of randomization, and presence/absence of aphasia.

Results: From the original three trials, data from 93 of the original study patients were eligible for the pooled analysis. Of this patient population, 51 had been originally randomized to decompressive surgery, and 42 to conservative management. As shown in Table 1, there were some differences in baseline patient characteristics between the two treatment groups and between the three trials. Otherwise, as shown in Figures 1 & 2, mRS scores differed significantly between the two treatment groups in the pooled analysis ($p < 0.001$), favoring surgery. Specifically, at 1yr, significantly fewer patients in the surgical treatment group had an unfavorable outcome (mRS of 5 or death) and fewer surgically-treated patients had an mRS >3, as compared to the conservative treatment group. Overall survival was also higher after surgical treatment as compared to conservative treatment. Such results were unchanged after controlling for the differences in baseline patient characteristics mentioned

[1] Exclusion criteria: pre-stroke MRS $\geq$ 2, two fixed/dilated pupils, contralateral ischemia, space-occupying hemorrhagic transformation, life expectancy of < 3yrs, other serious illness, known coagulopathy, pregnancy

above. Related to the three primary outcomes, the NNT to prevent an mRS of 5 - death was 2, the NNT to prevent an mRS of 4 – death was 4, and the NNT for survival was 2. Finally, in all three of the defined subgroup analyses (age > or < 50yrs old, presence or absence of aphasia, and time to randomization of > or < 24hrs), surgery remained beneficial (Figure 3).

Conclusions: Overall, the results from this pooled analysis of DECIMAL, DESTINY, and HAMLET suggested that decompressive surgery following a malignant MCA infarct, if performed within at least 48hrs of stroke onset, improves functional outcome and reduces mortality at 1 year post-stroke. Specifically, results from this study suggested that decompressive surgery increases the probability of survival (alone) from ~30% to 80% and doubles the probability of survival with an mRS ≤ 3. Notably, however, as in Fig 1, the chance of survival with an mRS of 4 (i.e., in a state requiring assistance from others) also increases by ~10x with decompressive surgery, so the willingness to accept survival with this moderate degree of disability is an important consideration to discuss. Another caveat to this study was that all included patients were ≤ 60yrs old, so data from this study cannot be entirely applied to those > 60yrs of age (see below for a follow up study conducted in an older age group). Regardless, data from this study largely suggested that decompressive surgery at least increases survival without increasing the number of severely disabled individuals post-stroke. For this reason, the option should be offered to the appropriate patient population and in the appropriate clinical setting.

Additional Reading, if interested:

1) Juttler, Eric, et al., **Hemicraniectomy in Older Patients with Extensive Middle Cerebral Artery Stroke**. NEJM (2014), 370 (12): 1091 – 1100.