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Review

Single-center trials in neonatology: Issues to consider

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SUMMARY

Single-center randomized controlled trials confer certain advantages over multi-center trials, in that they are cheaper and easier to design and conduct. However, recent research suggests that single-center trials are likely to overestimate treatment effects. There are notable examples in neonatology where results from multi-center trials have contradicted results of single-center studies. In this paper we discuss issues around external generalizability of single-center studies, and methodological issues that may cause bias.

1. Introduction

In neonatology many drugs, interventions and practices have developed as a result of randomized controlled trials (RCTs) and meta-analyses. More trials need to be conducted, as there are uncertainties around treatments, and several drugs used in newborn infants are unlicensed [1]. These will need to be appraised and decisions will be made about whether the results should change practice. Some of these trials will be large multi-center studies, and others will be conducted in a single center. In this paper we consider issues around single-center RCTs.

2. The attractions of single-center studies

The obvious advantage of single-center studies is that they are logistically easier, and usually cheaper, than multi-center studies. With increasing numbers of centers participating in a trial, it becomes more complex and expensive to conduct and monitor site-specific training, administrative duties, and governance. It can also become more difficult for collaborators to reach agreement about the implications of the results and write the final report. Even though trial networks can foster collaboration and make this process easier, the cost of a multi-center study may be prohibitive in some situations. In low-income countries where there may not be a robust infrastructure for collaborative research, it may only be possible to conduct studies in one center.

Single-center trials are particularly appropriate for studies that may not require a large number of patients, such as early-phase, pilot or feasibility studies. Such trials can be invaluable for informing subsequent studies, such as testing validity and importance of outcome measures, evaluating study protocols, assessing participant recruitment rates, and generating data to inform future sample size calculations.

Single-center studies can provide useful estimates of benefits and harms, especially when aggregated in meta-analyses to help guide therapies. For example, a Cochrane review [2] comparing volume-targeted ventilation (VTV) with pressure-targeted ventilation included 12 trials (eight single-center, four conducted in two centers). VTV was found to reduce the risk of the composite outcome of death or bronchopulmonary dysplasia (BPD) [risk reduction (RD): −0.12 (95% CI: −0.21 to −0.03); number needed to treat (NNT): 8 (95% CI: 5 to 33)], and other clinically important outcomes.

3. Single-center studies show larger treatment effects

Estimates of treatment effect appear to be larger in single-center RCTs. Meta-epidemiological analyses using the summary statistic ratio of odds ratio (ROR) have systematically examined trials in several specialties; ROR <1 indicates a larger estimate of the intervention effect in single-center trials than multi-center trials. In two analyses [3,4], single-center trials were more likely to show greater benefit with regards to dichotomous outcomes {combined ROR: 0.73 (95% CI: 0.64 to 0.83) [3] and 0.64 (95% CI: 0.47 to 0.87) [4]}, and in one there was a trend towards this finding which was not statistically significant {ROR: 0.91 (CI: 0.79 to 1.04) [5]}. Another analysis reported that single-center trials showed larger

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intervention effects for continuous outcomes {combined difference in standardized mean differences −0.09 (95% CI: −0.17 to −0.01, $P = 0.04$) [6]}.

A combination of various factors probably causes this phenomenon. Single-center studies tend to recruit fewer patients, and it is recognized that smaller studies show greater effects [7]. In some studies the sample size may be so small that it is purely due to chance that a treatment has shown a benefit. However, in one analysis, the overestimation of treatment effect in single-center studies appears to remain consistent even when results are adjusted for sample size [3].

Publication bias, or selective reporting of trials based on the results, is well recognized [8]. One strategy to improve publication rates of trials is to prospectively list them in a registry, but whether single-center studies are less likely to be registered has not been tested. One meta-epidemiological study [9] combined results from three reports that examined full publication of abstracts of RCTs that were initially presented at conferences and found that single-center studies were no less likely to be published [risk ratio (RR): 1.27 (95% CI: 0.95 to 1.70)]. Another analysis found that single-center studies were more likely never to have started after they had been planned, or to have been abandoned after they started [123/337 (36%) vs 28/163 (17%); $P < 0.0001$], but single-center status did not predict whether a study was published or not [10].

In this paper we consider two other reasons why single-center studies may show greater treatment effects. The first is the likelihood that there are particular features of the center or investigator that may affect the magnitude of treatment effect, and hence the external generalizability of the results. The second is that some aspect of the methodology in single-center studies makes it more likely that treatments are shown to be beneficial (in other words, single-center studies may be prone to bias).

4. Are the results of single-center studies externally generalizable?

Single-center studies are conducted in a more homogeneous population than multi-center trials. They are better suited therefore to efficacy (explanatory) trials, which test whether an intervention works in optimum conditions in contrast to effectiveness (pragmatic) trials which measure the effect in 'real world' settings.

When interpreting the conclusion of any RCT, it is important to determine why the study was conducted. A center may want to conduct a trial if a particular problem occurs frequently in its own institution. This has implications in areas of neonatology in which there are substantial differences in outcomes between institutions [11]. One notable example is the use of prophylactic fluconazole in preterm infants. A single-center study of 100 infants, randomized to intravenous fluconazole or placebo, showed that antifungal prophylaxis reduced fungal colonization [11/50 (22%) vs 30/50 (60%); RD: 0.38 (95% CI: 0.18 to 0.56); $P = 0.002$] and invasive fungal infection [0/50 vs 10/50 (20%); RD: 0.20 (95% CI: 0.04 to 0.36); $P = 0.008$] [12]. A Cochrane review of systemic prophylactic antifungal therapy for very-low-birthweight infants incorporated seven studies, of which five were in single centers, one in eight centres, and one in two [13]. Although the review found a significant reduction in invasive fungal rates among very-low-birthweight infants [RD: −0.09 (95% CI: −0.14 to −0.05), NNT: 11], the authors highlight that this may reflect the high incidence of systemic candidiasis in the control groups (mean 16%). In the UK, where the typical rates of invasive fungal sepsis are only 1% [14], a large number of infants would be exposed to potential risks of fluconazole but only very few would be expected to benefit.

Another reason why a center may wish to conduct an RCT is that it has particular experience or expertise with an intervention or strategy. For example, single-center trials have shown clear benefits of VTV, but it is uncertain whether other institutions can replicate the success of these studies, particularly as they may lack the clinical and nursing expertise available at the study centers.

5. Theoretical reasons why single-center studies are more prone to bias

Bias refers to aspects of the trial (other than the effects of the interventions) that give one treatment arm an unfair advantage over another. In the Cochrane Risk of Bias tool, aspects of methodology and reporting are categorized as low, high, or unclear risk of bias [15]. There are some specific important considerations around these domains in context of single-center studies. Evidence is lacking, however, as to whether single-center studies are more likely to be classed as having high risk of bias, so these are currently theoretical.

5.1. Selection bias

In an RCT, the groups of participants should be identical, except for the intervention they receive. If there are methodological reasons why this may not happen, the study is prone to selection bias, and is more likely to show greater treatment effects [16]. Avoidance of selection bias relies on two things – first that the participants are allocated to groups at random, and second that those enrolling participants into the trial are unaware of the treatment group to which they will be allocated.

There is no specific reason why the process of randomization should be flawed in single-center studies. For this aspect of the trial to be classed as low risk of bias, a method should be used that allocates patients completely at random (for example by using random number tables or computerized random number generators) rather than by using a systematic approach to randomization (such as allocating participants to groups on the basis of date of birth, day of admission, or patient identification number).

However, it is possible that in some single-center studies the process of allocation concealment is less optimal. This is important as studies with inadequate allocation concealment can overestimate treatment effects by 40% [16]. To prevent investigators from knowing the allocated groups of subsequent participants in advance (and hence affecting whether they are enrolled in the study or not), a trial can use allocation procedures at a separate central location (which could be telephone, web-based, or pharmacy-controlled), or measures to hide the allocation until the patient is enrolled (such as sequentially numbered drug containers of identical appearance, or opaque, sealed envelopes). Although there is no specific reason why single-center studies should not employ such methods (other than cost) it is more likely that the randomization schedule (i.e. the groups to which patients will be allocated) will be held locally rather than centrally, so unless appropriate concealment measures are taken, the study is at high risk of bias.

In a commentary about single-center studies in adult critical care, the author suggests that it may be more difficult to conceal the likelihood of randomization to a particular group if a trial is conducted in one center [17]. This relates to the use of block randomization (i.e. randomization within blocks of smaller numbers of participants, to try to ensure fairly equal numbers in each group). If an investigator knows the block size, in an unblinded single-center study, they may be able to foresee the next treatment allocation.