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Original Article

Safety and immunogenicity of tetanus toxoid in pregnant women

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Abstract

Objectives : To assess immunogenicity and safety of tetanus toxoid in pregnant Indian women. *Methods :* A post marketing surveillance study was conducted in 300 pregnant women of 28-36 weeks of gestation, who were administered 2 doses of 0.5 ml of tetanus toxoid one month apart as per WHO recommendations. Immunogenicity was assessed by determining serum and tetanus IgG antibody titre, pre and post-vaccination and safety was assessed by monitoring adverse events actively following each dose. Results : Irrespective of the prevaccination serostatus, all 300 pregnant women (100%) became seroprotected, 6-8 weeks postvaccination. A fourfold increase was observed in anti tetanus IgG antibody titres post vaccination ($p<0.0001$) in all women. Local and systemic adverse events were mild, and comparable to earlier studies. No serious adverse event was observed. *Conclusion :* Tetanus toxoid is safe and immunogenic in pregnant women and additionally confers protection in neonates due to transplacental transfer of maternal antibodies.

Key words : tetanus toxoid, safety, immunogenicity, pregnancy

Introduction

Tetanus is an infectious bacterial disease caused by Clostridium tetani and affects any age group. Majority of tetanus cases are birth associated and occur in developing countries among newborn babies or in mothers following unclean deliveries and poor postnatal hygiene. Incidence of neonatal tetanus is alarmingly high in India and contributes to approximately 25% of the world's neonatal tetanus. In the year 2005, number of reported neonatal cases globally was 9,782. In India in 2006, there were 600 reported cases of neonatal tetanus though actual figures may be higher due to underreporting [1]. Protection against tetanus is antibody (tetanus antitoxin) dependent and can be achieved only through active immunization with tetanus toxoid or passive (tetanus specific Immunoglobulin) immunization. Maternal tetanus antitoxin passes via the placenta to the fetus. Hence when pregnant women receive a booster dose or the second dose of the primary series at least two weeks before delivery, both mother and child are protected against birth associated tetanus. In countries with effective immunization programmes and good standards of hygiene, maternal and neonatal tetanus (MNT) has been largely eliminated, defined as <1 case per 1000 live births at the district level. Despite

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a highly effective vaccine being available for protection against tetanus, in 2004 an estimated 40 million pregnant women were still in need of immunization against birth associated tetanus and about 27 million children did not complete their primary tetanus immunization series (WHO). It is recommended that in countries where MNT remains a public health problem, special attention should be given to immunizing women of childbearing age. Pregnant women with an inadequate or unknown immunization history should always received two doses of tetanus toxoid containing vaccine; the first dose as early as possible during pregnancy and the second dose at least 4 weeks later [2]. This schedule appears to provide protective levels of antibody for well above 80% of newborns also.

Post marketing surveillance is an important activity in order to reconfirm the safety and efficacy of licensed vaccines. Further, safety and efficacy profile of any medicinal product/vaccine especially when used by large population can provide valuable insights about the product's safety, immunogenicity and also help detect adverse events not observed earlier. This study was planned to evaluate immunogenicity and reactogenicity of Tetanus Toxoid (Adsorbed) manufactured by Serum Institute of India Ltd in pregnant women. The dose, dosage schedule and potency of vaccine used in this study was as per WHO recommendations [3].

Methods

This was a phase IV post marketing surveillance study conducted in the Department of Obstetrics and Gynaecology, Government Medical College and associated SMGS Hospital, Jammu (J & K). The study was conducted according to Declaration of Helsinki and ICH-GCP guidelines. Good laboratory practice (GLP) were followed during serological testing. The study was cleared by the Institutional Ethics Committee and composition of this committee complied with ICH – GCP (International Conference on Harmonization – Good Clinical Practice) guidelines. The evaluable sample size was 300 pregnant women (28-36 weeks of gestation) attending the antenatal clinic who met the inclusion criteria and gave their written informed consent for participating in the study. Details such as past medical history, and obstetric history have recorded on case record form. Physical and obstetric examination was conducted for assessing eligibility. Inclusion criteria were age group 18-45 years, gestational age of 28-36 weeks, free from obvious health problems as established by medical history and clinical examination before entering into study, written explained signed informed consent willingness to provide 2 blood samples for immunogenicity assessment and availability for the observation period of 4 weeks after each dose. Exclusion criteria were use of any investigational or non registered drug/ vaccine other study vaccine during the study period or within 30 days preceding first dose of study vaccine, administration of immunoglobulins/any blood products, simultaneous participation in any other clinical trial, history of allergic diseases or reactions likely to be exacerbated by any component of the vaccine, any known immunological, neurological, hepatic, cardiovascular, renal, respiratory, endocrine or hematological disorder.

Vaccine : Tetanus Toxoid (adsorbed) was used in this study. Composition of each 0.5 ml dose of study vaccine was Tetanus Toxoid $\geq$ 5Lf ($\geq$ 40 IU), adsorbed Aluminium Phosphate ($AIPO_4$) $\geq$ 1.5 mg, and 0.01% Thiomersal as preservative.

Immunogenicity Assessment : Two ml blood was drawn utilizing vacutainers with gel separators and sera were obtained at prevaccination (baseline) and postvaccination periods (six to eight weeks after second dose of vaccine) for determining serum anti-Tetanus IgG antibody titres using Enzyme Linked Immuno Sorbent Assay (ELISA) in the Department of Pathology, Government Medical College Hospital, Jammu (J&K). Sera samples were stored at -20^{0}C. Standard commercially available kits (IBL, Hamburg, Germany) approved by Director General Health Services, New Delhi – with standard positive and negative controls were used. Seronegativity was defined as Anti Tetanus IgG Titre <0.01 IU/ml. Seroconversion was defined as change from pre-immunization seronegative to post-immunization seropositive status i.e. Anti Tetanus IgG Titre $\geq$ 0.01 IU/ml or a four fold increase in antibody tire in previously seropositive women. Number of mothers achieving titres > 1 IU/ml indicative of long term protection were quantified [4].

Safety Evaluation : Safety of Tetanus toxoid (adsorbed) was determined by active follow up of vaccines for monitoring and management of adverse events. The details (onset, duration severity, concomitant medication) of solicited and unsolicited local and systemic adverse events were recorded on Case record form (CRF). The vaccines were observed closely for at least 30 minutes for any immediate reaction like

anaphylaxis. Active followup by home visits by doctors and social workers was done following each dose of the vaccine daily for 3 days and thereafter once a week over a period of four weeks after each dose of vaccine. Subjects were instructed to inform the doctor of any serious adverse event (SAE) by telephone / fax and consult him in case of a SAE.

Statistical Analysis : Geometric Mean Titre (GMT) and 95% Confidence Interval (95% CI) of Anti tetanus IgG antibody before and after vaccination was calculated. Pre and post-vaccination Geometric Mean Titres were compared by Paired 't' test and Wilcoxon's Signed Rank test. Percentage of each adverse event was calculated. These were compared to incidence of such adverse events as quoted in literature observed with previous studies.

Results

All 300 enrolled women completed the study, there were no dropouts. Mean age of women was 28.54 ± 5.08 years. Age range was 18-45 years. 94 (31.33%) women were gravida 3 (G3) and 93 (31%) women were primigravida. Prevaccination 21 (7%) women were seronegative (GMT: 0.0048 IU/ml) and 279 (94%) were seropositive (GMT: 0.41 IU/ml) Post vaccination, all 300 women developed protective antibody titre (GMT: 4.13 IU/ml) depicting a fourfold rise in postvaccination titre. This increase in titre was clinically relevant and statistically significant (P<0.0001) by Wilcoxon's signed rank test and paired 't' test (Table 1). There was 100% seroprotection (Figure 1). 298 (99.33 %) women had postvaccination anti tetanus IgG antibody level of ≥ 1.0 IU/ml which is indicative of long term protection. One woman had antibody level 0.1 – 1 IU/ml and one had antibody level of 0.01 to 0.1 IU/ml. There was no significant difference between postvaccination GMTs in previously seronegative and previously seropositive women in this study. It can therefore be implied that Tetanus toxoid (Adsorbed) is safe and immunogenic and provides adequate protection against tetanus in pregnant women.

Commonest local adverse event observed was redness in 11 (3.66%) subjects. Other local adverse events were pain : 9 (3%) subjects, and swelling : 9 (3%) subjects. The commonest systemic adverse event was rash, in 8 (2.66%) subjects. 5 (1.66%) women out of 300 experienced pruritus. 2 (0.66%) had fever and 3 (1%) had dizziness. All adverse events were mild in nature and resolved within 48 hours. No serious adverse event was reported.

Table 1. Anti Tetanus IgG Geometric Mean Titre (IU/ml) (n=300).

	Pre-vaccination	Post-vaccination
GMT	0.30	4.13
95% CI	0.24 to 0.38	3.91 to 4.35

'Paired t'; 'p' value & Stat. Significance : 23.98;

Comparison between pre and postvaccination GMT **p<0.0001 Highly Significant** Wilcoxon's Signed Rank test. 0.0; P<0.0001 Highly Significant

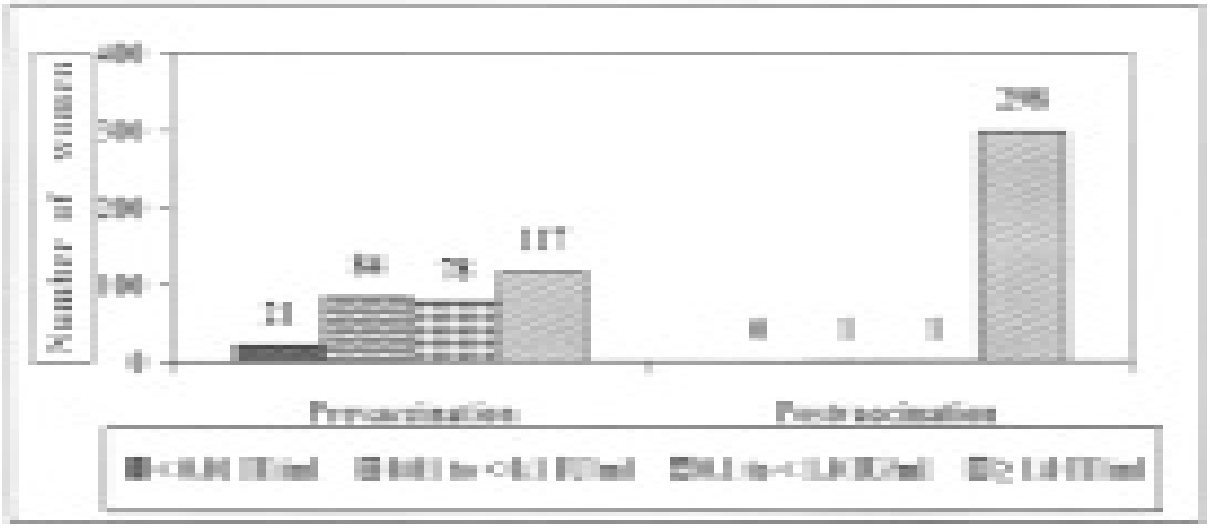

Figure 1. Distribution of women according to Anti tetanus IgG antibody levels.

Discussion

21 (7%) women were unprotected at prevaccination. 93 (31%) women were primigravida. 207 (69%) women were having history of previous pregnancy while 140 (46.66%) women had history of abortion. These women received tetanus toxoid earlier and this led to prevaccination seropositivity. 84 (28%) women had prevaccination antitetanus IgG antibody level indicative of minimal protection (0.01 to 0.1 IU/ml). 105 (35%) women out of 300 were either not protected or were minimally protected.

A fourfold rise in postvaccination titre was observed in all women in the study. Several studies have evaluated the efficacy of tetanus toxoid administered to pregnant women, [5,6] Local reactions are reported in 0% to 9.5% of recipients depending on the definition. Systemic reactions following tetanus toxoid inoculation are less common [4].

Conclusion

The authors conclude that Tetanus toxoid (adsorbed) is a safe and immunogenic vaccine with an excellent tolerability profile and provides long term protection to antenatal women and neonates against tetanus.

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