Letter to the Editor

Randomised control trials for delirium: Current evidence and statistical methods

We read with great interest Grover et al.’s [1] paper describing a randomised controlled trial (RCT) that compared olanzapine, risperidone and haloperidol for treatment of delirium in a general hospital setting. This is a most welcome addition to rather limited information in the field of delirium research, and we congratulate the authors on their well-conducted study. We offer here an amendment to the introduction of the paper, and suggest possible improvements to their statistical methods that might be used for similar RCTs in future delirium research.

Grover et al. failed to identify the only published placebo controlled RCT [2] of an atypical antipsychotic for treatment of delirium in a general hospital setting. The other placebo controlled RCT [3] is in a critical care setting. The Chinese RCT [4] comparing olanzapine and haloperidol was not placebo controlled, contrary to Grover et al.’s description. Two other RCTs were omitted by the authors [5,6], perhaps for similar reasons (namely, small sample size) as the NICE guideline made the same omission [8]. The remaining RCTs for treatment of delirium are adequately summarised elsewhere [7,8]. It is worth noting that, to date, the largest sample size for a placebo controlled RCT in delirium is for rivastigmine (54 rivastigmine, 50 placebo) [9].

We now turn to statistical issues. The small sample sizes that are typical in delirium studies mean that whatever analytical approaches are employed need to make efficient use of available data. This begins at the design stage, where sample size or power calculations should anticipate the use of more sophisticated statistical methods. However, sample size is not the only statistical issue; delirium can fluctuate and improve irrespective of the treatment given, and drop outs from treatment trials are common. For all of these reasons, some standard statistical methods that might be used for similar RCTs in future delirium research.

1. Our main analysis [2] made use of a nonlinear mixed effects model. This model was used to estimate (and test for) differences in recovery rates between treatment groups. We were able to demonstrate that a group of patients treated with quetiapine improved 82.7% faster (SE 37.1%, p = 0.026) than the placebo group. A crucial point is that this advantage would not have been revealed by a single, end-of-trial comparison, where no significant differences were found.

2. We also considered the computationally simpler, but still flexible, saturated linear mixed model. By considering the average area under each patient’s DRS-R-98 trajectory, we were able to compare treatment groups across the whole trial period. This can be accomplished in SPSS using a custom hypothesis test, but is equally achievable in other statistical software. The main qualitative aspect to emphasise is that mixed models incorporate the correlation between a patient’s responses.

3. An alternative is to explicitly impute any missing data. This can be achieved in a way that respects the nature and prognosis of delirium, with or without treatment [9]. Though it is certainly not the only possibility, we imputed the midway point between the patient’s last observed DRS-R-98 and its mean at the time in question among those who actually completed the trial. Other examples of imputation in delirium are baseline observation carried forward (BOCF) and last observation carried forward (LOCF) [11]. However, these imputations do not typically capture the kind of trajectories seen in delirium trials, and tend to place unwarranted emphasis on end-of-trial comparisons.

4. Devlin et al. [3] correctly recognise that delirium can improve without any intervention. Consequently, they choose to summarise recovery trajectories by measuring time to first delirium resolution. This approach has the advantage that trial dropouts can be incorporated in a reasonably straightforward fashion, but lacks a standardised definition of delirium resolution.

All these approaches are, in fact, widely used in other areas of research, but to date have been little used in delirium treatment RCTs. These methods are not substantially more difficult to implement than existing statistical procedures (such as BOCF or LOCF) but can substantially improve our understanding of delirium resolution.

Reassuringly and interestingly, although the nonlinear model, linear model and delirium-appropriate realistic imputations emphasise different aspects of our trial’s results, we found much consistency as well [13]. In all cases, severity and non-cognitive sub score trajectories of DRS-R-98 were improved in the quetiapine group. Collectively, quantitative data analyses can give a rounded qualitative impression of how different treatments can make a difference to a patient suffering from delirium.

We commend these methods to delirium researchers in the hopes that they will contribute to enhance our understanding of delirium.

References


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28 October 2011