Comparison of urokinase and video-assisted thoracoscopic surgery for treatment of childhood empyema

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 use of percutaneous chest drain insertion with an intrapleural fibrinolytic (urokinase) and primary video-assisted thoracoscopic surgery (VATS) for the treatment of childhood empyema. The dose used was 10,000 U in 10 mL normal saline in children under one year of age, and 40,000 U in 40 mL in children over one year of age. The chest drain was inserted using the Seldinger technique. For VATS, either one lung or both lungs were ventilated, depending on the size of the child.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients younger than 16 years of age who had radiographic evidence of empyema. The inclusion criteria were persistent fever of at least 38 degrees Celsius after more than 24 hours of parenteral antibiotic treatment or respiratory distress caused by the pleural collection. The exclusion criteria were previous attempt at thoracocentesis or chest drain insertion at the referring hospital, history of underlying cardiac disease or previous cardiac surgery, or known immunodeficiency.

Setting
The setting was tertiary care. The economic study was carried out in London, UK.

Dates to which data relate
The effectiveness and resource use data related to 2002 to 2005. The price year was 2005.

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

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

Study sample
The authors stated that a difference of 2 days in length of post-intervention hospital stay would be considered clinically important. On this basis, using a significance level of 5%, it was estimated that at least 29 patients would be needed in
each arm to achieve a power of 80%. Patients were recruited from those referred to Great Ormond Street Hospital (GOSH) for the treatment of parapneumonic effusions. Eighty patients were referred to GOSH, of whom 20 were not included in the study. Four patients refused to participate, 13 did not meet the inclusion criteria and 3 were excluded for "other reasons". The total sample size was therefore 60 patients, with 30 assigned to each treatment group. Among the patients recruited, all those with low platelets or abnormal clotting received VATS, even if randomised to the urokinase arm. This suggested that some patients included in the study sample were not considered clinically appropriate for randomisation between the two treatments. The authors stated that the patients included were diverse and representative of the UK as a whole.

Study design
The study was a single-centre, prospective, randomised controlled trial (RCT). Patients were randomised using an internet website. The trial coordinator held the randomisation code during working hours and the attending paediatrician had access to the code out of hours. The patients were followed up for 6 months. The authors reported that 16 patients (6 from the VATS arm and 10 from the urokinase arm) were lost to follow-up at 6 months. The study does not appear to have been blinded. The nature of the interventions may have prevented the blinding of patients or doctors.

Analysis of effectiveness
The analysis of effectiveness conducted on an intention to treat basis. The primary health outcome was length of post-intervention hospital stay. The secondary health outcomes were the number of days with chest drainage, total hospital stay, failure rate of assigned treatment, adverse events, and chest X-ray changes at 6 months after the intervention. The authors reported that, at analysis, the groups were comparable in terms of their demographics and baseline characteristics.

Effectiveness results
The median length of post-intervention hospital stay was 6 days (range: 3 to 16) in patients randomised to VATS and 6 days (range: 4 to 25) in patients randomised to urokinase. The difference in length of stay was not statistically significant (p=0.311; 95% confidence interval of median difference: -2 to 1 days).

There were no significant differences in the secondary health outcomes.

There were no adverse events directly related to the treatment in either group.

Clinical conclusions
The authors concluded that there was no significant clinical difference in length of hospital stay after intervention between percutaneous chest drain with intrapleural urokinase and primary VATS for the treatment of empyema in children.

Measure of benefits used in the economic analysis
No summary measure of health benefits was used in the economic analysis. In effect, a cost-consequences analysis was performed.

Direct costs
The resource use quantities were not reported separately from the costs. The study included direct hospital costs relating to the study interventions and length of post-intervention hospital stay. These included the costs of procedures, surgery following the intervention, and pre-intervention computed tomography (CT). The unit costs were estimated from actual price data at the hospital used in the study. Discounting was not relevant given that the follow-up period was less than one year. The study reported the average costs. The price year was reported to be 2005.
Statistical analysis of costs
The authors provided mean and median costs. The costs in each treatment group were compared using non-parametric methods, which are preferable to parametric methods that rely on an assumption of normality for the analysis of cost data. The study employed the Mann-Whitney test, Kolmogorov-Smirnov test and the Wald-Wolfowitz test. The power calculations were not based on cost data.

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

Currency
US dollars ($). The authors did not report details of the currency conversion used.

Sensitivity analysis
The authors assessed the sensitivity of the results to the exclusion of the costs of CT, which had been undertaken on all patients in the study but may not be routinely used in practice.

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

Cost results
The mean cost was $11,379 in the VATS group compared with $9,127 in the urokinase group. The difference in costs was statistically significant, (p<0.001).

Synthesis of costs and benefits
If the costs of CT chest scans were excluded, the mean cost in the VATS group was still significantly higher ($10,515) than that in the urokinase group ($8,955).

Authors' conclusions
The authors concluded that there was no evidence for a clinically significant difference in post-intervention length of hospital stay following treatment with chest drain and urokinase or primary video-assisted thoracoscopic surgery (VATS). They stressed that the study was not designed as an equivalence study. However, the authors suggested that the cost results indicated that intrapleural urokinase should be the primary treatment of choice for uncomplicated empyemas in children.

CRD COMMENTARY - Selection of comparators
The authors chose to compare primary VATS with urokinase in children, as equivalent comparisons were only available in adults. The study did not include the full range of relevant comparators, which include antibiotics, thoracocentesis, alternative fibrinolytics, mini-thoracotomy and open decortication. You must decide whether the interventions examined are relevant in your own setting.

Validity of estimate of measure of effectiveness
The estimate of effectiveness was based on a single-centre, prospective RCT. The study design was appropriate for the study question. The authors stated that, although only a single centre was used, the referral of patients from the whole south east of the UK and the use of three surgeons trained in different centres mean that the results should be generalisable to the whole of the UK. However, the study included some patients who were not considered appropriate for randomisation to urokinase. The patient groups were shown to be comparable at analysis. The analysis of
effectiveness was handled credibly and was conducted on an intention to treat basis.

Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit. The analysis was therefore a cost-consequences study.

Validity of estimate of costs
The authors did not state the perspective of the analysis, but it appears that a hospital perspective has been used. In the study setting, CT was routinely requested before primary VATS but not for patients in the urokinase arm. The sensitivity of the results to the exclusion of CT costs was examined. The unit costs were reported but quantities used in the study were not, which will limit the generalisability of the authors’ results. An appropriate non-parametric comparison of average costs was performed. The unit costs were derived from the study setting. The authors acknowledged that these may not be generalisable to other settings. A statistical analysis of the prices was not conducted. The authors reported costs in US dollars, hence a currency conversion must have been applied to the UK unit costs; details of this conversion were not provided. The costs were, appropriately, left undiscounted since they were all incurred during a 6-month period. The date to which the price data referred was reported, which will aid any future inflation exercises.

Other issues
The authors compared their findings with those from similar studies in adults and with case series conducted on children. The issue of generalisability to other settings was addressed. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors acknowledged that the small size of the study may reduce confidence in the cost results. In addition, they acknowledged that only costs were considered in the analysis.

Implications of the study
The authors recommended that intrapleural urokinase should be the primary treatment of choice in the treatment of uncomplicated empyemas in children. They made no recommendations for further research.

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