Treatment of achalasia: botulinum toxin injection vs. pneumatic balloon dilation. A prospective study with long-term follow-up

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 two endoscopic treatment options, botulinum toxin (BTX) injection and pneumatic balloon dilation for the treatment of achalasia. Balloon dilation was performed in accordance with a standardised protocol, using a polyurethane balloon (Rigiflex, Boston Scientific, Waterdown, USA) with 3.5 cm for the first dilation, if this was not successful a second dilation, balloon size 4cm, was carried out. The BTX used initially was Botulinum toxin A in the form of Dysport (Proton Products Ltd, England) in a dosage of 100 IE (20 IE/ml). If necessary, the dosage then increased to 300 IE (60 IE/ml), and subsequently when required changed to Botox (Merz company, Germany) in a dosage of 100 IE dissolved in 5ml.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients with achalasia referred to the Technical University of Munich. Patients included had the characteristics, clinical, radiographic and manometric features of achalasia. The following exclusion criteria were applied: presence of esophageal varices, peptic complications and extraesophageal malignant disease, and secondary achalasia.

Setting
The setting was secondary care. The economic study was conducted in Munich, Germany.

Dates to which data relate
Dates of effectiveness evidence: patients were recruited between 1994 and 1996, evidence was collected for 4 years after initial treatment. No dates were given for the resource use data. No price year was given.

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

Link between effectiveness and cost data
The costing was carried out on the same sample as that used in the effectiveness analysis, and it appears to have been carried out retrospectively.
Study sample
No power calculations were reported. There was no sample selection; all patients who satisfied the inclusion criteria with achalasia were included. There were 37 patients in the study, 23 received BTX injections as their first treatment and 14 received balloon dilation as their first treatment. If patients did not experience clinical remission or had recurrent clinical symptoms they were offered the choice of receiving either of the treatment modalities again.

Study design
This appeared to be a non-randomised trial with concurrent controls carried out in a single centre. The follow-up was 4 years after initial treatment. After 2 years 3 BTX patients were lost to follow-up, no loss to follow-up was reported for the dilation patients.

Analysis of effectiveness
The clinical study was based on intention to treat. The primary health outcomes used were the following: a global symptom score ranging from 0 (no symptoms) to 10 (intolerable); occurrences of regurgitation, dysphagia and chest pain. These occurrences were scored as 0 never, 1 occasionally, 2 daily, 3 with each meal or constantly.

Lower esophageal sphincter pressure (LESP) was recorded and swallow induced relaxation was tested.

Patients were weighed before treatment and 6 months after treatment. The symptom free interval was measured, defined as the time until the next treatment was required or until the symptom score was greater than 6.

Clinical remission was defined as a global symptom score of less than or equal to 3.

The two groups’ baseline characteristics in terms of age, gender, clinical symptoms, body weight and LESP were given but no statistical methods were used to demonstrate comparability.

Effectiveness results
The authors gave effectiveness results for groups they described as the BTX group and the dilation group.

Of the original 23 patients in the BTX group, only 7 received 1 BTX treatment, 6 received more than 1 BTX treatment and 10 also received non-BTX treatments. Therefore only 13 patients received BTX only treatment. Similarly only 8 of the 14 original patients in the dilation group received dilation only treatments.

However, the authors counted patients in either the BTX or dilation group if they received one of the treatments under consideration. This led to a higher number of patients in each group as many received more than one intervention. In the final analysis the BTX group contained 29 patients and the dilation group contained 23.

The global clinical score pre-treatment 8.2 +/- 1.3 decreased to 2.9 +/- 1.6, (p<0.001) in the BTX group and 8.3 +/- 1.1 to 2.3 +/- 1.9, (p<0.001) in the dilation group;

additionally, in the individual symptom scores, regurgitation decreased from 1.9 +/- 0.8 to 0.6 +/- 1.1 for the BTX group and from 2.8 +/- 0.4 to 0.5 +/- 0.6, (p<0.01) in the dilation group.

Dysphagia decreased from 2.5 +/- 0.6 to 1.1 +/- 0.6, (p<0.01) in the BTX group and from 2.6 +/- 0.5 to 0.5 +/- 0.6, (p<0.01) in the dilation group.

Chest pain decreased from 1.6 +/- 1.1 to 0.8 +/- 0.8, (p<0.01) in the BTX group and from 1.7 +/- 1.1 to 1.0 +/- 0.9, (p<0.01) in the dilation group.

Both groups showed only a trend towards increased body weight, increasing from 71.1 +/- 17.6kg to 73.3 +/- 15.8kg in the BTX group and from 73.3 +/- 15.8kg to 76.6 +/- 13.2kg in the dilation group.

When the treatment choice was successful the symptomatic response was accompanied by a decrease of lower
esophageal sphincter pressure, in the BTX 37.6+/−12.6mmHg to 20.1+/−5.2mmHg at 1 week after injection, (p<0.001) and in the dilation group 36.6+/−13.2mmHg to 16.6+/−2.3mmHg, at one week after dilation, (p<0.001).

2 years after the initial treatment 7 of the 23 (30%) in the BTX group and 52.2% of the dilation patients were in remission in an intention to treat analysis. At 26 months the figure in the dilation group had decreased to 30.5%. For the dilation group the results were also reported only for patients in whom dilation had been successful.

4 years after the initial treatment none of the BTX patients and 30.5% of the dilation patients were in remission.

The median number of symptom free days was 357 for the BTX group and 708 for the dilation group, (p<0.05).

The actuarial analysis was carried out on four groups of patients. BTX initial single treatment, BTX retreatment, initial single dilation treatment and dilation retreatment. The symptom free period of time was then compared between the groups.

The results for symptom free days were not given according to the type of initial treatment.

After 1 year there was no significant difference between the 4 groups.

After 24 months a single dilation was significantly superior to a single BTX.

After 36 months this superiority gap increased.

No serious side-effects were reported for BTX, chest pain lasting up to 4 hours being the worst effect. Similarly, for dilation no serious side-effects were reported, chest pain lasting up to 6 hours being reported and 2 mucosal tears were detected.

**Clinical conclusions**

The authors concluded that dilation was superior to BTX for periods of longer than one year and therefore BTX can only be recommended for a limited category of patients: where dilation has already failed, where there is a perceived risk associated with dilation or where patients prefer BTX injection. They suggested that older patients might benefit from BTX but they did not provide evidence from their own study to support that suggestion.

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

No summary measure of benefit was used as a cost-consequences analysis was carried out.

**Direct costs**

No discounting was carried out even though costs were incurred over more than 2 years. The actual costs of treating the patients over different time intervals were given, but there was no breakdown of costs into prices and quantities. There was a breakdown of costs into prices and quantities for 1 round of BTX injections, 1 balloon dilation with 6-hour surveillance in outpatients and one balloon dilation with 1 day in outpatients. The following costs were given: endoscopy, single-use guide wire, balloon, dilation, Botulinum toxin, injection needle, esophagram, surveillance cost, inpatient hospital cost. The cost of each kind of treatment was given rather than the actual costs of treating the patients in the study. No price year was given. The resource use data were taken from the study. The prices were taken from DKG-NT (Deutsche Krankenhausgesellschaft-Tarife)(Association of German hospitals fees) catalogue and the EBM number (einheitlicher Bewertungsmassstab) (the universal standard of value) for medical procedures.

**Statistical analysis of costs**

No statistical analysis of costs was performed.

**Indirect Costs**
No indirect costs were calculated. This is appropriate given the perspective adopted in the study.

**Currency**
German marks (DM).

**Sensitivity analysis**
No sensitivity analysis was performed.

**Estimated benefits used in the economic analysis**
No summary measure of benefit was calculated; please refer to the effectiveness results above.

**Cost results**
Cost of treatment in BTX group 4 years after treatment started was DM 2,716.85 +/-1172.53.

Cost of dilation, (on an inpatient basis) 4 years after treatment started was DM 2,663.60 +/-1835.00.

The cost per symptom free day per treatment in the BTX group was DM 1.32 and in the dilation group DM 1.24. The differences in cost results between the two groups were not found to be statistically significant.

Costs of adverse effects were dealt with in the costing.

**Synthesis of costs and benefits**
Not relevant.

**Authors' conclusions**
The authors concluded that balloon dilation is more effective than BTX for periods of more than 1 year after treatment. They stated that there is no statistically significant cost difference between the BTX injection and the two balloon dilation treatments in terms of costs 4 years after treatment commenced though the costs of dilation were lower than those of BTX. When a shorter time span is considered, although there is no statistically significant difference between the two treatments, BTX is cheaper than dilation up to two years after treatment starts. Thus when patients have a short life expectancy BTX could offer a cost advantage over dilation.

**CRD COMMENTARY - Selection of comparators**
The choice of comparator, BTX injections as an alternative treatment to dilation for achalasia was justified as it provides an alternative to the gold standard treatment of dilation, which is not suitable for all patients. A long-term study was justified as previous studies have suggested that the beneficial effects of BTX decline over time. You, as a user of this database should decide if the comparator chosen is valid in your setting.

**Validity of estimate of measure of effectiveness**
The source of the effectiveness data was a single study however the study design may not have been appropriate for the hypothesis. The choice of initial treatment was based on the patient's preference and seven patients were considered unsuitable for dilation. After initial treatment was considered to be insufficient, patients were able to have subsequent treatments again based on their preference. Although some baseline characteristics were given patient groups were not shown to be comparable at analysis.

After the initial treatment had taken place there were no longer two distinct groups of patients receiving different treatments as patients could repeat the same treatment or switch to another treatment. This meant that the numbers
receiving any particular treatment path became smaller and smaller making it unlikely that there would be any statistically significant results. It also meant that it was unclear whether any reliable inferences could be made, as a treatment group defined by the authors contained patients with heterogeneous treatments. It was difficult to relate the text on long-term effectiveness with what the authors described as an actuarial analysis of long-term effectiveness.

The authors' measures of effectiveness could have been improved. They used a measure of clinical remission which was different from that used to measure a symptom free day. They also discussed the fact that patients' perceptions of their symptoms are very subjective for this illness but they did not use any patient centred assessment of their health or quality of life; similarly they did not assess the patients' perception of their experience of the two alternative treatment processes. No statistical analysis was conducted to account for potential biases and confounding factors; hence the internal validity of the study may be weak.

**Validity of estimate of measure of benefit**
No summary measure of benefit was used; the reader is therefore referred to the effectiveness comments above.

**Validity of estimate of costs**
All categories of cost relevant to the perspective adopted were included in the analysis. The authors did not choose a societal perspective and as such did not include indirect costs in the analysis. It is difficult to know how this will have affected the analysis, as one round of dilation takes more time than the BTX injections, but the procedure does not have to be repeated so often. When the costs of one round of each kind of treatment were given, quantities were given separately from prices. But when actual long-term costs were given for each patient group (on the basis of their primary therapy), there was no distinction between prices and quantities. When the authors compared the costs of the two kinds of treatments they decided to use inpatient costs rather than outpatient costs for dilation, however they did not provide any justification for this decision.

**Other issues**
The authors made appropriate comparisons with other studies, but did not address the issue of generalisability to other settings. The authors did not appear to recognise two major drawbacks of their study; the patients were not randomly selected for the treatment they undertook and there was no attempt to ensure that treatment groups were homogeneous in the type of treatment they received. The results of the analysis were reported comprehensively and the final conclusions drawn reflected the results obtained by the authors.

**Implications of the study**
The authors conclude that, for two years after treatment there is no difference in the effectiveness of the two treatments, but that, after two years, dilation becomes more effective than BTX. They also concluded that the costs of dilation become cheaper than those of BTX after two years.

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