Coagulation disorders induced by L-asparaginase: correction with and without fresh-frozen plasma


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 intervention health technology was the use of heat-inactivated concentrates of fibrinogen and antithrombin III and low-dose heparin during L-asparaginase therapy in patients with de novo acute lymphoblastic leukaemia. L-asparaginase is a potent inhibitor of protein synthesis that may cause deficiencies in several haemostatic proteins, including fibrinogen and antithrombin III with consequent haemorrhagic or thrombo-embolic complications.

Type of intervention
Treatment; secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of patients with de novo acute lymphoblastic leukaemia who received 5,000 U/m^2^ L-asparaginase for 14 days.

Setting
The study setting was hospital. The economic analysis was carried out in Bonn, Germany.

Dates to which data relate
Effectiveness and resource use data for the intervention group were collected between June 1991 and March 1994. The corresponding period for the control group was between January 1990 and May 1991. The price year was 1994.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.

Link between effectiveness and cost data
Costing appears to have been conducted both prospectively (for the intervention group) and retrospectively (for the control group) on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were not used to determine the sample size. The study sample consisted of thirteen patients with de novo acute lymphoblastic leukaemia who received 5,000 U/m^2^ L-asparaginase for 14 days. Eight patients were substituted with fibrinogen and antithrombin III (group A), and 5 patients with fresh-frozen plasma and antithrombin III (group B). Three patients in group A were excluded, as they could not complete L-asparaginase therapy due to sepsis or
involvement of the central nervous system.

Study design
The study design was not defined but appears to have been a non-randomized study with historical controls. The study was carried out in a single centre. The duration of follow-up was not explicitly specified. There was no loss to follow-up, except for the three patients who were excluded from group A. According to the German multicentre trial for acute lymphoblastic leukaemia (ALL), all patients received prednisolone 3x20 mg/m^2 p.o. (day 1-28); vincristine 2 mg i.v. (day 1, 8, 15, 22); daunorubicin 45 mg/m^2 i.v. (day 1, 8, 15, 22); methotrexate 15 mg intrathecal (day 1); and L-asparaginase 5,000 U/m^2 (day 15-28). Patients in group A received 2g fibrinogen/day when plasma levels were between 0.5 and 0.8 g/l and 4g fibrinogen/day when plasma levels were below 0.5 g/l. Antithrombin III was substituted when plasma activity was below 65%. Patients received a 30min bolus infusion of 10 units per litre of the calculated plasma volume for each percent antithrombin III activity below 80% followed by a continuous infusion of 10% of this dose per hour for 16 hours. The effect of this substitution therapy was examined by coagulation analysis, and the antithrombin III dosage was adjusted as described above, corresponding to the daily determined antithrombin III activity. Patients in group B received between 2 and 6 units of fresh-frozen plasma when antithrombin III activity or fibrinogen levels were below 65% or 0.8 g/l, respectively. If transfusion of fresh-frozen plasma did not result in an adequate rise of antithrombin III activity, therapy was complemented by antithrombin III concentrates. These substitution regimens for fibrinogen and antithrombin III, and daily coagulation analyses were continued until after the end of L-asparaginase infusion (day 28), the antithrombin III activity was above 80% or the fibrinogen plasma level was above 0.8 g/l. Starting one day prior to therapy with L-asparaginase, all patients received 100-500U/h heparin as continuous infusion when platelets were above 50 G/l.

Analysis of effectiveness
The principle (intention to treat or treatment completers only) used in the analysis of effectiveness was not explicitly specified, but, given the exclusion of three patients in group A, it appears to have been treatment completers only.

Regarding the clinical outcome measures, the following coagulation parameters (normal ranges in brackets) were determined at least daily using standard methods until normalisation was achieved: prothrombin time (range: 70 - 130%), thrombin time (range: 13 - 15 s), activated partial thromboplastin time (aPTT) (range: 28 - 35 s), reptilase time (range: 17 - 19 s), fibrinogen (range: 2.0 - 4.0 g/l), antithrombin III activity (range: 70 - 120%), coagulation factors II, V, VII, X (range: 70 - 120%).

Antithrombin III activity was determined by a chromogenic assay and fibrinogen according to Clauss. In addition, a daily platelet count (150-350 G/l) was performed, using an electronic particle counter or manual enumerating when the platelet concentration was less than 30 G/l. Comparability of the patients in terms of baseline characteristics was not addressed.

Effectiveness results
The effectiveness results were as follows:

In all 13 patients median plasma levels of fibrinogen and antithrombin III decreased within 7 days after initiation of L-asparaginase treatment to 0.087 g/l (range: 0.055 - 0.303 g/l) and 62% (range: 43 - 69%), respectively. Appropriate substitution by both regimens prevented a further decrease of fibrinogen and antithrombin III.

Group A received a median total of 13,350U antithrombin III (range: 5,000 - 23,800U) and 4,000 mg of fibrinogen (range: 2,500 - 15,000 mg), group B received 3,420 ml (range: 1,140 - 6,270 ml) of fresh-frozen plasma and 8,500U (range: 2,500 - 15,000 U) antithrombin III, (p=0.107 for the administration of antithrombin III).

Despite the different replacement regimes, no significant differences in fibrinogen plasma levels or antithrombin III activities were found between the two groups.

Among both groups a moderate prolongation of the reptilase time from baseline values of 17.5 (range: 16.3 - 19.8 s) to median peak values of 23.7 (range: 22.5 - 27.8 s) on day 12 of therapy could be observed, (p=0.594 compared to...
baseline values).

As a result of heparin treatment, the aPTT increased from 28.5 s (range: 21.9 - 39.7 s) to a peak value of 45.6 s (range 36.0- 98.6 s) on day 3 after the end of L-asparaginase therapy, (p=0.289 compared to baseline values).

Other coagulation parameters did not reveal significant changes. In particular, there were no significant differences between the groups.

One thrombo-embolic event occurred; this patient had not received heparin due to thrombocytopenia (platelet count 20 G/l). On day 5 his antithrombin III activity was 59% and he received 1,500 U antithrombin III over 16 hours. On day 7 his platelet count was 20 G/l, aPTT 35.2 s, fibrinogen 3.03 g/l, and antithrombin III activity 68%. At this time he experienced a mild pulmonary embolism documented by a pulmonary perfusion and ventilation scan. The source of the embolus could not be found. After this event the patient received antithrombin III (15,66 U in 13 days), and low-dose heparin infusion (100 U/h) was initiated despite his thrombocytopenia. Following this treatment the patient recovered completely.

**Clinical conclusions**
Following an adjusted substitution regime based on a day-to-day laboratory evaluation of standard coagulation parameters, no differences in plasma levels of antithrombin III activity and fibrinogen levels were found between the two groups. The results support the authors’ contention that transfusion of fresh-frozen plasma can be abandoned in the treatment of L-asparaginase-induced coagulation disorders.

**Measure of benefits used in the economic analysis**
No summary benefit measure was identified in the economic analysis, and only separate clinical outcomes were reported (see effectiveness results above).

**Direct costs**
Costs were not discounted due to the short time frame of the cost analysis. Resource use and cost profiles were not reported separately. The cost analysis covered the costs associated with drugs. The perspective adopted in the cost analysis was not explicitly specified. Drug costs were calculated according to the September 1994 purchase prices (VAT not included).

**Statistical analysis of costs**
For statistical comparisons the two-sided Mann-Whitney-Wilcoxon U test was used.

**Indirect Costs**
Indirect costs were not included.

**Currency**
German marks (DM). No conversion was made to any other widely used currencies.

**Sensitivity analysis**
No sensitivity analysis was conducted.

**Estimated benefits used in the economic analysis**
See effectiveness results above.
Cost results
Median total drug costs did not differ significantly between group A: DM5,083 (3,060-10,472), and group B: DM4,668 (2,184-7,035), (p=0.380).

Synthesis of costs and benefits
Not applicable.

Authors' conclusions
The use of fibrinogen and antithrombin III can replace fresh-frozen plasma during L-asparaginase therapy without increasing the cost of treatment.

CRD COMMENTARY - Selection of comparators
A justification was given for the choice of the comparator. Fresh-frozen plasma has been used to prevent complications of therapy with L-asparaginase. You, as a database user, should consider whether this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results can not be reasonably assured due to the non-randomised nature of the study design, and the small sample size. Furthermore, the comparability of the two study groups was not addressed and the possibility of confounding variables affecting the effectiveness results was not investigated. These shortcomings may, however, be justifiable given the rarity of the disease or the technical impossibility of having a large enough sample in a specific time frame. In view of the lack of a clear set of inclusion/exclusion criteria, it is hard to judge whether the study sample was representative of the study population.

Validity of estimate of measure of benefit
No summary benefit measure was identified in the economic study, and as a result, the study was of cost-consequences design.

Validity of estimate of costs
This study lacked a systematic and comprehensive evaluation of the resources involved in the treatment of patients. It also lacked information on the perspective adopted in the cost analysis and the possibility of indirect costs accruing to the parties involved in the treatment. However, the price year was given and statistical analysis was performed on the cost outcomes.

Other issues
Given the limitations the study design, and the lack of sensitivity analysis, the study results may need to be treated with some degree of caution. The issue of generalisability to other settings or countries was not addressed, although appropriate and comprehensive comparisons were made with other studies. The degree to which the study sample was representative of the study population was not discussed in the authors' comments.

Implications of the study
With regard to the apparent inherent difficulty of the studies conducted in this context in achieving a statistically robust sample size (all of the studies reported from the literature had small sample sizes), it may be necessary to carry out a multi-centre or multinational study to validate these results.

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