Magnesium for aneurysmal subarachnoid haemorrhage: quantifying effect size by trial sequential analysis

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In patients with aneurysmal subarachnoid haemorrhage (aSAH), intravenous magnesium has been studied as a neuroprotective agent to reduce the occurrence of delayed cerebral ischaemia and improve outcomes. Several randomized controlled trials (RCTs) have addressed this issue. As indicated by the meta-analysis by Dorhout Mees and co-workers [1], the data from 6 RCTs (published between 2002 and 2010) did not provide any conclusive result; the pooled risk ratio for the comparison of magnesium vs. placebo was 0.88 (95% confidence interval [CI]: 0.73 to 1.07) with respect to the end-point of 'poor outcome' defined as a modified Rankin Scale score of 4 or 5, or death at 3 months after haemorrhage.

More recently, a large-scale multi-centre RCT has been published in which approximately 600 patients per arm were enrolled [1]. The primary end-point was 'poor outcome' again, and the results showed no difference between magnesium and placebo (risk ratio: 1.03; 95%CI: 0.85 to 1.25).

The overall information from the aforesaid 7 RCTs suggests that magnesium is not superior to placebo after aSAH (end-point: poor outcome; risk ratio: 0.96 with 95%CI of 0.84 to 1.10; analysis carried out using the same statistics employed by Dorhout Mees and co-workers [1]). The conclusion is therefore no proof of efficacy.

Based on these 7 RCTs, we employed trial-sequential analysis (TSA) [2;3] to determine whether the effectiveness data on this treatment simply indicate no proof of effectiveness or, in contrast, these results are conclusive and demonstrate futility (i.e. proof of no effectiveness). In the first case, conducting further trials on this issue would be worthwhile, whereas in the latter case no further trials would be justified. Of course, the distinction between inconclusiveness and futility is not assumption-free, but depends on the choice of a specific threshold for incremental clinical effectiveness. In our TSA, the threshold for incremental clinical effectiveness was set at values of relative risk reduction (RRR) of 12% or 15%; these two values were derived from the results of the "most positive" trials. The main result of TSA was expressed through the graph of cumulative zcurve. The supplementary web document describes the other statistical assumptions of our analysis.

Figure 1 shows our results. According to both thresholds of RRR=12% and RRR=15%, our TSA indicated futility, i.e. proof of no effectiveness; in fact, the z-curve touched or crossed the boundary of futility in both Panels A (futility for RRR up to 12%) and B (futility for RRR up to 15%). Interestingly enough, although both cumulative numbers of enrolled patients (N=2047) were less than the respective optimal information size, the final part of the curve was, in both cases, within the boundary of futility.

The conclusions of our analysis depend on whether or not the two thresholds of incremental effectiveness are thought to be acceptable, or, in other words, if they are thought to reasonably reflect the threshold of clinical relevance. If this assumption is accepted, our results can be seen as the proof of no effectiveness of magnesium after aSAH; consequently no further trials should be performed to assess its efficacy in this clinical condition.

References

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