IMMUNOGENICITY AND SAFETY OF HEPATITIS B VACCINE (SHANVAC-B) USING A NOVEL PRE-FILLED SINGLE USE INJECTION DEVICE UNIJECT IN INDIAN SUBJECTS

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ABSTRACT

BACKGROUND: Hepatitis B is a major public health problem, which has now been controlled to some extent by vaccination especially with the recombinant hepatitis B vaccine, which has been proven to be safe and efficacious since its introduction in the 1990s. But problems of unsafe injection practices still persist. Now newer delivery devices like uniject are available for making vaccination very safe.

OBJECTIVE: To evaluate the immunogenicity and safety of the Hepatitis-B (Shanvac-B) vaccine in Uniject pre-filled device administered to healthy adults and infants at 0, 1, 2 months schedule.

METHODS: A total of 122 healthy subjects (62 adults and 60 infants) were administered three doses of the recombinant Hepatitis-B vaccine using Uniject pre-filled device. Blood samples for antibody titer estimation were taken before vaccination and 4-6 weeks after third dose. Subjects, parents or guardians were given diary cards to record any adverse reactions.

RESULTS: Protective immune responses to the vaccine were seen in 96.4% of adults and 100% of infants who completed the study. The Geometric Mean Titers (GMT) in adults and infants were 518.5 and 385.41 mIU/ml respectively. Mild fever, itching, and swelling at injection site were the most common side effects observed.

CONCLUSION: The safety and immunogenicity of the Hepatitis B Vaccine in the novel pre-filled device Uniject was effectively demonstrated in the present study.

Key Words: Hepatitis B vaccine, Uniject, Pre – filled device.

INTRODUCTION

Hepatitis B virus (HBV) infection is an important public health problem worldwide with over 350 million carriers of the virus worldwide, of these 25-30% will die as a consequence of the infection.\textsuperscript{1,2} India is in the intermediate zone of endemicity with a prevalence of 4.7% and contributing 10-15% of the total infected population worldwide. In

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Key Words: Hepatitis B vaccine, Uniject, Pre – filled device.
India 250,000 infants get infected every year and 90% of these consequently will develop chronic infection. Vaccination against hepatitis B virus has proved an effective means of protection and was introduced in Immunization schedules worldwide in 1980. Initially the vaccines were used were purified plasma derived from sera of chronic HBsAg carriers and, since the 1990, the more effective recombinant DNA technology based peptide vaccines.

Improper injection practices have posed problems over the years in universal vaccination programmes. Ironically, the diseases most frequently transmitted through unsafe injection practices are Hepatitis B, Hepatitis C and HIV. Unsafe injections account for 33% of new HBV infections in developing countries amounting to a total of 21.7 million infections each year (WHO website, Unpublished data) and 16.7% of pediatric HIV infections identified clinically (http://bmj.bmjournals.com/cgi/eletters/327/7423/1075).

Single-use devices such as Uniject could significantly reduce the incidence of disease transmission between injection recipients. Uniject could reduce the transmission of blood borne pathogens and lead to a reduction in treatment costs for infectious diseases. WHO is also evaluating the possibility of using hepatitis-B vaccine in Uniject device for use beyond the cold chain under certain conditions. This would have greater implications in future especially for India. In this present study we evaluated the immunogenicity rate and safety of the Hepatitis-B (Shanvac-B) vaccine in Uniject pre-filled device.

MATERIALS AND METHODS

Subjects
Selection criteria: Participants in this study were healthy adults of either sex between 18 to 55 years along with HbsAg, Anti-HbsAg and Anti-HbcAg negative with normal liver function and healthy infants between 0 to 7 days of age, born after normal gestational period (36-42 weeks) and to mothers who were negative for HbsAg during pregnancy.

Adults and infants with known congenital or acquired immunodeficiency, fever at the time of vaccination, hematological, hepatic, renal, cardiac or respiratory disease on long-term medication, pregnant or lactating women and subjects simultaneously participating in any other study were excluded. Further following each dose of the vaccine, the infants with body temperature ≥40.4 °C, persistent screaming or crying for 3 hours within 48 hours of vaccination, and hypersensitivity reactions were excluded from receiving subsequent doses of the Hepatitis-B vaccine. Written informed consent was obtained from the subject or parent or the legally acceptable representative before inclusion into the study. The study was approved by the individual ethics committee of the participating centers and was conducted in accordance to Declaration of Helsinki and Good Clinical practice.

Study design
After written informed consent process, the physicians and the pediatricians at the study centers examined the subjects and assessed selection criteria. The eligible subjects received three doses of the hepatitis-B vaccine (0.5 ml infants, 1 ml adults) according to 0, 1, 2 months Schedule. All vaccine doses were administered intramuscularly in the anterolateral thigh region in infants and deltoid region in adults. Venous blood samples (5 ml for adults and 1.5 ml for infants) were taken for determination of hepatitis B antibody analysis and other biochemical markers prior to first dose of vaccine. Four to six weeks following administration of the last dose of vaccine one more venous blood sample was taken for antibody analysis.

For the first 30-60 minutes following each dose, the subjects were observed for any adverse reaction following which the subject (adults) or parents/guardians (Infants) were given diary cards to record observations until the following visit. The diary cards were designed to record information on specific local, systemic and other unsolicited reactions.

Injection Device
Uniject is a plastic disposable injection device, pre-filled with a single dose of vaccine or medication (Figure 1), which is enclosed in a sealed blister and a permanent needle is attached. The Uniject devices used in this study were pre-filled to deliver 0.5 or 1 ml of HB vaccine with a 23 gauge needle. The device was activated by pushing the needle cap toward the body hence opening the fluid path between the needle and the blister. The cap was then removed the needle inserted into the subject, and the dose was delivered by squeezing the blister until it collapsed. The device is designed such that it cannot be reused but collected and incinerated.

Figure 1: Shanvac B Uniject Prefilled Device

Study Vaccine
The Hepatitis-B vaccine (Shanvac-B) used in this study manufactured by Shantha Biotechnics Pvt Ltd, Hyderabad, is approved by WHO. Each 0.5 ml or 1 ml dose of Uniject pre filled device contained 10 or 20 μg of hepatitis B surface antigen with 0.025 or 0.05 mg of thiomersol as preservative and 0.625 or 0.5 mg of aluminum phosphate adjuvant respectively. The vaccine in the Uniject device was stored at +2 to +8°C.

Sero logical Analysis
Serological analysis for anti HBsAg antibodies estimation was carried out by solid phase immunoassay (Anti Surase B-96, General Biologicals, Taiwan). Analysis was carried out in accordance to manufacturer's instructions. Anti-Hbs titers were determined using sets of standards (0, 10, 50 and 100 mIU/ml). Upper and lower 95% confidence intervals were calculated for all GMTs.

RESULTS
One hundred and twenty two subjects were recruited in the study of which 62 were adults, while 60 were infants. All the subjects were evaluable for safety while 107 (55 adults and
52 infants) were evaluable as per protocol for immunogenicity. Of the 15 subjects who were excluded 11 were lost to follow up during course of the study and 4 were excluded for protocol violation. The demographic profile of the adult subjects and infants recruited is shown in Table 1.

### Immunogenicity

Protective immune responses to the vaccine were seen in 53 (96.4%) out of 55 adults and 52 (100%) infants who completed the study. The Geometric Mean Titers (GMT) in adults and infants were 518.5 mIU/ml (2.2-10446) and 385.4 mIU/ml (70-2320) respectively.

### Reactogenicity

All Subjects were included in analysis of reactogenicity. All the local and systemic adverse events observed in adults and infants are represented in Table 2.

### DISCUSSION

Recent surveys in developing countries have revealed that up to 30% of injections used for immunization are not sterile. Disposable syringes are reused and reusable syringes are often improperly sterilized, resulting in a significant risk of transmission of blood borne pathogens.\(^\text{10}\) Autodestruct syringes and single use pre filled devices can reduce disease transmission by averting inappropriate reuse. In addition, single - dose formats like Uniject avoid the waste associated with multi-dose vials.\(^\text{10}\)

The safety and efficacy of Shanvac-B has firmly been established in previous studies.\(^\text{7,11,12}\) In this present study the recombinant hepatitis B vaccine (Shanvac-B) administered using Uniject device was highly immunogenic with 100% and 96.4% seroprotection in infants and adults respectively. In infants the Geometric Mean titre (GMT) of Anti – HBs following 3 doses of the vaccine was 385.41 mIU/ml which is similar to the results of a study in Indonesia using Uniject delivery device where the observed GMT was 312 mIU/ml.\(^\text{13}\) A previous study in healthy adults with Shanvac B a GMT of 419 mIU/ml was observed.\(^\text{12}\) In the present study in adults the GMT observed was 518.5 mIU/ml following administration of three doses of the vaccine. The adverse events observed with the vaccine in this present study were similar in nature and frequency to those observed previously.\(^\text{7,11,12}\) There was no serious adverse event reported during the study period.

A study using world bank model to evaluate the cost of interventions per disability adjusted life year (DALY) concluded that providing a HB vaccine birth dose with Uniject is roughly 20% more cost effective than immunization with a standard syringe at 6 weeks of age.\(^\text{13,14}\)

Hepatitis B vaccination has the advantage of having flexible schedules either used with the 0, 1 and 2 month schedule or in infants in combination with DPT.\(^\text{15}\) Various studies with either schedules have given a seroprotection rates of 100% in Indian subjects\(^\text{16,17}\) A randomized multicentric Comparative study conducted by Goldfarb et al using two schedules of 0,1,6 months and 0,1,2, months resulted in a more rapid seroprotective antibody titer at 3 months for the 0,1,2 months schedule.\(^\text{18}\)

In earlier studies in Indonesia and China the pre-filled single use Uniject device containing hepatitis-B vaccine was stored at ambient temperatures for up to one month in midwives homes and used during home visits to deliver the vaccine. The vaccine was efficacious with 88.2% seroconversion and the GMT observed in this study was 288 mIU/ml.\(^\text{10,13}\) This finding has important implications for immunization programs. Delivery of HB vaccine outside cold chain, especially in conjunction with a single use injection device could extend immunization coverage, timeliness, effectiveness and safety.\(^\text{15}\) Similar studies with Shanvac-B are required to confirm these findings, which are relevant to country like India.

The cost of Shanvac B is almost 50% lower than the other international brands. In fact after the introduction of Shanvac B the technology has been utilized to produce other brands of hepatitis B vaccine in a cost effective manner. The Hepatitis B vaccine (Shanvac-B) in Uniject delivery device has shown encouraging results with regards to safety and immunogenicity when administered to healthy adults and infants.

### CONFLICTS OF INTEREST

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**Table 1: Demographic profile of subjects recruited**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adults (Mean ± SD, range)</th>
<th>Infants (Mean ± SD, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± SD, range)</td>
<td>27.9 ± 8.1 years (18-48)</td>
<td>2.7 ± 1.6 weeks (0-7)</td>
</tr>
<tr>
<td>Sex (M: F)</td>
<td>1:4</td>
<td></td>
</tr>
<tr>
<td>Weight (Mean ± SD, range)</td>
<td>61.3 ±12.4 kg (34-89)</td>
<td>2.9 ± 45 kg (1.9-3.8)</td>
</tr>
<tr>
<td>History of Smoking</td>
<td></td>
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<tr>
<td>Alcohol intake</td>
<td>19.3%</td>
<td></td>
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<tr>
<td>Head circumference (Mean ± SD, range)</td>
<td>33.3 ± 1.3 cm (30-36)</td>
<td>47.8 ± 2.1 cm (40-52)</td>
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<tr>
<td>Length (Mean ± SD, range)</td>
<td></td>
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</tbody>
</table>

**Table 2: Local and systemic side effects**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Infants (%)</th>
<th>Adults (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local reactions</td>
<td>Pain 23.2</td>
<td>1.0</td>
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<tr>
<td></td>
<td>Swelling 5.1</td>
<td>0.5</td>
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<tr>
<td></td>
<td>Itching 3.9</td>
<td>1.1</td>
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<tr>
<td></td>
<td>Redness 0.8</td>
<td></td>
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<tr>
<td>Systemic</td>
<td>Fever Mild 18.5</td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>Moderate 2.2</td>
<td></td>
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<tr>
<td></td>
<td>High grade 0</td>
<td></td>
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<tr>
<td></td>
<td>Dizziness 0.5</td>
<td></td>
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<tr>
<td></td>
<td>Headache 0</td>
<td>6.0</td>
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<tr>
<td></td>
<td>Malaise 0</td>
<td>1.6</td>
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<tr>
<td></td>
<td>Crying 29.9</td>
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<tr>
<td></td>
<td>Irritability 14.2</td>
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<tr>
<td></td>
<td>Vomiting 1.3</td>
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REFERENCES


INTRODUCTION

Safe and legal abortion is considered a key intervention for improving women’s health and quality of life. Despite a liberal abortion law in India, (Medical Termination of Pregnancy Act of India 1971) of 6.7 million induced abortions every year only 10 percent are conducted...