Cost-effectiveness of N-butyl-2-cyanoacrylate (histoacryl) glue injections versus transjugular intrahepatic portosystemic shunt in the management of acute gastric variceal bleeding

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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 approaches for the treatment of bleeding gastric varices were examined. These were transjugular intrahepatic portosystemic shunt (TIPS), using either Wallstents or Memotherm stents, and the endoscopic injection of N-butyl-2-cyanoacrylate glue (Histoacryl).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with confirmed bleeding gastric varices on upper gastrointestinal endoscopy. This was defined as evidence of visible or active bleeding at the time of endoscopy, the presence of fresh clot on varices, or the presence of "red spots" on gastric varices with fresh or altered blood in the stomach without any other possible source of bleeding.

Setting
The setting was secondary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness and resource use data were gathered from January 1995 to December 1999 for the TIPS group, and from January 2000 to October 2001 for the cyanoacrylate glue group. The costs were estimated in the financial year 2000/2001.

Source of effectiveness data
The effectiveness evidence was derived from a retrospective single study.

Link between effectiveness and cost data
The costing was carried out retrospectively on the same sample of patients as that included in the effectiveness study.

Study sample
Power calculations to determine the sample size were not reported. Twenty patients who had undergone TIPS insertion were identified between January 1995 and December 1999. Their mean age was 52 (+/- 3) years and 13 were men.
Twenty-three patients who had received cyanoacrylate glue injections were identified between January 2000 and October 2001. Their mean age was 55 (+/- 3) years and 15 were men. It was unclear whether any patients were excluded from the initial study sample for any reason.

**Study design**

This was a retrospective comparative study with a historical control, which was carried out in a single centre. Follow-up was carried out until the time of liver transplantation or death. The median follow-up was 12 months (range: 0.1 - 60) in the TIPS group and 6 months (range: 0.25 - 20) in the cyanoacrylate glue group. No loss to follow-up was observed.

**Analysis of effectiveness**

The analysis of the clinical study conducted on an intention to treat basis. All the patients included in the initial study sample were considered in the analysis of effectiveness. The health outcomes used in the analysis were characteristics of the interventions, length of inpatient stay, mortality rates and rebleeding rates. The intervention characteristics considered were times of treatment, procedures performed and complications. The rates of survival and rebleeding were calculated using the Kaplan-Meier approach. The two groups were comparable at baseline in terms of their demographics, clinical characteristics and disease severity. However, on the day of admission, there was a significantly higher, mean serum haemoglobin in the cyanoacrylate glue group (8.7 +/- 0.46 g/dL) than in the TIPS group (7.6 +/- 0.35 g/dL), (p=0.038).

**Effectiveness results**

In the TIPS group, 15 of the 20 patients had the procedure performed within 24 hours of the haemorrhage and 90% of stent insertions were successful.

The TIPS stenosis rate was 15% (3 patients) over the 6-month follow-up.

In the cyanoacrylate glue group, 20 patients received glue injection within 24 hours. There were 3 (+/- 1.5) endoscopies and 2 (+/- 1) injections per patient with a 96% initial haemostasis over the 6-month period.

In terms of complications, there were 2 cases of pulmonary oedema and 2 cases of severe encephalopathy in the TIPS group. There was one case of (glue) pulmonary embolism and one occlusion of the endoscope front lens, which required repair, in the cyanoacrylate glue group.

The early rebleeding rate (defined as less than 30 days) was 30% in the cyanoacrylate glue group and 15% in the TIPS group, (p=0.005).

The overall rebleeding rate during the median follow-up period was 35% in the cyanoacrylate glue group versus 20% in the TIPS group, (p=0.005).

The inpatient stay was 18 (+/- 2) days in the TIPS group and 13 (+/- 1) days in the cyanoacrylate glue group, (p=0.05).

There was no statistically significant difference in survival rates between the two groups.

**Clinical conclusions**

The effectiveness analysis showed that there were fewer complications in the cyanoacrylate glue group than in the TIPS group and hospital stay was shorter. However, the rebleeding rates were significantly higher than in the TIPS group. No statistically significant difference in mortality rates was observed.

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

The health outcomes were left disaggregated and no summary benefit measure was used in the economic analysis. In effect, a cost-consequences analysis was carried out.
Direct costs
Discounting was not relevant since the costs were incurred during 6 months. The unit costs were reported separately from the resource quantities. The health services included in the economic evaluation were TIPS, endoscopic cyanoacrylate injection, inpatient stay in the liver ward, general medical ward or intensive care unit, diagnostic procedures and surgery. The cost of TIPS included all equipment, medical and radiological staff time, medication and an allotted 2 hours for general anaesthesia. The cost of endoscopic cyanoacrylate injection covered all equipment, medical and nursing staff time, and endoscopy unit sessions. The cost of inpatient stay included nursing staff, administrative and clerical staff, consumables, equipment, overheads and capital costs. The diagnostic procedures considered were ultrasound scan and Doppler. The costs of surgery were for mesocaval shunt, splenectomy and gastric devascularisation. The cost/resource boundary of the NHS was adopted.

The quantities of resources used were derived from actual data related to the patients involved in the effectiveness study. It was assumed that there would be no differences between the two groups in ward staff fee, routine blood investigations, standard vasoactive drugs and basic radiology. The analysis of the costs was carried out on an intention to treat basis. Institutional charges were used as estimates of the costs. The estimation of the costs was based on the Healthcare Resource Grouping codes for the UK NHS at the study hospital for the financial year April 2000 to March 2001.

Statistical analysis of costs
The Mann-Whitney U test was used to test the statistical significance of differences in the costs between the groups.

Indirect Costs
The indirect costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analyses were performed.

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

Cost results
Over the 6 postoperative months, the median costs were $4,138 (interquartile range: 3,009 - $8,290) in the cyanoacrylate glue group and $11,906 (interquartile range: 8,200 - 16,770) in the TIPS group, (p<0.0001). The main cost drivers were the TIPS procedure and the increased length of hospital stay.

Synthesis of costs and benefits
The costs and benefits were not combined as a cost-consequences analysis was carried out.

Authors’ conclusions
Cyanoacrylate glue injection proved to be a far less expensive treatment for bleeding gastric varices than transjugular intrahepatic portosystemic shunt (TIPS) insertion. Survival, morbidity and complication were comparable between the two groups of patients. The authors concluded that cyanoacrylate glue injection was more cost-effective than TIPS in the treatment of acute gastric variceal bleeding.
CRD COMMENTARY - Selection of comparators
The authors provided a justification for the choice of the procedures under evaluation. TIPS was the recommended treatment for patients with bleeding gastric varices, while endoscopic treatment with cyanoacrylate glue was reported to be an effective option. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The basis of the analysis of effectiveness was a retrospective comparative study with a historical control. This represents a weak source of evidence due to the potential for bias and confounding factors. The authors acknowledged that the level of haemoglobin was different between the groups, but this was not considered a significant confounding factor due to the lack of any difference in haemodynamic parameters or blood product requirement. However, the authors admitted that, as the two groups were not studied concurrently, some changes in treatment patterns, personnel, patient selection criteria and speciality interests might have changed over time, which was likely to affect the results of the analysis. To address this issue, the authors stated that both the inclusion criteria and treatment protocol did not change over the study period. Finally, the main threat to the internal validity of the analysis was the small group of patients considered in each group and the lack of power calculations to determine an appropriate sample size.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because a cost-consequences analysis was conducted.

Validity of estimate of costs
The perspective of the study was implicitly stated and it appears that all the relevant categories of costs have been included. The indirect costs, such as productivity losses, were not considered in the economic analysis. The authors stated that the indirect costs would not have been significantly different between the groups, as the hospitalisation periods were similar. The unit costs for each main category of costs were reported and the source of the cost data was given. The authors noted that institutional charges were used to estimate the economic impact of the procedures under evaluation, and charges might not always reflect true costs. The (financial) price year was reported, which will aid reflation exercises in other settings. Statistical tests of the costs were carried out. The cost estimates were specific to the study setting, but no sensitivity analyses were performed. This limits the transferability of the results to other settings since wide variations in costs may occur in other contexts.

Other issues
The authors made explicit comparisons of their findings with those from published studies to show the similarity of rebleeding rates among patients treated for bleeding gastric varices. The study referred to patients with bleeding gastric varices and this was reflected in the authors’ conclusions. The issue of the generalisability of the study results was not addressed and sensitivity analyses were not performed. Therefore, the external validity of the analysis was low. Caution is required when extrapolating the results of the analysis to other settings because the study reflected treatment patterns at a single institution. The authors discussed some strengths and limitations of their analysis.

Implications of the study
The authors suggested that cyanoacrylate glue injection should be used as first-line therapy for patients with bleeding gastric varices, while TIPS should be reserved for cases in which glue therapy is likely to fail. Although the results of the study confirmed and supported prior research, the authors stressed that a prospective, randomised controlled trial with long-term follow-up should be carried out to confirm the conclusions of the present economic evaluation.

Source of funding
None stated.

Bibliographic details

PubMedID
14687818

DOI
10.1111/j.1572-0241.2003.08769.x

Indexing Status
Subject indexing assigned by NLM

MeSH
Acute Disease; Cost-Benefit Analysis; Enbucrilate /economics; Esophageal and Gastric Varices /complications; Female; Gastrointestinal Hemorrhage /prevention & control; Humans; Injections; Male; Middle Aged; Portasystemic Shunt, Transjugular Intrahepatic /economics; Recurrence; Retrospective Studies; Statistics, Nonparametric

AccessionNumber
22004000119

Date bibliographic record published
30/09/2004

Date abstract record published
30/09/2004