INTRODUCTION
Vaccine preventable diseases including tetanus neonatorum cause high number of morbidity and mortality in developing countries.\(^1\) The annual worldwide burden of tetanus neonatorum is approximately 800,000 cases.\(^2\) In 2008, the total cases of tetanus neonatorum reported from Pakistan were 809.\(^3\) Mortality and morbidity caused by neonatal tetanus is significant in spite of all available treatments. Neonatal tetanus is still a major cause of neonatal death in many countries, with reported mortality in patients in hospital ranging between 55% and 86%.\(^4\) Maternal immunization with tetanus toxoid has prevented approximately 725,000 cases of neonatal tetanus annually but still more than 270,000 newborns and 30,000 women die of tetanus worldwide.\(^5,6\)

Tetanus is an acute spastic paralytic illness caused by tetanus toxin, the neurotoxin produced by Clostridium tetani. In neonates infection usually spreads by contamination of umbilical cord. Tetanus neonatorum usually manifests within 3-12 days of birth.\(^7\) Shorter the incubation period worse is the prognosis.\(^1\) Patients can be graded for the severity using the classification of Patel and Joag. Considering the presence of locked jaw, spasms, incubation period of 7 days or less, onset of convulsions within 48 hours or less, axillary or rectal temperature of at least 37.2°C at admission or within 24 hours of admission. Patients with all five features are classified as having grade V severity, those with four were grade IV, those with only three were grade III, and so on.\(^8\)

Initial studies reported favourably on the use of either intrathecal ATS (anti-tetanus serum) or TIG (tetanus immunoglobulin).\(^9\) In a recent study, intrathecal TIG were found effective in the treatment of mild and moderate tetanus.\(^10\) Recent advances in treating tetanus include frequent and effective use of aggressive treatments including tracheostomy, artificial paralysis and artificial respiration.\(^11\) An alternate effective treatment is intrathecal use of human immunoglobulin. Physiologically, intrathecal administration of TIG would be preferred due to its higher concentration in the cerebrospinal fluid.\(^12\) The meta analysis on intrathecal therapy done by Abruytyn was inconclusive.\(^13\) Tetanus is common in underprivileged socioeconomic strata of Pakistan with lack of antenatal care. The aim of this study was to evaluate the effect of intrathecal human immunoglobulin as an adjuvant to the standard treatment in terms of mortality and hospital stay.

ABSTRACT
Objective: To determine the outcome of tetanus in neonates treated with intrathecal tetanus immunoglobulin in terms of mortality and hospital stay.
Study Design: Experimental study.
Place and Duration of Study: Paediatric Unit I, Bahawal Victoria Hospital, Bahawalpur, from April 2004 to December 2007.
Methodology: Seventy neonates with diagnosis of neonatal tetanus were included in the study. The neonates with fits due to causes other than tetanus were excluded. Thirty five patients received intrathecal immunoglobulin in addition to standard treatment (group A) while, the other 35 patients received only standard treatment (group B). The mortality and duration of hospital stay in 2 groups were recorded.
Results: In group A, mean duration of hospital stay was 10 days while, in group B it was 13 days (p < 0.001). One patient from group A and 8 patients from group B expired (p = 0.026). The occurrence of refractory fits, repeated apnoeic episodes and high grade fever did not show any statistically significant difference in the 2 groups.
Conclusion: Intrathecal anti-tetanus immunoglobulin in addition to the standard improved the outcome of neonatal tetanus in terms of mortality and hospital stay.

Key words: Tetanus. Neonate. Intrathecal immunoglobulin.
METHODOLOGY

This was an experimental study conducted at Paediatric Unit I, Bahawal Victoria Hospital, Bahawalpur, from April 2004 to December 2007. Neonates (aged < 28 days) with diagnosis of neonatal tetanus defined by WHO as trismus (inability to open the mouth) or Risus Sardonicus (sustained spasm of facial muscles) or painful muscular contraction,13 were included. The neonates with fits due to causes other than tetanus were excluded from the study. The Proforma with history and examination was filled after getting written consent from the parents. They were divided into two groups by simple randomization into odd and even numbers, to receive either intrathecal anti-tetanus human immunoglobulin (treatment group = group A) or not (control group = group B) in addition to the standard treatment which included sedation, ATS, Benzyl Penicillin and nursing care. Assisted ventilation was given to patients of any group when needed. The effectiveness of treatment was assessed by mortality and duration of hospital stay. For intrathecal therapy, 250 IU of a lyophilized human immunoglobulin were injected by lumbar puncture after removal of a corresponding volume of cerebrospinal fluid.

SPSS 15.0 was used for analyzing data. Students’ t-test was used to calculate p value for quantitative data like mean duration of hospital stay while chi-square and Fisher's exact test were used to analyze qualitative data like presence or absence of fever, apnea, refractory fits or death in the studied population. P-value < 0.05 was taken as significant.

RESULTS

Seventy newborns were divided in group A (treatment group) and group B (control group) with 35 patients in each group. Three children from group A and three from group B left against medical advice. Mean age at onset was 6.34 ± 1.71 days in group A, while it was 6.53 ± 1.86 days in group B. All the patients belonged to either grade IV or V according to the Patel and Joag classification for severity of tetanus.

In group A, mean duration of hospital stay was 10.00 ± 2.10 days, while in group B it was 13.2 ± 2.64 days (p < 0.001). Apnea was observed in 16 patients (50%) of group A and 12 patients (37.5%) of group B (p=0.313). Fever was observed in 17 patients (53%) of group A and 14 patients (43%) of group B (p=0.453). In group A, refractory fits were observed in 14 patients (43%), 8 patients (25%) in group B (p=0.114). One patient from group A and 8 patients from group B expired (p=0.026), (Table I).

No neurological or local side effects of the intrathecal route were observed.

DISCUSSION

In developing countries, tetanus neonatorum is still a major cause of mortality and morbidity. Some of the factors contributing to persistence of this disease are lack of public awareness about maternal tetanus immunization during pregnancy, false belief about vaccination, delivery in unhygienic conditions and cutting the umbilical cord with unsterilized blades, knives and other instruments. Mortality is still high with the available treatment options. Controversies are still persisting regarding neutralization of toxins in tetanus with reference to dosage and route of administration of anti toxin or TIG. Intrathecal administration has been used to improve the outcome in neonatal tetanus.

The mean duration of stay of the group treated with intrathecal TIG was statistically shorter as compared to the other group in this study. A study also observed significant reduction of hospital stay in neonates who were given intrathecal treatment.14 Miranda-Filho and co-workers also demonstrated short duration of stay in patients treated with intrathecal TIG as compared to intramuscularly.15 This means not only giving TIG is important, but the route of administration of TIG is also important. In the study of Miranda-Filho, 1000 I.U. (high dose) of TIG were used, while in this study 250 IU (lower dose) were used.12,15 The study by Miranda-Filho was conducted on patients aged above 12 years. It means that TIG is effective in the treatment of tetanus regardless of the age. At the same time, TIG also causes reduction in the hospital stay regardless of dose. However, the lower dose given in this study was administered to neonates who obviously have lower body weight than older patient. While in a study by Neequaye, no beneficial effect of intrathecal ATS was noted.16 The reduction in hospital stay has also been documented by Chugh et al.17 This study was also conducted in the patients of tetanus neonatorum and the hospital stay was short in the group of neonates who were given intrathecal TIG.

Regarding the impact and outcome of intrathecal TIG or ATS on patients with reference to mortality, there was statistically significant reduction in the rate of mortality in this study. A meta-analysis performed by Kabura et al. confirmed that intrathecal administration of ATS or TIG is more beneficial than intramuscular administration in

<table>
<thead>
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<th>Features</th>
<th>Group A=32</th>
<th>Group B=32</th>
<th>P-value</th>
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<td>Mean hospital stay (days)</td>
<td>10.00 ± 2.10</td>
<td>13.2 ± 2.64</td>
<td>&lt; 0.001 (t-test)</td>
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<tr>
<td>Fever</td>
<td>17</td>
<td>14</td>
<td>0.453 (Chi-square test)</td>
</tr>
<tr>
<td>Apnea</td>
<td>16</td>
<td>12</td>
<td>0.313 (Chi-square test)</td>
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<tr>
<td>Refractory fits</td>
<td>14</td>
<td>08</td>
<td>0.114 (Chi-square test)</td>
</tr>
<tr>
<td>Death</td>
<td>01</td>
<td>08</td>
<td>0.026 (Fisher’s exact test)</td>
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the treatment of tetanus. The superiority of intrathecal therapy was also found when the analysis was performed in subcategories of both adults and neonates and for high and low dose of intrathecal serotherapy.\textsuperscript{15} Miranda-Filho found no statistically significant reduction in mortality, with intrathecal TIG.\textsuperscript{15} The reason might be the use of TIG in both groups through different routes. Although, Singh used intrathecal ATS which reduced the mortality.\textsuperscript{18} Intrathecal ATS did not reduce the mortality in the study by Neequaye.\textsuperscript{16} In another study, use of intrathecal tetanus immunoglobulin in the management of tetanus showed significant reduction in mortality.\textsuperscript{10}

In this study, there was no difference in the occurrence of fever, refractory fits or apnea in the control and treatment group. All these parameters showed improvement in the study by Miranda-Filho et al.\textsuperscript{15} The age of the patients can be contributing factor for this effect.

Keeping in mind the importance of the topic, further studies are needed to evaluate the role of intrathecal immunoglobulin in the treatment of tetanus neonatorum.

**CONCLUSION**

In this study, there was significant reduction of duration of hospital stay as well as mortality. Keeping in mind the high rate of mortality and morbidity in the tetanus neonatorum, intrathecal anti-tetanus immunoglobulin are beneficial in the management of this disease.

**Conflict of interest:** Authors declare no commercial conflict of interest related directly or indirectly to this article.

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