Intradermal versus intramuscular hepatitis B re-vaccination in non-responsive chronic dialysis patients: a prospective randomized study with cost-effectiveness evaluation

Fabrizi F, Andrulli S, Bacchini G, Corti M, Locatelli F

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
Re-vaccination of chronic dialysis patients, who had not responded to a reinforced protocol of hepatitis B vaccine.

Type of intervention
Prevention.

Economic study type
Cost-effectiveness analysis.

Study population
Patients undergoing dialysis who have failed to produce antibodies to HBsAg antigen after hepatitis B (HB) vaccination.

Setting
Hospital. The economic study was carried out in Lecco, Italy.

Dates to which data relate
Dates were not explicitly given. A vaccination dialysis programme was begun at the unit in January 1991. After 193 patients had completed a full course of HBV vaccination with a reinforced schedule the present study was begun. The dates of the 2 publications used in the review were 1988 and 1994. Costs were based on prices paid by the medical centre at the time of the single study.

Source of effectiveness data
Evidence for final outcomes was derived from a single study, and, for 2 comparators, from a review.

Link between effectiveness and cost data
Costing was undertaken retrospectively on the same patient sample as that used in the effectiveness study.

Study sample
Of 193 chronic dialysis patients who completed a full course of HBV vaccination (3 x 40micrograms doses of recombinant HB vaccine by intramuscular route) 66 did not show anti-HBs antibody and were classified as non-responders. Of these non-responders, 50 patients, chosen randomly, were included in the study with 25 being assigned to the intra-dermal (id) group and 25 to the intra-muscular (im) group. It was not stated whether power calculations determined the sample size and neither was it reported whether any patients refused to participate or were excluded for any reason.
Study design
Randomised controlled trial. The study was single centred. Patients were allocated to the 2 groups using a table of random numbers. Blinding was not possible in the treatment and is not mentioned in the measurement or interpretation of results. Strategy A treatment continued for 16 weeks and follow up results are given for both strategies for 20 months after that. Reasons for loss to follow up were not given but it seems to have been high.

Analysis of effectiveness
The analysis was based on treatment completers only. Primary health outcomes were the seroconversion rate expressed as a percentage, the proportion of patients who elicited anti-HBs titres (seroprotection) and the levels of anti-HBs expressed as geometric mean titres and 95% confidence intervals. Groups were comparable in age, sex distribution, body weight and underlying nephropathies. There was no statistical difference in the proportion of diabetic patients, the median duration of chronic hemodialysis (HD) treatment or any other clinical characteristics but there was a significant difference in the numbers who had received blood transfusions before the start of the programme.

Effectiveness results
One month after strategy A treatment finished, 100% (25/25) of patients in the id group had developed seroconversion and 48% (12/25) in the im group (p = 0.008). 96% (24/25) showed seroprotection in the id group and 40% (10/25) in the im group (p = 0.001). The levels of anti-HBs expressed as geometric mean titres and 95% confidence intervals were 100 (44-187) for id and 26 (14-52) for im (p = 0.018). Twelve months after treatment finished differences were not significant. 57% (8/14) of patients in the id group had developed seroconversion and 14% (1/7) in the im group (p = 0.158). 59% (7/14) showed seroprotection in the id group and 0% (0/7) in the im group (p=0.072). Twenty months after treatment differences were not significant. 54% (7/13) of patients in the id group had developed seroconversion and 0% (0/7) in the im group (p=0.2). Side effects were self reported by patients but were minor and temporary.

Clinical conclusions
Hepatitis B vaccine, administered intradermally, shows higher immunogenicity compared to the same vaccine administered intramuscularly over a 20 month follow up period.

Outcomes assessed in the review
A review supplied other effectiveness information: the seroprotection rate expressed as a percentage of non-responder patients in the 2 comparator strategies (Strategy C, intramuscular vaccination using thymopentin and HB vaccine, Strategy D, intramuscular vaccination using interleukin-2 and HB vaccine).

Study designs and other criteria for inclusion in the review
Not stated.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
None are described.

Methods used to judge relevance and validity, and for extracting data
None are described.
Number of primary studies included
Two primary studies were used.

Methods of combining primary studies
Studies were not combined. Each provided a separate comparator.

Investigation of differences between primary studies
Differences were not investigated.

Results of the review
In strategy C, intramuscular vaccination using thymopentin and HB vaccine, a seroprotection rate of 86% was achieved. In strategy D, intramuscular vaccination using interleukin-2 and HB vaccine, a seroprotection rate of 56% was achieved.

Measure of benefits used in the economic analysis
No single measure of benefit was produced by the authors.

Direct costs
For the clinical trial of strategies A and B, costs of recombinant B vaccine only were included. The price of a 20micrograms vial paid by the hospital at the time of the study was given and used to calculate the cost of drugs per patient. Labour costs were not included because, as the authors stated, dialysis patients receive intense care and undergo regular follow up in any case. Labour resources used would not otherwise have been the same for both strategies. Costs of storage/refrigeration and of needles or other equipment were not given. For the other comparators the price that the hospital would have paid for drugs at the time of the study is used to calculate a cost per patient. Again only costs of drugs are given. The viewpoint is that of the hospital.

Statistical analysis of costs
Costs were not analysed stochastically.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analysis was performed.

Estimated benefits used in the economic analysis
Not applicable.

Cost results
Costs of strategy A and strategy B were the same. 80micrograms of recombinant B vaccine (Energix-B in 20micrograms vials) cost $92 per patient. Strategy C, intramuscular vaccination using thymopentin, cost $945 per patient, and Strategy D, intramuscular vaccination using interleukin-2, cost $807 per patient. In the cost analysis, Strategy E (intramuscular vaccination using 3 doses of recombinant B vaccine) cost $138 per patient, and strategy F (intramuscular vaccination using gamma-interferon) cost $489 per patient.
Synthesis of costs and benefits
Costs and benefits were not combined since intradermal administration of recombinant B vaccine was the dominant strategy.

Authors' conclusions
For the same cost, the intradermal administration of small doses of HBsAg is more clinically effective for re-vaccinating non-responding chronic dialysis patients than 2 doses of HBsAg administered intramuscularly. It is also the most effective and least expensive method of re-vaccination when compared with other strategies. However, compared with other immunisation programmes, costs are high and HB vaccination and re-vaccination strategies would only be cost effective in centres where the incidence of hepatitis B is high.

CRD COMMENTARY - Selection of comparators
The choice of strategy B as a comparator is clear. The use of strategies C & D is explained but the authors have not given enough detail, either of benefits or of costing, to make the comparison valid. Strategies E & F are used only in a cost analysis and are irrelevant in the cost-effectiveness evaluation.

Validity of estimate of measure of benefit
The authors have used only the first months' results in their comparison. Later follow up showed insignificant differences because numbers were too small. Practical protection against hepatitis B has not been demonstrated.

Validity of estimate of costs
It is difficult to assess whether all relevant cost have been included.

Other issues
The unexplained loss to follow up is very high: only 40% of patients remained in the study by the 20th month. Analysis should have been based on intention to treat. In the text it is stated that 16 doses of 5micrograms of vaccine were given per week but it is apparent from tables and costs that the treatment consisted of 16 doses given at the rate of 1 per week. Appropriate comparisons were made with other studies, however, the results of the study might not be generalisable to other settings or countries.

Source of funding
Supported in part by the Stefano Casati Memorial Award 1994 (to Dr Fabrizi) from the Association for the Study and the Care of Renal Diseases at the Nephrology Division (Dir Prof C Ponticelli), Hospital 'Maggiore Policlinico', IRCCS, Milano, Italy.

Bibliographic details

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Aged; Aged, 80 and over; Antibody Formation; Comparative Study; Cost-Benefit Analysis; Female; Hepatitis B /prevention & control; Hepatitis B Antibodies /blood; Hepatitis B Surface Antigens /administration & dosage; Hepatitis B Vaccines /administration & dosage; Humans; Immunization Schedule; Injections, Intradermal; Injections, Intramuscular; Male; Middle Aged; Prospective Studies; Renal Dialysis; Research Support, Non-U.S. Gov't; Uremia
/therapy; Vaccination /economics /methods

AccessionNumber
21997000981

Date bibliographic record published
31/03/1999

Date abstract record published
31/03/1999