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# Vaccination against hepatitis B: comparison of intradermal and intramuscular administration of plasma derived and recombinant vaccines

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SUMMARY

A retrospective analysis of levels of antibody to hepatitis B surface antigen in 1419 health care workers was carried out to compare the efficacy of intramuscular and intradermal administration of plasma derived and recombinant hepatitis B vaccines. No significant difference was detected between the response to intradermal and intramuscular plasma derived vaccine. However of those who received intramuscular recombinant vaccine 81·6%, 13·8% and 4·7% were good ($\geq$ 100 miu/ml), low (10–99 miu/ml) and non-responders ($<$ 10 miu/ml) respectively, compared with 51·1%, 29·8% and 19·2% of the intradermal group ($P < 0{\cdot}0001$). Low dose intradermal administration of recombinant vaccine did not produce satisfactory levels of antibody to hepatitis B surface antigen.

Hepatitis B vaccines are expensive and as the intradermal dose is normally one tenth of the intramuscular dose use of the intradermal method could result in considerable cost savings. Early studies which compared the efficacy of intramuscular and intradermal plasma derived hepatitis B vaccine suggested that there was little difference in the results [1–3]. Recombinant yeast derived vaccine has also been used intradermally but the results suggest that low dose intradermal inoculation of recombinant vaccine is less immunogenic than is intramuscular administration [4–6]. In order to address this question we have analysed data on 1419 health care workers who have completed hepatitis B vaccination in Leicestershire Health Authority, where both types of vaccine and both inoculation routes have been used.

An intradermal vaccination programme against hepatitis B virus was started for the health care staff of Leicestershire Health Authority in October 1988. Because hepatitis B vaccine is less effective in older people those $>$ 30 years old received intramuscular injections as did staff at high risk. Two vaccines were used, a plasma derived vaccine (H-B-Vax, Merck Sharpe and Dohme) and a recombinant

yeast derived vaccine (Engerix B, Smith Kline and French). Intramuscular injections (20 $\mu$g) were given into the deltoid muscle and intradermal injections (2 $\mu$g) were given in the upper arm. Injections were given at 0, 1 and 6 months and antibody to hepatitis B surface antigen (anti-HBs) was measured 1 month after the third injection.

Anti-HBs was detected by radioimmunoassay (Abbott). Quantitation was achieved by including five standard dilutions of anti-HBs in each assay. Results were expressed as miu/ml up to 500 miu/ml and levels above were reported as $>$ 500 miu/ml. Results were grouped into three categories according to anti-HBs level: Good responders ($\geqslant$ 100 miu/ml), low responders (10–99 miu/ml) and non-responders ($<$ 10 miu/ml).

*Plasma derived vaccine*

No significant difference in seroconversion rates was found between the intramuscular and intradermal groups and in both groups over 85% were good responders (Table 1). In the intradermal group, there was no significant difference in age between the three response levels (Table 1). However in the intramuscular group, the non-responders were significantly older than the good responders ($P = 0{\cdot}0012$) (Mann–Whitney test). The analysis was repeated after excluding those $>$ 30 years old and there was still no significant difference in response level between the intramuscular and intradermal groups (Table 1).

*Recombinant vaccine*

Subjects in the intramuscular group achieved significantly greater seroconversion rates than did those in the intradermal group ($\chi^2 = 97{\cdot}62$, 2 D.F., ($P <$ 0·0001). Of the intramuscular group, 81·55% were good responders compared with 51·05% in the intradermal group (Table 1). In the intradermal group, there were no significant differences in age between the three response levels (Table 1). However, in the intramuscular group the non-responders ($P = 0{\cdot}044$) and the low responders ($P < 0{\cdot}0001$) were significantly older than the good responders. After excluding those $>$ 30 years old the intramuscular group still had significantly greater seroconversion rates than did those in the intradermal group ($\chi^2 = 41{\cdot}8$, 2 D.F., $P < 0{\cdot}0001$) (Table 1).

*Plasma derived* v. *recombinant vaccine*

Of all who received intramuscular injections, those who received plasma derived vaccine achieved slightly but significantly greater seroconversion rates than did those who received recombinant vaccine ($\chi^2 = 6{\cdot}55$, 2 D.F., $P = 0{\cdot}038$) (Table 1).

Analysis of the results according to sex showed significantly higher anti-HBs levels in females only in the group who had received recombinant vaccine by intradermal injection. In this group 133/242 women (55%) were good responders, 69 (28%) were low responders and 40 (17%) were non-responders. The corresponding figures for men were 11/40 (27·5%), 15 (37·5%) and 14 (35%) ($\chi^2 = 11{\cdot}96$, 2 D.F., $P = 0{\cdot}002$). However, the men (median age 25 years) were significantly older than the women (22·8 years) in this group ($P = 0{\cdot}0145$). It is possible that the age difference may have contributed towards the difference in results in this group.

Table 1. *Response to intramuscular or intradermal vaccination against hepatitis B with plasma derived or recombinant vaccine in all subjects and in subjects < 30 years old*

| | Plasma derived vaccine | | | |
|---|---|---|---|---|
| | All subjects | | Subjects < 30 years old | |
| Response* | *n* | Age† | *n* | |
| Intramuscular | | | | |
| Good | 271 (88·0%) | 43 | 15 (93·0%) | |
| Low | 26 (8·4%) | 44 | 1 (6·2%) | |
| Non- | 11 (3·6%) | 55 | 0 | |
| | 308 | | 16 | |
| Intradermal | | | | |
| Good | 158 (85·9%) | 24 | 154 (85·6%) | |
| Low | 18 (9·8%) | 24 | 18 (10·0%) | |
| Non- | 8 (4·3%) | 25 | 8 (4·4%) | |
| | 184 | | 180 | |
| | Recombinant vaccine | | | |
| Intramuscular | | | | |
| Good | 526 (81·55%) | 41 | 61 (95·4%) | |
| Low | 89 (13·8%) | 48 | 2 (3·1%) | |
| Non- | 30 (4·65%) | 45 | 1 (1·5%) | |
| | 645 | | 64 | |
| Intradermal | | | | |
| Good | 144 (51·05%) | 23 | 142 (51·3%) | |
| Low | 84 (29·8%) | 23 | 82 (29·6%) | |
| Non- | 54 (19·15%) | 23 | 53 (19·15%) | |
| | 282 | | 277 | |

* Response refers to anti-HBs levels in miu/ml: good ($\geqslant 100$), low (10–99), non- ($< 10$).
† Age is median age in years.

Our finding that responses to low dose intradermal recombinant vaccine are significantly inferior to intramuscular vaccine shows that any saving from the use of the intradermal technique is likely to be outweighed by the cost of boosters and further follow up. The US Centers for Disease Control has recently published similar reports of poor response after intradermal hepatitis B vaccination [7]. Revaccination of non-responders incurred substantial additional costs.

A number of small studies have previously suggested that low dose intradermal vaccination with plasma derived vaccine produced a seroconversion rate similar to that by intramuscular vaccination [1–3]. Our results on 492 subjects given plasma derived vaccine are consistent with these findings and indicate that the intradermal method is as effective as the intramuscular method for plasma derived vaccine. However, plasma derived vaccine proved unacceptable to some health care workers because of their unfounded fear that it might transmit the human immunodeficiency virus. Recombinant vaccine is now the only hepatitis B vaccine available in the UK. There have been few studies of the efficacy of intradermal recombinant vaccine. Lancaster and colleagues [8] achieved seroconversion in 26/32 (81%) subjects, but did not compare anti-HBs titres. Both Gonzalez and

colleagues [4] in a study of 51 subjects and Wiström and colleagues [5] in a study of 80 subjects reported significantly higher seroconversion levels and geometric mean titres of anti-HBs with intramuscular than with intradermal administration. Bryan and colleagues [6] in a study of 153 volunteers compared intramuscular recombinant vaccine, intradermal recombinant vaccine and intradermal plasma derived vaccine. They found that significantly fewer of those in the intradermal recombinant vaccine group developed anti-HBs levels $\geqslant$ 10 miu/ml compared to the other two groups. It is clear from our results on the 927 subjects who received recombinant vaccine, that a low dose given intradermally provides much less satisfactory anti-HBS levels than the standard dose given intramuscularly and is not an adequate strategy for protection of health care workers against hepatitis B.

Persistence of anti-HBs depends on the initial antibody level [9], and as long-term protection is related to the maximal antibody response [10] intradermal recombinant vaccine is less likely to provide prolonged protection than intramuscular recombinant vaccine.

Low dose intramuscular recombinant vaccines given in various doses have produced good results in children and young adults, [11, 12] but need further evaluation in older adults before they could be recommended for a high risk group such as health care workers.

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