Original research

Booster hepatitis B vaccination in haemodialysis patients: five-year prospective observational study

Casey Light and Hemant Kulkarni
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Abstract

Background Guidelines for haemodialysis patients unresponsive to the primary hepatitis B three-dose vaccination regimes (Initial Non-responders) is less well defined in the literature, with regard to dose, frequency, duration, route of administration and clinical impact of repeat vaccinations. We studied the safety and efficacy of three annual booster vaccinations, aiming for the protective serological response (Anti-HBs > 10 mIU/mL) of the Initial Non-responders in a five-year study.

Aim To determine the efficacy of three annual hepatitis B boosters in the primary non-responders in haemodialysis population.

Method Serological response to the primary vaccination (Initial Responders) and those needing booster vaccinations (Initial Non-responders) was evaluated for the magnitude (titre) and duration of the protective response.

Results Forty-six haemodialysis patients (M=26; F=20) were evaluated over the five-year study period. Twenty Initial Responders did not require booster vaccination whilst 26 Initial Non-responders received the annual booster vaccination. Three (Late Responders) of the 26 patients demonstrated protective serological response. Two of these three revealed weak (Anti-HBs <21 mIU/mL) and short-lived (<12 months) response to two boosters, whilst one patient had strong long-term response (>36 months) with Anti-HBs >100 mIU/mL). There was no hepatitis B transmission either before or during the study period.

Conclusions Our findings suggest limited benefit of booster vaccinations in unresponsive haemodialysis patients beyond three years. Continued practice of standard universal precautions should be performed in this high-risk population. The alternative protocol of repeating the primary vaccination should be considered and studies confirming the benefit would be useful.

Keywords
Haemodialysis, hepatitis B virus, vaccination, kidney disease.

Introduction

The incidence and severity of some vaccine-preventable diseases such as hepatitis B is higher in persons with altered immunocompetence. Certain vaccines such as inactivated hepatitis B vaccines are recommended specifically for persons who are immune compromised including those with chronic kidney disease (CKD) and the dialysis population. During a period of altered immunocompetence these vaccines might be less effective. In order to maximise the likelihood of vaccine-induced immunity, strategies for immunisation

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should be formulated early in the course of progressive renal disease (Einollahi, 2011). Higher vaccine dosages of 40 ugm compared to 20ugm for the immunocompetent population or an increased number of doses from two to three/four doses are recommended for patients undergoing haemodialysis (CDC, 2012).

In 1969–1970, an outbreak of hepatitis associated with haemodialysis occurred in two Edinburgh hospitals, resulting in 24% mortality among renal patients and 31% in staff members (Bone et al., 1970). Since then, measures in preventing hepatitis B virus (HBV) transmission in the dialysis units have been a high priority. Since the recommendation of hepatitis B vaccinations in 1982, the rate of hepatitis B infection in the haemodialysis population has declined by approximately 95% (Janus et al., 2008). However, incidents of outbreaks of hepatitis B infection transmission in renal units in recent years can still occur (Edey, 2010; Fabrizi et al., 2015; Victorian Renal Clinical Network, 2017) highlighting the continued risk for infection in this population.

Haemodialysis patients are less likely to have protective serology (anti-HBs titre of $\geq 10$ mIU/mL) after standard vaccination compared with immunocompetent adults (Janus et al., 2008). Poor seroconversion in this population includes malnutrition, ureaemia, immunosuppression in the state of renal failure (Einollahi, 2008). Even in patients with different stages of CKD, who received the vaccine, the seroconversion rates differ (Hashemi, 2011). Different modalities have been used in attempts to produce an immune response in those non-responders to a primary three-dose vaccine series. The strategies include double dosing (Bonazzi, 2008), more frequent dosing (Rubin, 2014), intradermal vaccine (Barracough, 2009), adjuvant vaccines (Saade, 2013), recombinant vaccine (Akbar et al., 2016) with variable efficacies. Despite all these strategies, there were no official guidelines available for standardised revaccination regimes for the non-responders (Walayat et al., 2015). The aim of this paper was to study the effectiveness of our unit protocol involving three annual boosters for the non-responders to the primary three-dose regime.

Method

This prospective study was a part of the Renal Nurse Practitioner Clinical Practice Protocol at a haemodialysis unit in the Armadale Health Service in Western Australia (WA). The study was conducted in the haemodialysis unit, Armadale, Western Australia. All patients ($n=141$) entering this haemodialysis unit between 2008 and 2014 were screened and considered for the hepatitis B vaccination regime and inclusion for the study. Forty-six patients were eligible for vaccination and completed the surveillance period of five years. Thirty-nine patients have yet to complete the five-year surveillance and thus excluded from the study. Fifty-six patients were excluded from the study; these patients had documented completion of hepatitis B vaccination or past exposure prior to the entry, previous hypersensitivity to the vaccination, non-responsive to more than three annual booster doses, or failed renal transplantation patients who would have received vaccination as part of the transplant work-up.

The primary vaccination schedule in this study involved three doses of hepatitis B vaccine 40 mcg given at 0, 1 and 6 months intramuscularly. Follow-up annual anti-HBs levels were performed, booster vaccinations of hepatitis B vaccine 40 mcg given intramuscularly were administered every year up to three years, if anti-HBs levels were $<10$ mIU/mL. Anti-HBs levels were performed for further two years without vaccination for all the study patients. The patients who showed serological response (anti-HBs titres $>10$ mIU/mL) after the primary vaccination schedule were classed as ‘Initial Responders’. Patients who did not respond to the primary vaccinations schedule were classed as ‘Initial Non-Responders’. Those from the Initial Non-Responders group who subsequently developed protective antibodies after the booster revaccination were classed as ‘Late Responders’.

Results

Patient profile

The patient profile in the study (46) was as shown in Table 1; and characteristics of the Initial Responders (20) and Initial Non-Responders (26) was in Table 2. The 46 patients studied ($M=26$, $F=20$) were of median age of 62 years (range 20–90 years), average body weight of 81 kg (range 42–135.5 kg). Forty-three patients were dialysed with native arteriovenous fistula, whilst three patients were dialysed with central venous catheters. Thirty patients were diabetics, 28 patients had cardiovascular disease. 21 of the 46 patients had received blood transfusions totalling 149 units of red packed cells, blood

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
<th>Age Median: IQR (25–75)</th>
<th>Weight Median: IQR (25–75)</th>
<th>AVF</th>
<th>CVC</th>
<th>Diab</th>
<th>CVD</th>
<th>Blood transfusion recipients</th>
<th>Units of blood received</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>20</td>
<td>62 (53–71)</td>
<td>81 (63–93)</td>
<td>43</td>
<td>3</td>
<td>30</td>
<td>28</td>
<td>21</td>
<td>149</td>
</tr>
</tbody>
</table>
or blood product. All these patients had received the blood products routinely screened by the Red Cross prior to their transfer to our unit or during their admissions to the tertiary hospitals in Western Australia. Forty-six patients received primary vaccination of three doses with 100% compliance and booster vaccinations were given to 26 Initial Non-Responders. At the end of the five years of study, 23 patients were lost for follow-up as a result of renal transplant (n=1), inter-unit transfer (n=1) and deaths (n=19). There was no difference in the mortality between the patients in the Initial Responder group and the Initial Non-Responder group over the study period (41% vs 42% respectively), P>0.05. Since the inception of this unit in 1998, there were two patients with hepatitis B antigen positivity receiving dialysis in the unit, there was no history of acquired hepatitis B infection in the unit since its inception 19 years ago. The dialysis unit follows standardised universal protection measures and does not reuse dialysis components.

**Initial Responders**

The anti-HB titres, mIU/mL in median and interquartile ranges, of the Initial Responders was as shown in Table 3. All Initial Responders (n=20) developed protective antibodies after the primary vaccination and sustained to continue the protective levels to the end of the study. At the end of the study, eight patients died, one transferred to another unit, one received a renal transplant and exited the study. The remainder 10 of the 20 Initial Responders continued to maintain protective levels.

**Initial Non-Responders**

The anti-HB titres, mIU/mL in median and interquartile ranges, of the Initial Non-Responders (n=26) and Late Responders (n=3) was as shown in Table 4. Twenty-three of the 26 Initial Non-Responder did not respond to the three-yearly booster vaccination regime, whilst three patients seroconverted after the second booster and thus did not receive the third booster. These three patients were re-classed as Late Responders. As shown in Table 4, the mean anti-HBs titres of these three Late Responders were significantly lower than the Initial Responders (Table 3) despite receiving the two boosters. Two of these three Late Responders did not sustain protective response, whilst one maintaining the anti-HBs titre of 11.6 mIU/mL, which was just above the protective level at the end of study. There was no adverse effect to the vaccination schedule and there were no sentinel events in any of the studied patients.

**Discussion**

This study conducted in a single unit over a period of five years demonstrated a low number of responders to the three annual booster hepatitis B vaccination in haemodialysis patients: five-year prospective observational study.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Initial Responders (20)</th>
<th>Initial Non-Responders (26)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>10</td>
<td>16</td>
<td>26</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Age</td>
<td>60 (48–47)</td>
<td>65 (55–73)</td>
<td>63(53–71)</td>
</tr>
<tr>
<td>Weight</td>
<td>79(60–103)</td>
<td>82(62–91)</td>
<td>81(63–93)</td>
</tr>
<tr>
<td>Arteriovenous fistula</td>
<td>19</td>
<td>24</td>
<td>43</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>12</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>Blood transfusion recipients</td>
<td>8</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>Total units of blood received</td>
<td>84</td>
<td>65</td>
<td>149</td>
</tr>
</tbody>
</table>

**Table 2: Patient characteristics: Initial Responders (20) and Initial Non-Responders (26)**

<table>
<thead>
<tr>
<th>Initial Responders (n=20)</th>
<th>Anti-HBs mIU/mL Median (IQR 25–75)</th>
<th>Booster requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>187 (62–677)</td>
<td>Nil</td>
</tr>
<tr>
<td>Year 2</td>
<td>119 (18–399)</td>
<td>Nil</td>
</tr>
<tr>
<td>Year 3</td>
<td>115 (25–257)</td>
<td>Nil</td>
</tr>
<tr>
<td>Year 4</td>
<td>153 (33–423)</td>
<td>Not for booster</td>
</tr>
<tr>
<td>Year 5</td>
<td>91 (31–238)</td>
<td>Not for booster</td>
</tr>
</tbody>
</table>

**Table 3: Anti-HBs titres and booster requirement for the Initial Responders**
booster vaccination for those who showed anti-HBsAb of < 10 mIU/mL after the primary vaccination regime of 0, 1 and 6 months. The majority of those who received the booster vaccination in the first two years remained negative; only three patients after receiving the third-year booster dose showed anti-HBsAb levels slightly above > 10 mIU/mL, with follow-up testing showing declining levels in the next two years. The outcome could indicate that those who did not respond were unlikely to respond in the future; those responded later were of low levels which waned over time. The poor response of 43% to the primary hepatitis B vaccination regime in our study correlate to the other published literature of approximately 42% non-responders to the hepatitis B vaccination in the haemodialysis population (Barraclough et al., 2009). Our findings showing rapid decline or short-lived antibodies in the poor responders, “Late Responders” group in Table 4, were also consistent with other published results (Chevas et al., 2011). Currently there are limited data and outcomes available from studies on the effect of revaccination of non-responders and on the duration of immunity in the haemodialysis population (Chevas et al., 2011). However, there are many new emerging studies demonstrating the long-term immune memory of vaccination (Gilca et al., 2013; Schonberger, 2013). Thus, even though our study might show low response rate, revaccination with boosters remains beneficial as memory B lymphocytes are elicited through vaccination and could involve in long-term immunity and protection against hepatitis (Leuridan & Van Damme, 2011). Haemodialysis remains a high-risk environment for hepatitis B transmission with immunocompromised patients. Recent cases of transmission between patients despite rigorous unbreached standard precautions in a Victorian dialysis unit indicates the highly infectious hepatitis B virus particle (Victoria Renal Network, 2017). It is vital for strict adherence to infection control measures and continuation of hepatitis B vaccination and revaccination regimes to promote optimum patient safety. It is thus recommended that patients with severe renal impairment close to starting dialysis should commence vaccination to improve seroconversion (CDC, 2012). It is also advisable for renal transplant recipients to be vaccinated as a measure to prevent the risk of infection from the transplanted organ (Australian Immunisation Handbook, 10th edition, 2016).

Conclusions

Our findings suggest limited benefit of three-yearly booster vaccination regimes in haemodialysis patients unresponsive to the primary three-dose series. The dialysis setting remains a risk factor for transmission of HBV and an outbreak of hepatitis B could result in significant mortality (Fabrizi et al., 2015; Victorian Renal Clinical Network, 2017). Continued practice of standard universal precautions and vaccination should be performed in this population and expand to late CKD patients close to starting dialysis to improve seroconversion. The exploration of effective revaccination regimes should be encouraged. Recent publication of an alternative protocol of repeating the primary vaccination provided a positive option (Richards & Hayney, 2012). A protocol change by our unit from three annual boosters to a repeated three-dose series at 0-, 1- and 6-month intervals is being considered for the non-responders to the primary vaccination regime.

Study limitation

This is a study of small population size of 46 patients and limited to one dialysis unit over a period of five years. Future larger studies are recommended for more robust data to confirm efficiency of booster revaccination in the continued research and standardise practice.

References


