Comparison of outcome in patients with cirrhosis and ascites following treatment with albumin or a synthetic colloid: a randomised controlled pilot 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
Two treatments for patients with cirrhosis and ascites were examined, albumin and synthetic colloid (SC). Albumin patients were infused with 20% human albumin, while SC patients were infused with 3.5% polygeline.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with cirrhosis and ascites who needed to receive a plasma expander for at least one of three indications: ascites removal by paracentesis, renal impairment and marked hyponatraemia. The patients had to be aged between 18 and 74 years. Other inclusion criteria were no history of allergy to albumin or gelatins, asthma, coronary heart disease, cardiac failure, respiratory disease or hepatocellular carcinoma and serum potassium < 6 mmol/L. The exclusion criteria were:
- septic shock, spontaneous bacterial peritonitis, gastrointestinal bleeding or dehydration within the previous 2 weeks;
- therapeutic paracentesis within the last week;
- serum creatinine 42.49 mg/dL (220 mmol/L);
- treatment with non-steroidal anti-inflammatory drugs, aminoglycoside antibiotics, vasopressin analogues, somatostatin, or its analogues;
- the presence of other diseases that could affect short-term prognosis;
- the presence of a portosystemic intrahepatic or peritoneovenous shunt; and
- liver transplantation scheduled within the next 3 months.

Setting
The setting was a hospital. The economic study was carried out in France.

Dates to which data relate
The patients enrolled to derive the effectiveness and resource use data were contacted between May 2000 and June 2001. The price year was 2002.
**Source of effectiveness data**
The effectiveness evidence was derived from a single study.

**Link between effectiveness and cost data**
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness analysis.

**Study sample**
Power calculations were performed on the basis of a published study. These suggested that a sample size of 325 patients per group was needed for the composite item was in order to detect a difference of 10% between the two groups (alpha 5%; beta 10%). However, the study was prematurely discontinued because of safety concerns about bovine-derived products that emerged during the study period. Of the 81 patients initially identified, 3 untreated patients were excluded. Thus, 78 patients were included in the safety population, 34 in the albumin group and 44 in the polygeline group. A further 10 patients were excluded for eligibility violations or because no post-treatment data were available. Thus, 68 patients were included in the efficacy population, 30 (87% men) in the albumin group and 38 (79% men) in the polygeline group. The mean age of the patient was 54 (+/- 9) years in the albumin group and 56 (+/- 8) years in the polygeline group.

**Study design**
This was a prospective, double-blind, randomised clinical trial that was carried out in 18 university teaching hospitals in France. Randomisation was based on random numbers in a 1:1 ratio. It was performed using stratification on the centres and marked hyponatraemia or renal impairment factors. The units of albumin and polygeline were placed in identical carton boxes to mask the contents from investigators and patients. Only designated nurses were aware of the allocated treatment, in order to regulate the flow to obtain the same time of infusion per unit of colloid. The length of follow-up was 6 months. Data were collected at each scheduled visit (2, 4 and 6 months) or during any hospitalisation that occurred between two scheduled visits. As reported above, 13 patients were excluded from the final analysis. A further patient who was treated with albumin was excluded from the primary end point analysis.

**Analysis of effectiveness**
The primary end points were a composite of renal impairment and marked hyponatraemia after fluid loading; and survival. However, when the study was interrupted, the new primary end point was the occurrence of a first liver-related complication such as death, episode of recurrent ascites requiring paracentesis, renal impairment, hyponatraemia, bacterial infection, encephalopathy, portal hypertensive bleeding, and any other complication related to cirrhosis. The secondary outcome measures were:

- occurrence of each first liver-related complication;
- first occurrence of renal impairment or hyponatremia;
- incidence of liver-related complications;
- incidence of recurrent ascites;
- total number of fluid-loading sessions and total amount of colloid units administered;
- unblinded colloid administration;
- treatment with a peritoneovenous shunt, transjugular intrahepatic portosystemic shunting, administration of a vasopressin analogue, somatostatin or an analogue, or liver transplantation; and
- safety.

Efficacy end points were only assessed during the treatment period with the assigned colloid (from the first
administration to the last follow-up visit, death, trial discontinuation, first unblinded colloid administration, dropout, or loss to follow-up). The study groups were comparable at baseline in terms of the clinical and laboratory values.

**Effectiveness results**

The proportion of patients who developed at least one liver-related complication was 83% in the albumin group and 84% in the polygeline group, \( p=0.485 \).

The median time to first complication was not significantly longer in the albumin group than in the polygeline group (20 versus 7 days; \( p=0.086 \)).

The risk for developing a liver-related complication was not significantly higher in the polygeline group than in the albumin group (hazard ratio 1.56, 95% confidence interval, CI: 0.92 to 2.64; \( p=0.098 \)).

When the excluded patient was taken into account, there was a significant difference between the two treatment groups for time to first complication, \( (p=0.044) \), with a similar risk (hazard ratio 1.68, 95% CI: 0.99 to 2.85; \( p=0.053 \)).

Twenty-one (70%) patients in the albumin group and 31 (82%) in the polygeline group had at least one episode of recurrent ascites.

The total number of liver-related complications adjusted to a 100-day period was significantly lower in the albumin group (absolute difference -5.3, 95% CI: -10.0 to -0.6; \( p=0.018 \)).

For recurrent ascites, the total number was also significantly lower in the albumin group (absolute difference -3.7, 95% CI: -6.7 to -0.7; \( p=0.011 \)).

The total number of fluid-loading sessions was significantly lower in the albumin group (absolute difference -6.7, 95% CI: -12 to -1.3; \( p=0.010 \)).

The differences in other clinical outcomes did not reach statistical significance.

In terms of safety, two patients in the albumin group had a non-serious adverse event related to the assigned colloid, while only one serious adverse event occurred in a patient in the polygeline group.

**Clinical conclusions**

The effectiveness analysis showed that albumin was more effective in preventing liver-related complications than SC in patients with cirrhosis and ascites.

**Measure of benefits used in the economic analysis**

The health outcomes were left disaggregated and no summary benefit measure was used in the economic evaluation. In effect, a cost-consequences analysis was performed.

**Direct costs**

The analysis of the costs took the perspective of the hospital. It included the direct medical costs associated with the management of cirrhosis and ascites (protocol-driven procedures were excluded). The costs recorded were for inpatient and outpatient admissions in the hepatology ward, type and volume of plasma expander, number of days of hospitalisation in other hospital wards, and clinic visits to hospital physicians. The unit costs and the quantities of resources used were not presented separately, although some unit costs were reported. Resource use was estimated using data derived from the sample of patients included in the effectiveness study. The costs were estimated using current tariffs for procedures (imaging, biological testing, endoscopy, surgery) from the Assistance Publique-Hopitaux de Paris accounting system for per diem hospital costs (excluding procedures) and from French public market prices for costs of plasma expanders. Discounting was not relevant as the costs were incurred during a short timeframe. The price year was 2002.
Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the economic evaluation.

Currency
Euros (EUR).

Sensitivity analysis
Sensitivity analyses were not performed.

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

Cost results
The total median cost adjusted to a 30-day period was EUR 1,915 in the albumin group and EUR 4,612 in the polygeline group, (p=0.004).

Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant since a cost-consequences analysis was carried out.

Authors’ conclusions
Human albumin was more effective than synthetic colloid (SC) in preventing liver-related complications in patients with cirrhosis and ascites, thus resulting in decreased hospital costs in France.

CRD COMMENTARY - Selection of comparators
The authors provided a clear justification for the choice of the comparators. You should decide whether they are valid interventions in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were estimated using a clinical trial, which was appropriate for the study question. In general, the use of a double-blind, randomised clinical trial ensures a high internal validity. However, the trial was interrupted due to safety concerns, and the power calculations that were initially performed were rendered irrelevant. In effect, a lower number of patients than initially required was recruited and the authors stated that their analysis should therefore be considered as a pilot study. Moreover, different clinical outcomes were used in the effectiveness analysis. Some patients were excluded from the analysis and the reasons for these exclusions were provided. The strengths of the analysis were the multi-centre design and the baseline comparability of the study groups. The authors noted that the period during which patients received the assigned treatment was longer in the albumin group, thus the differences in outcome would probably have been more marked if the duration had been similar in the two groups.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted. Please refer to the comments in the 'Validity of estimate of measure of effectiveness' field (above).
Validity of estimate of costs
The analysis undertaken was consistent with the stated study perspective. A detailed breakdown of the cost items was not given since only a list of main cost categories was provided. Further, few unit costs were presented and there was no information on resource consumption. This limits the possibility of replicating the analysis in other settings. Statistical analyses of the costs were not carried out. The price year was reported, which will facilitate reflation exercises in other time periods. The impact of variations in cost estimates was not addressed. The sources of the data were reported for all costs.

Other issues
The authors stated that their findings differed from those reported in other published studies, and discussed some of the possible explanations for these differences. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not carried out. This reduces the external validity of the analysis. The study referred to patients with cirrhosis and ascites and this was reflected in the authors' conclusions.

Implications of the study
The study results support the use of albumin for the treatment of patients with cirrhosis and ascites. The authors noted that the current results should be corroborated in an adequately powered clinical trial.

Source of funding
Supported by the Laboratoires Francais du Fractionement et des Biotechnologies.

Bibliographic details

PubMedID
16420509

DOI
10.1111/j.1478-3231.2005.01188.x

Other publications of related interest


Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Albumins /adverse effects /therapeutic use; Ascites /pathology /therapy; Confidence Intervals; Dose-Response Relationship, Drug; Drug Administration Schedule; Female; Follow-Up Studies; Humans; Liver Cirrhosis /drug therapy /pathology; Liver Function Tests; Male; Middle Aged; Paracentesis /methods; Pilot Projects; Polygeline /adverse effects /therapeutic use; Probability; Reference Values; Risk Assessment; Severity of Illness Index; Statistics, Nonparametric; Treatment Outcome
AccessionNumber
22006000849

Date bibliographic record published
31/08/2006

Date abstract record published
31/08/2006