AN OPEN-LABEL, SINGLE-TREATMENT, SINGLE-PERIOD, SINGLE DOSE, CLINICAL PHASE 1 STUDY TO ASSESS THE SAFETY AND TOLERABILITY OF TETANUS VACCINE IN HEALTHY, ADULT SUBJECTS IN INDIA

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ABSTRACT

BACKGROUND

Tetanus toxoid vaccine has always been an indelible constituent of the Universal Immunization Programme in India. Besides being given to pregnant women in two doses, it used to be given in children at the ages of ten and sixteen. Gradually with the coming down of the burden of communicable diseases, the vaccine is now even recommended in five years age besides as a prophylactic vaccine for any injury of moderate to severe degree in the tropical situations. With India achieving Neonatal Tetanus Elimination in 2015, the pressures to ensure the availability of cost-effective vaccine has gone up. To cope with the increased demand of this vaccine in India, a bio similar tetanus vaccine vial for the Indian market is proposed and hence the Phase 1 study to validate the dose and the safety of the interventional product was planned at Kalinga Institute of Medical Sciences, Bhubaneswar in the eastern part of India under stringent regulatory guidelines of Central Drug Standards Control Organization (CDSCO), and adhering to the good clinical practice guidelines.

MATERIALS AND METHODS

24 recruits (healthy adults aged 18-45 years) were taken up for the study with lab screening for blood parameters both pre- and seven days post vaccination. 23 subjects completed the study as per the protocol and were included in the Efficacy Analysis. Only solicited local adverse events were reported in the trial. Total number of solicited adverse events reported in the trial was 15 (62.5%) The maximal incidence of any local reaction after immunizations within 7 days of vaccination was 58.3% (Pain/Tenderness) followed by swelling/induration in 1 (4.2) subject.

RESULTS

IgG antibody response after single dose of vaccine was optimal in study population. There is a statistically significant difference between pre-vaccination and post-vaccination values for IgG response against Tetanus antibodies, after single dose. Pre-vaccination GMT of study changed from 2.24 IU/ml to 12.81 IU/ml, indicating significant results.

CONCLUSION

In our study, in a mixed age and gender group, the seroconversion was nearly 76% and the AEs were 62.5% all of which subsided on their own without medication, which suggests that the vaccine is effective and can proceed onto Phase 2 and 3 trials for further in-depth assessments of the safety and primarily immunogenicity of the vaccine.

KEYWORDS

Phase 1 Trial, Tetanus Vaccine, Adverse Events (AE), Seroconversion Titres.

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BACKGROUND

Tetanus, caused by potent exotoxin released by bacteria Clostridium tetani is a painful and fatal disease. Burden of the disease is however controllable as an effective vaccine available is available. Universal primary immunization and timely booster doses to maintain adequate tetanus antitoxin levels are necessary to protect all age groups. Immunization of women with tetanus toxoid (TT) is a central strategy of the Maternal and neonatal tetanus elimination (MNTE) initiative. This initiative aims to achieve the elimination goal

of <1 neonatal tetanus (NT) case per 1000 live births per year in all districts of India by end of 2015 which is achieved.[1,2]

In India, the general immunization schedule advocates Tetanus toxoid administration till 10 years of age, as well as immunization of pregnant and child-bearing age women.[3] In addition, Tetanus vaccine is also recommended for booster immunization for the prevention of Tetanus in healthy individuals & individuals with clean minor or major wounds. In order to support vaccination as per the above recommendations, a bio similar Tetanus Toxoid vaccine was taken up as a Phase 1 trial among Indian subjects of 18-45 years of age in a site in Bhubaneswar to meet the increasing demand of the tetanus vaccine under the programmatic cover in the country.

Primary Objective

To evaluate the safety and tolerability of the new Tetanus Vaccine (Adsorbed) in healthy subjects 18-45 years of age.

Secondary Objective

Preliminary assessment of immunogenicity of Tetanus Vaccine (Adsorbed) IP in healthy subjects 18-45 years of age.

MATERIALS AND METHODS

An open labeled study in adults aged 18-45 years was done, after seeking Institutional ethical approval and then screening for qualification of the subjects as per inclusion & exclusion criterion and taking informed consent from study subjects. Enrollment of 24 healthy subjects (including anticipated dropout of 2 participants) was done, the total study period being 3 days enrollment period along with 5 weeks post therapy and follow-up. Sample of 24 subjects was optimal to illustrate the increase in incidence of each solicited symptoms that can be detected in test vaccine group with 80% power. One-sided test for inequality was considered since it was not expected for the safety profile to improve as compared to the pre-vaccination status.

Since, it was a single arm, non-comparative Phase 1 study randomization procedure was not applicable. Each study subject was assigned one allocation number.

Study subjects were enrolled at the clinical facility lab and were monitored till 8-hour after vaccination of 0.5 ml of test vaccine, done in the upper right arm of each subject on Day 2, post screening of lab reports (to confirm the healthy status of the subject).Clinical examination of the subjects was done at the time of screening, during planned visits to site/clinic on Day 01, Day 7, and finally Day 28.

Subjects were monitored specifically for local adverse reactions (soreness, redness, swelling, pain, tenderness, induration and ecchymosis), systemic reactions (headache, muscle ache, fever (>37^{o}C), nausea, vomiting, diarrhoea, shivering, fatigue and malaise). This was done over telephonic interview for 7 days post vaccination on diary card, which was collected on the 7th day of follow up.

Laboratory assessments of haematology, liver function and renal function tests were done on the day of screening and Day 7 post vaccination. The data was analysed and compared for safety using standard statistical tests. Evaluation of safety and tolerability (adverse events, vital signs, and clinical laboratory tests) were done on the basis of clinically significant changes observed post vaccination.

Blood samples were collected pre-vaccination (screening) & post-vaccination (day 28) to determine anti-tetanus antibody titre as secondary outcome of study. The sero-protective cut-off titre for serum anti-tetanus antibodies is 0.1 IU/ml.[4,5] The seroconversion response to vaccination was considered as per following criteria.[6]

Post-vaccination titre of ≥ 0.4 IU/ml for individuals with pre-vaccination antibody concentrations of <0.1 IU/ml or;

Four-fold or greater antibody rise post-vaccination for participants with pre-vaccination antibody concentrations ≥0.1 IU/ml but <2 IU/ml or;

Two fold or greater antibody response post-vaccination for participants with pre-vaccination antibody levels ≥2 IU/ml.

In addition, subjects who had very high pre vaccination antibody titres at baseline, antibody levels ≥4 IU/ml, maintenance of same or higher titres were considered seroconverted.[7,8]

47 samples were tested for Tetanus antibodies at the certified lab of Department of Serology, Quest Diagnostics, India to estimate the absolute values in IU/ml. The testing was performed by IBL kit in singlicate run. Testing platform used is Manual ELISA with reading on PR 4100 BIORAD ELISA READER. All the reports were verified by the supervisor and Manager separately for a thorough check. The QCs and plotted graph were found to be satisfactory.

An Adverse Event (AE) was defined as any unfavourable and unintended sign, symptom or disease not solicited, whatever their nature, severity, seriousness, and the supposed role (causality) of the product administered or the experimental procedure.[3,5]

The investigator reported all AEs, all abnormal findings from laboratory and other specific examinations, which were clinically apparent, or in the investigator's opinion clinically significant, on the AE form of the Clinical Report Form (CRF).

Geometric Mean Titres (GMTs) for anti-tetanus Ig G titters were calculated by taking the exponential of the mean of log 10 transformed antibody titres for pre-dose (visit 1) and post vaccination (visit 3). The change in GMT from baseline (visit 1) to visit 3 was to be tested for statistical significance using paired t-test.

Paired t-test was to be employed for comparing pre-dose (visit 1) and post dose (visit 3) antibody titres for Tetanus IgG.

RESULTS

Thus 24 subjects were screened and enrolled out of which one failed to come within the stipulated time for the follow up visit.

	n	(%)
Total Number of Subjects	24	100
Number of Subjects:		
With no Adverse Event	9	37.5
With One or More Adverse Events	15	62.5
Solicited Local Adverse Events	15	62.5
Solicited Systemic Adverse Events	0	-
Unsolicited Adverse Events	0	-
With Vaccine-Related* Adverse Events	15	62.5
With Serious Adverse Events	0	-
Discontinued due to an Adverse Event	0 (0.0)	-

Table 1. Safety Analysis for Subjects (N=24)

The 24 subjects within 7 day follow up reported 62.5% of adverse events (Table 1). All AEs were attributed to the vaccination procedure (deep intramuscular administration in the right arm as per protocol) and it was self-remitting in all cases without use of any analgesics. In some cases, application of ice swabbing was advised for comfort.

Solicited Local Adverse Event		Dose 1	Overall		
		N	n (%)	N	n (%)
Pain/ Tenderness	All	24	15 (62.5)	24	15 (62.5)
	Mild		12 (80)		12 (50)
	Moderate		3 (20)		3 (12.5)
	Severe		0		0
Redness/ Erythema	All	24	0	24	0
	<5 mm Mild)		0		0
	5-20 mm (Moderate)		0		0
	>20 mm (Severe)		0		0
Induration	All	24	0	24	0
	<5 mm (Mild)		0		0
	5-20 mm (Moderate)		1 (4.2)		1 (4.2)
	>20 mm (Severe)		0		0

Table 2. Local and Systemic Reactions within 7 Days of Administration of IP [No. of Subjects (%)]

In Table 2 elucidates the AEs in detail wherein pain /tenderness was seen in 15 out of 24 subjects; total 62.5% AEs were reported and in 1 case both pain and induration was reported which for total AE analysis was reported as one event but in the above table each AE is taken as an isolated event.

Vitals		Baseline (N=24)	Post Treatment Follow up (N=24)
Pulse (Beats/Min)	N	24	
	Mean	80.06	80.03
	Range	72-88	72-86
Body Temperature (°F)	N	24	
	Mean	37.06	37.00
	Range	37-37.6	37-37.2

Table 3. Vital Signs/Temperature at Baseline and Post 7 day Follow Up

As table 3 depicts no variation in the vitals when compared for the screening and the 7th day follow up. Blood samples were sent for routine haematology and biochemistry before the vaccine administration and at the time of first follow-up visit (7 days after the single dose of vaccine). Wilcoxon Signed Rank test was used to calculate the p value. The results showed no significant difference in analysis of mean compared to pre and post vaccination status for any of the parameters. In addition, individual values showed that none of the results were outside the acceptable range as mentioned in the protocol.

Pre-Vaccination TT IgG Titers	Total Subjects -N	Seroconverted -N (n/N Rate)	P Value
Subjects with pre-dose IgG between 0.1-2 IU/ml	9	7 (77.7%)	< 0.05
Subjects with pre-dose IgG between 2-4 IU/ml	9	6 (66.6%)	< 0.05
Subjects with pre-dose IgG of 4 IU ml and above	5	5 (100%)	< 0.05
All subjects seroconversion rate	**23**	**17 (78.26%)**	< 0.05

Table 4. Percentage of Subjects Who Sero-Converted

*As per seroconversion used earlier.

There is a statistically significant difference between pre and post values for IgG response against Tetanus antibodies, after single dose of vaccine. As noted in earlier studies and reports,[6,7] prevalence of antibodies against tetanus toxoid (tetanus antitoxin titre) in adults is found to be 97%, taking as criterion the threshold value of 0.1 IU/ml, as adequate tetanus immunity. Hence, we used modified seroconversion criterion (given in methodology) as all subjects in this study (23, excluding the dropout) have higher baseline IgG titters against tetanus toxoid even during prevaccination.

	GMT	GMR
Predose	2.24	5.70
28 Days After Vaccine Dose	12.81	

Table 5. GMT of TT IgG Antibody Titres

Table 5 shows the Pre-dose and follow-up Geometric Mean Titre (GMT) of IgG antibody titres. GMT of IgG antibody increase from 2.24 IU/ml to 12.81 IU/ml. These results corresponded to a GMR ratio of 5.70 which indicates optimal immunological response.

DISCUSSION

Tetanus can be fully controlled, as it can be preventable by vaccination. However, it cannot be eradicated, because Clostridium tetani is a widely distributed microorganism in the environment. Hence, immunization is essential, providing restricted duration protection (3 to 5 years) and is recommended for the whole population in general, even though booster doses are required to maintain seroconversion titre, after the first vaccination.[9]

The current study has the limitation of being a Phase 1 study for a bio similar tetanus vaccine. Current mix of studies have come a long way of testing use of combination vaccines like Td(tetanus diphtheria), DTap (Diphtheria Tetanus and a cellular Pertussis), Tdap (Tetanus diphtheria and acellular Pertussis) and typhoid tetanus conjugate vaccines in the adolescent age groups and not tetanus toxoid; and many countries are recommending the use of conjugate vaccines.[10] However, in our country given the cost restraints of the conjugate vaccines and the declining incidence of Diphtheria and Pertussis in the country, tetanus vaccine gains importance and preference to be offered under the programmatic banner.

Most individuals usually develop an adequate anti-tetanus antibody titre following administration of a single dose of tetanus vaccine. A history of past immunization is a good predictor of becoming adequately immunized which in this case was shown with the cascading seroconversion being achieved in 78.26% on the basis of pre-vaccination titters. In the Indian scenario, tetanus combination vaccines are adequately spaced out in the form of DPT vaccines in the infant age groups and as boosters after 1, 5 and 10 years of age. Missing even one of the opportunities does not dramatically hamper the titters. However, looking at the persisting risk of tetanus across all age groups, the non-feasibility of offering conjugate vaccines in adolescent age groups and the cost advantage of plain tetanus toxoid, the latter qualifies as a good choice for booster doses.

What is evident from the study that even in the small sample that was taken up, which is because of the Phase 1 trial scenario, the prevaccination IgG titters varied considerably which indicated that tetanus boosters are useful. However, the routine boosters need not be administered more frequently than every 10 to 20 years, provided an adsorbed toxoid has been used to initiate active immunization.[11] As per the study by Breman et al[11] the follow up was done for 12 months after which 59% of the participants had antitoxin titres of >/=0.01 IU/ml, a titre usually considered protective. The mean titre and the proportion of those protected decreased substantially with increasing age; overall, females gave somewhat greater serological responses than males. This kind of long follow up could not be done in this study and in that cohort too the side effects were neglible. Thus, it is important that physicians follow the current recommendations for adult immunization and initiate campaigns to ensure that the older population is protected against tetanus.[9]

A non-inferiority trial done comparing the tetanus toxoid in controlled temperature to cold chain also showed 2.7% AEs self-reported in the 7 day period which were mostly local reaction at the injection site with pain and swelling accompanied by fever in 13 cases and headache in 8, though in our study fever and headache were not reported at all.[12] The safety parameter of the vaccine which is the main objective of the study is well addressed, given that it is a Phase 1 study; although it needs reinforcements with a bigger sample in the subsequent phases of the trials as a secondary objective.

Antitoxin titres were usually well above the threshold level defining serological protection and seropositivity (>0.01 IU/ml) in a Multiple Indicator Cluster Survey (MICS) done in 2002 in 60 countries performed for Neonatal Tetanus Elimination study.[13] In our study, in a mixed age and gender group, the seroconversion was nearly 76% and the AEs were 62.5% all of which subsided on their own without medication, which suggests that the vaccine is effective and can proceed onto Phase 2 and 3 trials for further in-depth assessments of the safety and primarily immunogenicity of the vaccine.

The interventional product now is planned for detailed immunogenicity results in Phase 2 trial with multiple sites across the country.

CONCLUSION

In our study, in a mixed age and gender group, the seroconversion was nearly 76% and the AEs were 62.5% all of which subsided on their own without medication, which suggests that the vaccine is effective and can proceed onto Phase 2 and 3 trials for further in-depth assessments of the safety and primarily immunogenicity of the vaccine.

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