Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared intravenous treatments for critically ill children diagnosed with status asthmaticus and impending respiratory failure. The treatment strategies assessed were theophylline alone (plus placebo), terbutaline alone (plus placebo), or theophylline and terbutaline together.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised children aged between 3 and 15 years old who had a history of asthma, and who had been admitted for 2 hours or less to the paediatric intensive care unit (PICU) with severe status asthmaticus and impending respiratory failure. History of asthma was defined as previous evaluation by a physician for recurrent wheezing. Severe status asthmaticus was defined as intractable wheezing requiring continuous nebulised albuterol and a modified Becker Clinical Asthma Score (CAS) of less than or equal to 7. The exclusion criteria were a known allergy or hypersensitivity to any methylxanthine, beta-agonist or anticholinergic medication, the use of either study drug during the 24 hours before enrolment, the presence of underlying cardiovascular disease, and pregnancy.

Setting
The setting was tertiary care. The economic study was carried out in Cincinnati, Ohio, USA.

Dates to which data relate
The effectiveness and resource data referred to 1996 to 2001. The prices year was 2003.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The resource use data were collected prospectively for the same patient sample as that used in the effectiveness study.

Study sample
A power calculation was performed at the planning phase of the study. Based on an estimated 15% difference in mean CAS, the power calculation determined the sample size needed to provide 80% power at a significance level of 0.05.
Consecutive patients admitted to the PICU in the daytime were screened for possible enrolment in the study. An interim analysis revealed no significant differences between the study groups in terms of the primary outcome variable, and a revised power calculation indicated that a sample size of several hundred patients would be required to detect any significant difference. The trial was halted as a result of the interim analysis. The authors reported that the age of the patients recruited into the study ranged from 34 months to 19 years. The inclusion of patients older than 18 years of age may be inappropriate given that the clinical study question addressed treatment in children.

In total, 336 children were admitted to the PICU in the study period. Of these, 168 were admitted during the night and were excluded, while 110 either failed to meet the inclusion criteria (80) or met the exclusion criteria (30). Fifty-nine patients who met the inclusion criteria were screened for possible enrolment in the study, 19 of whose parents refused consent for the study. The final study sample comprised 40 patients, of which 13 were randomised to theophylline, 16 were randomised to terbutaline, and 11 were randomised to receive both study drugs.

**Study design**
The study was a single-centre, randomised controlled trial. Patients were randomised using a sealed envelope technique. The patients were followed up until the end of the clinical episode, and there was no loss to follow-up. Hospital staff and study investigators were blinded to the treatment. Intravenous saline was used as a dummy to ensure that all patients received the same amount of intravenous fluids.

**Analysis of effectiveness**
The analysis of the clinical study was conducted on an intention to treat basis. The primary health outcome was the change in CAS over time, as assessed by study investigators. The group randomised to receive theophylline and terbutaline had significantly higher Paediatric Risk of Mortality (PRISM) scores than the other groups, (p=0.006), and significantly higher serum glucose levels than the group randomised to theophylline, (p=0.005). A lower percentage of children in the terbutaline group received adjunctive medication than in the other two groups.

**Effectiveness results**
There were no significant differences between the groups in terms of improvement in CAS.

There were significantly higher median levels of nausea and tremors in the group randomised to theophylline and terbutaline compared with the group randomised to terbutaline, (p<0.05).

**Clinical conclusions**
The authors concluded that theophylline was as effective as terbutaline in treating critically ill children with status asthmaticus.

**Measure of benefits used in the economic analysis**
No summary measure of health benefit was used in the economic analysis. The authors assumed that the clinical effectiveness results were equal on the basis of the primary outcome measure, and conducted a cost-minimisation analysis.

**Direct costs**
The resource use quantities were not reported separately from the costs. The study recorded the direct costs of the study medication to the hospital, and also the additional costs of laboratory tests for theophylline levels in the group randomised to receive theophylline alone. The source of the direct cost data were the hospital charges for the patients in the study, while unit costs were based on the average wholesale price of the study medications. Discounting was not relevant given the short follow-up period. The study reported the median costs. The price year was 2003.
Statistical analysis of costs
The authors specified that continuous data that were not normally distributed would be analysed using a Kruskal-Wallis one-way analysis of variance. The analysis compared median costs between the three study groups. No power calculation was performed for the cost data.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
US dollars ($).

Sensitivity analysis
Sampled cost data were available for statistical analysis, so a sensitivity analysis was not required.

Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The median cost for patients randomised to theophylline was $280. This was significantly lower than the median costs in the other two study groups, (p<0.0001).

The median cost for patients randomised to terbutaline was $3,908.

The median cost for patients randomised to receive both study drugs was $4,045.

The costs of adverse events were not included in the analysis.

Synthesis of costs and benefits
The costs and benefits were not combined.

Authors’ conclusions
Theophylline was the most cost-effective treatment strategy for the treatment of critically ill children with status asthmaticus.

CRD COMMENTARY - Selection of comparators
The authors stated that a no-treatment or placebo arm was not considered in the study, owing to ethical concerns about withholding an intravenous bronchodilator in such critically ill children. The interventions compared were additional treatments not routinely used in the study setting. You should consider whether the comparators are appropriate in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a randomised controlled trial, which was appropriate for the study question. The study sample was not entirely representative of the study population, as it contained patients aged up to 19 years who would not normally be considered children. The patient groups were not shown to be comparable at analysis. The authors acknowledged this limitation in their discussion, but stated that the results were robust to a sensitivity analysis in which the PRISM score was included as a covariate, although this analysis was not reported. However, the study was
underpowered to detect a difference between the treatment groups, so it is unsurprising that any differences remained statistically insignificant in both the base-case and sensitivity analyses.

Validity of estimate of measure of benefit
The analysis of benefits was based on the therapeutic equivalence of treatment alternatives. This is, arguably, a limitation given that the study sample was too small to detect differences between the groups in the primary outcome measure. In addition, a test for equivalence would have been underpowered, and also was not performed.

Validity of estimate of costs
Although the authors used a hospital perspective for the cost analysis, only the costs of study medication and laboratory tests for theophylline were included. The study did not include the costs of adverse events, adjunctive medication or length of stay in the hospital. The omission of these costs could have affected the authors' conclusions since the use of adjunctive medication and the incidence of certain adverse events was higher in the group randomised to theophylline, which the authors judged to be the least costly treatment strategy. The limited cost data included in the analysis may limit the study's generalisability. A statistical analysis of the costs was undertaken, but given the limitations of the analysis the results may be compromised in terms of the study question regarding which strategy is most cost-effective. The price data were based on average wholesale prices in the USA. You should compare these to the unit costs of the study drugs in your own setting. The authors reported the date to which the price data related. Discounting was not relevant given the short follow-up period of the study.

Other issues
The authors stated that no other studies compare the study drug in this particular study population. The issue of generalisability to other settings was not addressed. The authors did not present their results selectively. The authors concluded that the study provided evidence of the therapeutic equivalence of the treatment strategies compared in critically ill children with status asthmaticus. The strength of this conclusion may be questionable given the study results.

Implications of the study
The authors concluded that, although further studies may be helpful, theophylline should be considered for use early in the treatment of critically ill asthmatic children. Further research may be helpful in confirming these results, given the limitations of the present study.

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