Cost-effectiveness of hydroxyurea in sickle cell anemia
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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
The use of hydroxyurea, a cytotoxic agent, to decrease the frequency of painful crises in patients with sickle cell anemia. Patients assigned to hydroxyurea received an initial dose of 15 mg per kilogram of body weight per day, and the dose was increased by 5 mg per kilogram of body weight per day every 12 weeks, unless marrow depression (indicated by a neutrophil count below 2,000 per cubic millimetre, a reticulocyte or platelet count below 80,000 per cubic millimetre, or a haemoglobin level below 4.5 g per decilitre) was present. If marrow depression occurred, treatment was stopped until blood counts recovered. Treatment was then resumed at a dose that was 2.5 mg/kg lower than the dose associated with marrow depression, starting a new 12-week cycle.

Type of intervention
Palliative care and secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
Patients enrolled in the study had sickle cell anemia, were at least 18 years old, had had at least 3 painful crises the previous year and were not chronic users of large amounts of opiate analgesics. Patients known to have sickle cell-beta^+-thalassemia and sickle cell-beta^o-thalassemia were excluded, but those with sickle cell-alpha-thalassemia were included. If patients had received transfusions, hemolysates of their red cells could not contain more than 15% hemoglobin A at the time treatment began. Other reasons for exclusion from the study included pregnancy, known narcotic or regular consumption of more than 30 oxycodone capsules (or the equivalent) every two weeks, participation in a long-term programme of transfusion, concurrent treatment with another potential antisickling agent, pretreatment blood counts that could not be distinguished from levels considered to indicate marrow depression, a history of stroke during the preceding six years, prior hydroxyurea therapy, and the presence of antibody to the human immunodeficiency virus (HIV).

Setting
The setting was a hospital. The economic analysis was carried out in the USA.

Dates to which data relate
Effectiveness and resource use data were taken from the patients enrolled and treated in the Multicentre Study of Hydroxyurea in Sickle Cell Anemia (MSH) between January 1992 and June 1994, the results of which were published in 1995 and 1996. The price year was 1995.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.
Link between effectiveness and cost data
Costing was conducted retrospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were used to determine the sample size. It was reported that the MSH was designed to have an adequate statistical power to detect a meaningful difference in crisis rates, but no power analysis was reported in the paper giving the MSH results (Charache, 1995). 299 patients were randomized to either the placebo group (n=147, mean age 31 years) or to the hydroxyurea group (n=152, mean age 30 years).

Study design
This was a double-blind, randomised, placebo-controlled trial, carried out in 21 sites in the USA and Canada. The mean duration of follow-up was 21 months. Because of the beneficial effects observed the trial was stopped before the planned 24 months of treatment were completed for all patients. About 8% of patients in the MSH discontinued therapy permanently because of various reasons including pregnancy, myelotoxicity, and need for transfusion therapy. Treatment was permanently stopped for medical reasons in 14 patients in the hydroxyurea group and 6 patients in the placebo group: 10 patients or their partners became pregnant and their treatments were stopped. After an initial 4-week run-in period, during which only folic acid tablets were dispensed, the patients were randomly assigned to one of the two study groups. Neither the patients nor the investigators and staff members at the clinical sites were aware of the patients’ treatment assignments. To maintain blinding, the dose of the placebo was adjusted by the data coordinating centre in a similar manner to the hydroxyurea therapy. Treatment assignments could be revealed if knowledge of the assignment would alter a patient’s subsequent medical care. In such cases, the study treatment was stopped, but follow-up of the patients continued. Detailed diagnostic and treatment information was collected for each medical contact with the patient. The medical facilities could include the emergency department, outpatient clinic or physician’s office, or the hospital. Events were validated by medical records and were reviewed by an independent crisis review committee unaware of treatment assignment.

Analysis of effectiveness
The principle used in the analysis of effectiveness was intention to treat. The primary clinical outcome measure was the number of painful sickle cell crises, whether managed in the outpatient or inpatient setting. A painful crisis was defined as a visit to a medical facility that lasted more than 4 hours for acute sickling-related pain, which was treated with a parenteral narcotic. The other outcome measures were times to first and second crisis, the number of patients who had chest syndrome, the number of patients who had transfusions, and adverse effects. The study groups were comparable in terms of baseline demographic and prognostic characteristics.

Effectiveness results
The patients who received hydroxyurea had a statistically significant reduction in the annual rate of crises over 2 years compared to patients who received placebo (median, 2.5 versus 4.5 crises per year, p<0.001).

The median times to the first crisis (3.0 versus 1.5 months, p=0.01) and the second crisis (8.8 versus 4.6 months, p<0.001), were longer with hydroxyurea treatment. Fewer patients assigned to hydroxyurea had chest syndrome (25 versus 51, p<0.001), and fewer underwent transfusions (48 versus 73, p=0.001).

Treatment with hydroxyurea did not cause any important adverse effects.

Clinical conclusions
Hydroxyurea therapy can ameliorate the clinical course of sickle cell anemia in some adults with three or more painful crises per year. Maximal tolerated doses of hydroxyurea may not be necessary to achieve a therapeutic effect. The beneficial effects of hydroxyurea do not become manifest for several months, and its use must be carefully monitored.
The long-term safety of hydroxyurea in patients with sickle cell anemia is uncertain.

**Measure of benefits used in the economic analysis**
No summary benefit measure was used in the economic analysis and as clinical outcomes were left disaggregated, the study should be regarded as a cost-consequences analysis.

**Direct costs**
Costs were not discounted because of the short time frame of the cost analysis. Quantities were not reported separately from the costs (except for the assumed monitoring schedule). Unit costs were reported. The cost analysis covered the costs of crisis hospitalisation (painful crisis, chest syndrome), ambulatory visit, emergency department, opiate analgesics, monitoring (laboratory and clinic visits), transfusion, and hydroxyurea. The perspective adopted in the direct cost analysis was that of the insurer. The authors were able to use the detailed diagnostic and treatment information collected for each medical contact with the patient to assess resources used in the medical care of the patients on both study arms. A monitoring schedule was assumed for a patient starting on hydroxyurea to represent the real clinical practice rather than the trial setting. The cost data were based principally on the costs incurred by patients with sickle cell anemia in Maryland, which was perceived to represent a fair measurement of the actual costs of care. The outpatient visits, laboratory testing, radiology and drug costs were based on national averages. Emergency department costs were based on a single university hospital in Maryland, and were deemed to be the least likely to be generalisable nationally. All costs were adjusted to 1995 prices using the health care component of the Consumer Price Index.

**Statistical analysis of costs**
An average cost was calculated for the patients in each study arm with a 95% confidence interval estimated based on the standard error of the mean. Statistical comparisons of costs were carried out using the nonparametric Wilcoxon rank-sum test.

**Indirect Costs**
Indirect costs were not considered.

**Currency**
US dollars ($).

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

**Estimated benefits used in the economic analysis**
See the effectiveness results reported earlier.

**Cost results**
The mean annual cost was $16,810 (95% CI: $13,350 - $20,270) in the hydroxyurea group and $22,020 (95% CI: $17,340 - $26,710) in the placebo group (p = not significant), culminating in a cost difference of $5,210 (95% CI: -$610 to $11,030). The authors noted that the MSH was not designed to statistically test differences in medical care costs.

**Synthesis of costs and benefits**
Costs and benefits were not combined since the use of hydroxyurea was the dominant strategy.
Authors' conclusions
The analysis of resource utilisation suggests that using hydroxyurea to decrease the frequency of painful crises in patients with sickle cell anemia will result in reductions in the cost of management of crises that more than offset the increased costs associated with the drug and its clinical monitoring. Factors affecting variation in costs and effective sample size prevented the detection of a statistically significant in total costs. With this important caveat, this cost analysis of the MSH data indicates that hydroxyurea is not only effective but that it may also be cost-effective compared to placebo in the prevention of painful crises in sickle cell anemia.

CRD COMMENTARY - Selection of comparators
The strategy of using a placebo was explicitly regarded as the comparator. The authors did not discuss whether this was the standard practice for patients with sickle cell anemia. You, as a user of this database, should determine whether these health technologies are widely used in your own setting.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results is likely to be high given the randomised nature of the study design, the double blinding, the intention to treat analysis and the power calculations performed to justify the sample size (although these were not reported in detail). Furthermore, the study groups were comparable in terms of baseline characteristics. The study sample appears to have been 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 a cost-consequences analysis. It was noted that quality of life, which is affected because of reduced frequency of painful crisis, was not measured in this study.

Validity of estimate of costs
In general, this was a well-conducted cost analysis. Positive features of the cost analysis, likely to have enhanced its validity, were that some details of the methods of cost estimation were given, the price year and perspectives adopted in the study were specified and statistical analyses were performed on cost data. However, the MSH resource use profile was not reported separately, cost analysis was not based on true costs, some bias may have been introduced in the resource use profile due to the retrospective nature of the costing and the effects of alternative procedures on indirect costs were not addressed. Furthermore, no sensitivity analyses were performed to address the robustness of the cost results.

Other issues
The authors’ conclusions appear to be justified given the uncertainties in the data. The issue of generalisability to other countries was not fully and systematically addressed, although the authors did discuss the generalisability to other US states and some comparisons were made with other studies. The degree to which the study sample was representative of the study population was discussed in the authors’ comments. Given the high impact of the treatment on quality of life a cost-utility framework might have been a more fruitful approach in the context in question. It was noted that in actual clinical practice (in comparison with the trial setting), the difference in costs may not be as marked as in the MSH if non-compliance or cessation of therapy is even more frequent.

Implications of the study
The authors noted that if hydroxyurea can prevent development of chronic organ damage, long-term savings may be even greater. Although the authors believe that the study results are supportive of the dominant cost-effectiveness of hydroxyurea therapy, it will require further data on a larger population to make more precise estimates of the costs. Hydroxyurea cannot currently be recommended for children or for adults with sickle cell anemia who average fewer than three crises per year since it has not yet been proven efficacious and safe in these groups. A formal cost-effectiveness analysis remains to be carried out when sufficient data are available around bone marrow transplantation.
as a curative therapy in sickle cell anemia. Over periods of time longer than the 2 years of this trial, it is possible that
differences in the rates of death, stroke, renal failure, or other serious vascular events might emerge between the users
and nonusers of hydroxyurea. These might have implications for the medical care costs associated with hydroxyurea
use.

Source of funding
None stated.

Bibliographic details
American Journal of Hematology 2000; 64(1): 26-31

PubMedID
10815784

Other publications of related interest
Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. Effect of hydroxyurea on the frequency

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Anemia, Sickle Cell /drug therapy /economics; Antisickling Agents /administration & dosage /economics; Cost-
Benefit Analysis; Double-Blind Method; Female; Humans; Hydroxyurea /administration & dosage /economics; Male

AccessionNumber
22000000839

Date bibliographic record published
31/01/2002

Date abstract record published
31/01/2002