Critical appraisal of a randomised control trial: "Three day versus five day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial"

Essay Development Plan:

Evidence based medicine seeks to incorporate the best scientific research into clinical practice. It is therefore necessary to evaluate clinical trials using readily available tools. The research for this essay was focussed on the trial in question and the clinical background [1]. All scientific terms used in the appraisal tool were explained at the point of use in the essay.

The trial discussed here investigates amoxicillin treatment of non-severe pneumonia in children; it also looks at relapse. Respiratory infections kill two million children annually [2]. This is a randomized control trial with intention to treat basis [3],[4],[5]. The primary outcome of this trial is treatment failure; the rate of relapse was a secondary outcome. The CASP tool was used to appraise the trial [6],[7],[8]:

A) Are the results valid?

1. Did the trial address a clearly focussed issue?
2. Was the assignment of patients to treatments randomised?
3. Were patients, health workers and study personnel blinded?
4. Were the groups similar at the start of the trial?
5. Aside from the experimental intervention, were the groups treated equally?
6. Were all of the patients who entered the trial properly accounted for at its conclusion?

B) What are the results?

7. How large was the treatment effect?
8. How precise was the estimate of the treatment effect?

C) Will the results help locally?

9. Can the results be applied in your context?
10. Were all the clinically important outcomes considered?

The finding that three days of amoxicillin treatment is as efficacious as five day amoxicillin treatment is clear and convincing. Standard treatment length of seven days amoxicillin treatment was not part of the trial. Asthmatic patients are amongst the most vulnerable to pneumonia, it would have been good to include patients with asthma. No treatment recommendations can be made on the strength of the evidence presented in this trial.

Excluded aspects and potential further development of this essay

I felt it was beyond the scope of this review to discuss the stark similarities between this trial and an earlier multicentre double blind controlled trial investigating the same question [9]. Whilst the ethics of how the study was conducted are included in the essay, I did not investigate the ethics of instigating the trial. The trial adds limited new information to the field, furthermore there are some major flaws in trial design.

The suitability of the intention-to-treat approach and the block randomization were not included, since the appraisal was done using the CASP tool. Whilst CASP is very accessible, easy to use, and investigates transferability and local applicability of trials, it has a low sensitivity for measuring methodical soundness [7],[8]. To further develop this essay, it might be of interest to appraise the trial in question using the ETQS tool. One of my criticisms of the trial in question was that the participants' opinion on their cure was simply dismissed by the authors, this is something that could be addressed by using the JBI tool to appraise this paper [8].

To develop the essay further, it might be interesting to discuss whether the WHO management guides [10] for the treatment of pneumonia in children are sufficient or if it would be advantageous to use the more stringent British Thoracic Society [11]. The authors of this study do not allude to the fact that they use an atypical treatment length as control, something that is surely a hurdle if these results are supposed to be implemented in clinical practice.

Another interesting avenue would be looking at the diagnostics. In this trial, the diagnosis of pneumonia was relatively weak, to the point that one might argue the trial looked at suspected rather than confirmed pneumonia patients.

Whilst the premise of the essay was “Using the CASP Tool for randomised controlled trials, write a critical appraisal of the trial”; it has become clear that an appraisal could be greatly strengthened by using additional tools. Some of the major weaknesses of the trial discussed in this paper go undetected using the CASP tool, so an undeservedly high score is reached by this trial.

References

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The paper discussed:

This is a critical appraisal of a trial by the ISCAP study group from 2004 [1]. This trial attempts to improve treatment for pneumonia. Respiratory infections are a major international health concern. Every year, more than two million under-5s die globally from respiratory infections such as pneumonia [2].

The trial discussed investigates the effect of treatment length with amoxicillin for non-severe pneumonia in under-fives. The objective of this trial was to compare the number of children recovering from pneumonia at five days after the start of treatment. Another objective was to assess the proportion of children suffering from a relapse.

This is a randomized control trial. Randomized control trials are conducted to reduce bias. Potential participants are screened for eligibility and then assigned to either untreated control group or treatment group. The intervention in this trial was 31-54mg amoxicillin/kg bodyweight/day for days one to three and either amoxicillin or placebo for days four and five.

The data in this trial were analysed on an intention to treat basis, meaning that all participants, once randomized to a treatment, were entered into analysis [3]. This is independent of adherence or actual treatment. Intention to treat strategy is generally accepted as reflecting clinical reality, since it mimics real life non-compliance and deviations from an intended treatment protocol [4].

The primary outcome of this trial is treatment failure. A primary outcome measure is often difficult to assess, in this case, treatment failure needs to be defined. The authors considered chest in-drawing, inability to drink, increased respiratory rate and decreased oxygen saturation as treatment failure. These are surrogate outcome measures [5], because they alone do not define cure or failure of treatment. Because of the intention to treat approach, patients not adhering were also considered treatment failures. The rate of relapse was a secondary outcome. The treatment failure or success was assessed on day five; this is a very short follow up for pneumonia. The authors assessed microbiological outcomes by testing antimicrobial resistance in cultures isolated from nasopharyngeal swabs before treatment and after 14 days.

This trial was conducted in India. A randomised controlled trial in a similar population in Pakistan [6] showed similar rates of clinical cure using amoxicillin without an unusual number of adverse outcomes. It is questionable what this trial adds to current dogma and brings the ethics of conducting it into question. There are, however, potential positives to three day versus five day amoxicillin treatment. For instance, the earlier Pakistani trial found non-adherence a major risk factor for relapse and it can be argued that adherence might be higher in the three day group. This was not, however, one of the outcome measures in this trial. This trial did not have an untreated control group, since withholding treatment would have been unethical.

A major limitation of this trial is that it excludes children suffering from asthma as well as those with severe pneumonia. Both of these groups are especially vulnerable. Another limitation is the short follow up and that the disease history of the patients has not been sufficiently recorded or the cause of infections investigated. A further limitation is the measurement of adherence, which is done by simple pill count. For this to be accurate, a patient report on adherence (or patients bringing unused medication to the consultation) is required.

Self-reported adherence has been documented to be inaccurate [7], so in order to monitor adherence it would need to be measured, e.g., by serum test.

The Critical Appraisal Skills Programme (CASP) tool

Evidence based medicine seeks to improve clinical decision making by incorporating the current best scientific evidence in medical practice. It requires individual clinicians as well as governing bodies and learned societies to adopt a conscientious and critical approach to appraising scientific data and implementing the findings in the care for individual patients and patient groups alike [8]. A major obstacle for evidence based medicine is the lack of a universal means by which to assess published scientific research. There are several different critical appraisal tools currently in use [9]. The one used in this appraisal is the CASP tool [10].

CASP was initiated in 1993 by Sir Muir Gray during his tenure as Director of Research and Development at the Oxford Regional Health Authority. The CASP advisory group, founded in 2012, continues to develop the CASP tools. This critical appraisal uses the CASP tool for randomised controlled trials. This is a ten point questionnaire for the appraisal of research trials. It splits into three major sections that appraise the validity of the trial, the results and its usefulness in a local context.

The CASP tool is a popular instrument for the appraisal of research. The CASP tool is very accessible even to researchers with limited experience of evaluating clinical trials. The CASP tool is very useful for transferability, a very important concept in evidence-based medicine. It asks questions about the usefulness of a particular trial for the local population, even if this is different from the study population [11]. One of the limitations of the CASP tool is its relative insensitivity to methodological quality. It is possible to evaluate a trial quite positively, whilst the underlying research question is flawed.

A) Are the results valid?

1. Did the trial address a clearly focussed issue?

Yes, the trial addressed a clearly focussed issue; it investigated efficacy of a three day amoxicillin treatment with a five day course. The control group in this trial was the five day treatment group. Criticism can be levelled at the authors because the control group does not necessarily get the standard treatment for pneumonia in under 5's. The British Thoracic Society suggests that a course of seven to ten days of amoxicillin is given [12]. However, for low income countries, the WHO's clinical management guide suggests a five day course [13].

This trial's hypothesis is a null hypothesis, the authors assume at the start that three day amoxicillin is as effective as the traditionally used five day treatment. A null hypothesis is a statement that there is no relationship between phenomena, in other words, there is no treatment effect. The change in treatment investigated in this trial is the length of amoxicillin usage. The rationale for the null hypothesis was that short courses of amoxicillin have been proven to be effective in the treatment of other bacterial infections, such as middle ear infections, bacterial tonsillitis [14] and urinary tract infections [15].

2. Was the assignment of patients to treatments randomised?

Yes, the control (five days of amoxicillin) and treatment (three days amoxicillin) groups were block randomized for seven different study sites. Randomisation helps ensure that any findings are truly because of the treatment and reduces selection bias. In a multicentre trial, such as this one, randomization is often done in blocks at each site and can help prevent un-blinding.

3. Were patients, health workers and study personnel blinded?

Yes, this was a double-blind trial. Double-blinding means neither researchers nor the study subjects, or in this case, their care-givers, are aware whether they belong to the control or the

intervention group. Both the three day and the five day groups were given identical envelopes containing amoxicillin for the first three days. For the subsequent two days, the control group was given envelopes containing amoxicillin and the treatment group was given undistinguishable envelopes containing placebos. Randomization was done in blocks at each site of this multi-centre trial to allow for interim analysis and to prevent un-blinding [1]. The allocation of 3 day and 5 day amoxicillin treatment was concealed from researchers and participants alike. Such concealment is important to prevent clinicians from assigning a particular patient group, such as those most in need of treatment, to a particular treatment and, thereby, introducing bias [16].

4. Were the groups similar at the start of the trial?

Yes, all the patients were between 2 months and 4 years 11 months old. All patients presented with coughing, rapid breathing or other breathing difficulties at outpatient departments of seven different Indian hospitals. Confirmed asthmatics and patients with evidence of severe pneumonia were excluded. Treatment assignment was random, however, since the patient groups were not very well identified, it is difficult to confirm the similarity between groups clinically. Pneumonia was not confirmed by chest radiography, but defined as an increased breathing rate. The patients were recruited upon presentation with symptoms and no healthy baseline lung function measurements were available.

5. Aside from the experimental intervention, were the groups treated equally?

Yes, all patients were treated equally. The analysis in this trial was performed on an intention to treat basis [4].

6. Were all of the patients who entered the trial properly accounted for at its conclusion?

139 patients were lost to follow up. Any patients lost to follow up were defined as treatment failure, so no bias was introduced.

B) What are the results?

7. How large was the treatment effect?

Treatment with amoxicillin was as effective at three days as it was at five days. Cure on day five after treatment commencement was achieved for 89.5% of the patients in the three day group and 89.9% of patients in the five day group. For patients with evident wheezing on admission the rates of cure were 90.7% for the three day group and 89.8% for the five day group. As in previous studies, adherence to treatment was a predictor for treatment success, with 92.6% adherence in the group assessed as cured at five days and 20.9% adherence in the treatment failure group [1].

The incidence and nature of adverse reactions were comparable in the three day and five day treatment groups. There were no deaths, but there were 41 hospitalisations: 18 hospital admissions in the three day group and 23 in the five day group. Admissions to hospital must be considered a serious adverse reaction; there were cases of severe diarrhoea, vomiting, dehydration and cases of wheezing in children who did not wheeze on admission.

8. How precise was the estimate of the treatment effect?

The authors had hypothesised that treatment with a three day course of amoxicillin would be equally effective as a five day course. This was proved correct in the trial.

C) Will the results help locally?

9. Can the results be applied in your context?

It is difficult to estimate if the results of this trial can be applied in a global context. The authors compared "standard" five day amoxicillin treatment with three day treatment. The British

Thoracic Society's guidelines for the clinical management of pneumonia in children state a routine administration of amoxicillin for 7 days as standard [12].

10. Were all the clinically important outcomes considered?

The follow up period of the trial discussed in this paper was very short. A patient who is symptom free after five days might not necessarily be cured. Since the pneumonia was not confirmed at the beginning of the trial, it was difficult for the authors to consider this clinically important outcome. In order to confirm cure from pneumonia, more than confirmation of symptom improvement wold be required.

Treatment failure was insufficiently defined. Since no baseline lung function was tested and no radiography performed, it is difficult to assess cure from pneumonia. The care-givers' assessment of cure was less favourable than the clinicians' assessment and this was insufficiently discussed. Almost 50% of the care-givers of the patients disagreed with the clinical finding of cure. The care-givers' assessment was dismissed and a recommendation to council the care-givers was the only reference to the concern.

Summary

Whilst this trial shows convincing evidence that three days are as useful as five days treatment with amoxicillin for symptoms of non-severe pneumonia in children under the age of 5, several questions remain unanswered. The authors used a non-standard length of treatment as their control group. A major criticism is the fact that whilst the authors purport to study pneumonia, their study subjects are not thoroughly diagnosed. It could be argued that the authors are, in fact, studying patients with suspected rather than actual pneumonia. Some of the patient groups most vulnerable in pneumonia have been excluded, such as confirmed asthmatics.

It wold be interesting to repeat the trial including only patients confirmed to have pneumonia and use a control group treated for 7-10 days with amoxicillin. Since amoxicillin is an inexpensive, widely available drug, a saving of two days' worth of treatment might not be worth the potential risks. This might be applicable in very low income countries without universally accessible radiography, but it won't be applicable in high income countries. The cost of amoxicillin treatment per day in this trial was 4 Rupees, approximately £0.05, so this is unlikely to make a difference in all but the very poorest countries.

On the data of this trial, no treatment recommendations should be made. The patients are suspected, but not confirmed, to suffer from pneumonia. Furthermore, five days is too short a follow up to confirm clinical cure, and the definition of treatment failure is not rigorous enough.

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