

## Research Article

# Evaluation of beneficial effects of addition of intramuscular human tetanus immunoglobulin to intrathecal therapy in the treatment of tetanus

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### ABSTRACT

**Background:** The treatment of tetanus has evolved from supportive management only to specific treatment to neutralize the tetanus toxins – tetanospasmin & tetanolysin. Human Tetanus Immunoglobulin (HTIg) is a large molecule and cannot cross the blood brain barrier. Introduction of intrathecal therapy considerably decreased mortality in the disease. Combined administration of intramuscular and intrathecal HTIg should neutralize the tetanus toxins in the circulation and central nervous system simultaneously. The study was done to detect beneficial effects of adding intramuscular HTIg to the intrathecal therapy.

**Methods:** 125 patients of tetanus were randomized to two groups. Study group was given intrathecal plus intramuscular HTIg while control group was given intrathecal HTIg alone. Each group was subdivided into three grades according to severity. Mortality rate and three sequential recovery parameters i.e. duration of spasms, shift to oral therapy and duration of hospital stay were measured.

**Results:** No significant difference in mortality was found. However, in patients who survived, the addition of intramuscular HTIg lead to a benefit of 2.07, 2.67 & 2.31 days in mild, moderate & severe grades respectively in the duration of spasms. Further, it became possible to start oral therapy 2.13, 1.6 & 1.8 days earlier in mild, moderate & severe tetanus. Duration of hospital stay was reduced by 3.87 days, 2.36 days and 3 days in mild, moderate and severe tetanus respectively.

**Conclusions:** Though the addition of intramuscular HTIg to intrathecal therapy in tetanus does not confer any survival benefit, it causes faster recovery in patients who survive.

**Keywords:** Human tetanus immunoglobulin, Intramuscular, Intrathecal, Oral therapy, Spasms, Tetanus

### INTRODUCTION

The earliest record of tetanus is in Edwin Smith *Surgical Papyurs*, supposed to be dated 19<sup>th</sup> Century B.C. Hippocrates in 460 B.C. described the poor prognosis of this disease. Sushruta named the disease as '*dhanushtambha*'. In the clinical picture, he described the lockjaw as paralysis of jaw bone and opisthotonus as '*bahirayamma*'. Charak observed that it was due to provoked wind drying up the external nerves of the back

and the nape of the neck. He further recorded that either the disease killed the patient or caused deformity. Greek physician Aretaeus in first century A.D. mentioned it as "An inhuman calamity, an unseemly sight, a spectacle painful even to behold".

Sir Charles reported a case of tetanus in London. Pollack from Dalin reported a similar case. Bose gave first comprehensive description of the disease. Nicoliers produced tetanus by injecting animals with garden soil. His subsequent description of the bacillus obtained from

the site of injection resembled *Clostridium tetani*. Isolation of micro-organism, clostridium, was done in pure culture by Kitasato. Ehelich separated two distinct and different toxins - Tetanospasmin and Tetanolysin. Marier and Morax and Meyer & Ransom observed the central action of toxin. Tulloch observed different serologic types of the bacillus.

Until 19th century, the treatment was mainly based on volatile general anaesthesia. The physicians relied chiefly on opium and a variety of strange methods in an attempt to arrest the disease. The first hint of rational therapeutic approach came with introduction of the muscle paralyzing effect of crude curare preparations from South America. Sir Benjamin Collins Brodie showed that artificial respiration and bellows preserved the life of curarised animals.<sup>1</sup> Collen used large doses of opium and also recommended the frequent use of laxatives. O'Beirne treated 20 patients of tetanus with tobacco, gum elastic tube and croton oil. He claimed success in 11 of them.<sup>2</sup> Von Bellin and Kitasato did successful immunization against tetanus.<sup>3</sup> Ramon introduced tetanus toxoid 'anatoxine tétanique' as a prophylactic tool in order to prevent the tetanus disease in pets (with P. Descombey) and in humans (with Ch. Zoeller).<sup>4</sup>

*Clostridium tetani* is a gram positive, anaerobic, spore forming bacillus which produces devastating toxins, second only to botulinum in toxicity. The two important toxins produced by Cl. Tetani are tetanospasmin and tetanolysin. Tetanospasmin targets the somatic nerves and causes muscular tension and spasm by blocking the release of the inhibitory neurotransmitters glycine and gamma aminobutyric acid. Tetanolysin similarly inhibits the controlling mechanisms of autonomic nerves, resulting in a labile cardiovascular system, unpredictable respiratory function, sweating, hyperpyrexia and other symptoms of autonomic dysfunction.

The toxins released by the maturing bacilli, are taken up by the lymphatic and vascular circulations and distributed to the endplates of all nerves. This results in a virtual simultaneous uptake of the toxins by all nerves, which then conduct them centripetally to the central nervous system. The rate of transmission is fastest along the sensory and slowest along adrenergic neurons, but the greatest quantity is conducted by motor neurons. The shortest nerves are first to deliver the toxins which give rise to the usual early symptoms of back and neck stiffness and facial distortion. As the toxins are delivered to the spinal cord by the longer nerves, motor nerves are affected sequentially according to their length until all muscles become devoid of central nervous system (CNS) control and contract or go into spasm. Autonomic dysfunction becomes progressively evident as the level of CNS intoxication increases. Local tetanus is the exception to the normal spread of the toxins. It results from the lone intoxication of nerve endings at the site of infection.

The severity of signs and symptoms is directly related to the concentration of the toxin discharged into the blood stream and being transmitted by the nerves to the spinal cord. It is therefore vital to neutralize the toxins in the circulation before they are taken up by the nerves, and equally imperative to neutralize the toxins in cerebrospinal fluid (CSF) before they become fixed to the neurons. Elimination of the toxin in the circulation still leaves toxins passing along the nerves. Once the toxin becomes fixed, it cannot be dislodged. Its effect can only be minimized or prevented.

Conservative management of tetanus consists of good nursing care, keeping the patient in a quiet environment, antibiotics to counter the infection, sedatives and muscle relaxants. The specific management of tetanus is to neutralize unbound toxin by giving antitoxin along with life support.

The first antitoxin used was Antitetanus Serum (ATS) derived from horse serum. Due to the severe anaphylactic reactions it produced, it was superseded by Human Tetanus Immunoglobulin (HTIg) made from human sera. Tetanus Immunoglobulin was initially given by intramuscular route. It was postulated that being a large molecule, most of Tetanus Immunoglobulin cannot cross the blood-brain barrier and neutralize the toxin in the central nervous system.

Ildrim was the first to observe the superiority of intrathecal ATS over intramuscular ATS.<sup>5</sup> But in 1979, Sedaghatian observed that the mortality rate and duration of hospital stay were not significantly different when intrathecal therapy is given compared to intramuscular therapy.<sup>6</sup> Vakil found no significant difference between intrathecal and intravenous groups.<sup>7</sup> Opposite views came out in the studies of Bhandari which showed that intrathecal therapy lead to higher mortality than intramuscular therapy while Mongi showed that intrathecal therapy was superior to intramuscular in the treatment of neonatal tetanus.<sup>8,9</sup> Menon also observed the superiority of intrathecal treatment.<sup>10</sup>

In 2004, Miranda-Filho and colleagues compared the efficacy of intramuscular HTIg (3,000 IU) plus intrathecal HTIg (1,000 IU) with intramuscular HTIg alone and found no significant difference in mortality.<sup>11</sup> But a significant improvement was observed in the treatment group with regard to spasms and duration of hospital stay. Ahmad and colleagues found a significant mortality benefit and a shorter hospital stay when intrathecal HTIg was given for neonatal tetanus.<sup>12</sup>

In the first meta-analysis of intrathecal vs intramuscular therapy trials done by Abrutyn, no benefit of intrathecal serotherapy was found.<sup>13</sup> However not all trials in the meta-analysis were randomized. A meta-analysis of randomized controlled trials done by Kabura et al found a significant benefit of using intrathecal treatment compared to intramuscular treatment.<sup>14</sup> The meta-analysis

also found a significant benefit of using high dose (>250 IU) of intrathecal treatment. The maximum dose of intrathecal treatment was 1500 IU.

The present opinion is that intrathecal treatment is more effective than intramuscular treatment in the management of tetanus. Apart from intrathecal vs intramuscular route, intrathecal route has been compared with intravenous route and intrathecal plus intramuscular route has been compared with intramuscular route. However, there has been no study till date which explored the possibility of beneficial effect of adding intramuscular dose to the intrathecal therapy. The present study was undertaken to gauge whether any beneficial effects in the form of decreased mortality or faster recovery occur on adding intramuscular therapy of HTIg to the intrathecal therapy. It is postulated that while the intrathecal route neutralizes the toxins in the CSF, the toxins are still present in the circulation on which the intrathecal route is ineffective. The addition of intramuscular therapy should have an additive beneficial effect. The recovery parameters used in previous trials i.e. 'duration of spasms' and 'duration of hospital stay' were compared in the present study. Apart from these, 'shift to oral therapy' was also used as a recovery parameter for the first time in any study.

## METHODS

125 patients of tetanus were included in the study. Informed consent was taken from the patients. Those who agreed to participate in the study were randomized to two groups. 65 cases were allocated to the study group and 60 cases were allocated to the control group. Study group patients were given intrathecal plus intramuscular HTIg. These were compared with a control group consisting of 60 patients that were given intrathecal HTIg alone. Supportive treatment was similar in both the groups.

In the study group patients, a lumbar puncture was done under strict aseptic care and 2 ml of CSF taken out. Then HTIg was injected intrathecally. The puncture site was sealed properly. Simultaneously HTIg was injected intramuscularly. The dosages of HTIg in IU were as follows: 2-5 years - intrathecal 500 plus intramuscular 500, 5-10 years - intrathecal 1000 plus intramuscular 750, >10 years - intrathecal 1500 plus intramuscular 1000. In the control group, only intrathecal administration of HTIg as sited above was carried out. All patients were given routine regimen of injection Penicillin, Diazepam, Methocarbamol, Chlorpromazine, etc. Patients below 2 years or above 70 years of age and those who died within 12 hours of admission were excluded from the study.

Five criteria were used in grading the severity of the disease. Criterion (C) – 1: Lockjaw, C-2: Spasms, C-3: Incubation period of 7 days or less, C-4: Period of onset of spasms of 48 hours or less, C-5: Fever defined as axillary temperature of 99°F or rectal temperature of 100°F on admission or within 24 hours of admission.

This grading has been modified from criteria devised by Patel and Joag.<sup>15</sup>

The grading was done as follows:

- Mild: Only one or two of the five criteria, generally C-1 and/or C-2. Occasionally fever (C-5) with C-1 or C-2.
- Moderate: Consisted of three of the five criteria, i.e. C-1 + C-2 and any one of the other three criteria.
- Severe: Consisted of at least four of the five criteria.

A comparative study between each corresponding grade of the two groups was carried out regarding the survival rate, duration of persistence of spasms, shift to oral therapy, duration of hospital stay and any side effects.

Fisher Exact Test was used for comparison of mortality. Continuous variable data was compared by independent t-test and reported as mean  $\pm$  standard deviation (SD).  $p < 0.05$  was considered significant.

## RESULTS

The mortality was nil in mild tetanus in both the groups. No significant difference in mortality was found due to addition of intramuscular HTIg in moderate and severe tetanus (Table 1). Overall mortality was 15.38% in study group which was not significantly different from the standardized mortality for severity of the control group which was 14.88% (Table 1a).

Addition of intramuscular HTIg had a significant effect on the duration of spasms in mild, moderate and severe tetanus (Table 2). Spasms persisted for only an average of 0.33 days in mild tetanus in study group compared to 2.4 days in control group. In moderate & severe tetanus, the difference was very highly significant. The spasms lasted only an average of 1 day in moderate tetanus in study group compared to 3.67 days in control group. In severe tetanus they lasted for an average of 1.45 days & 3.76 days in study and control groups respectively.

Addition of intramuscular HTIg also facilitated earlier shift to oral therapy (Table 3) which was an average of 5.08 days in mild tetanus in study group compared to 7.21 days in control group. In moderate tetanus shift to oral therapy occurred in 5.9 days in study group while it was 7.5 days in control group. In severe tetanus, the oral therapy was started in 8.61 days in study group and 10.41 days in control group. All the differences were statistically significant.

Overall benefit was also found in duration of hospital stay in the study group (Table 4). The mean duration of hospital stay ranged from 10.92 days in mild tetanus, 12.7 days in moderate tetanus and 15.82 days in severe

tetanus. This was earlier than in control group which ranged from 14.79 days in mild tetanus, 15.06 days in

moderate tetanus and 18.82 days in severe tetanus.

No side effects of HTIg were observed in either group.

**Table 1: Comparison of mortality rates in study and control groups.**

Severity	Study group			Control group		
	Patients	Expired	Mortality (%)	Patients	Expired	Mortality (%)
Mild	12	0	0	19	0	0
Moderate	11	1	9.09	19	1	5.26
Severe	42	9	21.43	22	5	22.73
Total	65	10	15.38	60	6	10.00

Fisher test statistic value =1, not significant

**Table 1A: Standardized mortality of control group vis a vis study group.**

	Study group	Control group (Standardized)
Mortality (%)	15.38	14.88

Fisher test statistic value =1, not significant

**Table 2: Mean duration of persistence of spasms (in days).**

	Study group	Control group	p value
Mild	0.33 ± 0.3	2.4 ± 1.27	0.035
Moderate	1 ± 0.34	3.67 ± 1.53	<0.0001
Severe	1.45 ± 1.19	3.76 ± 2.31	<0.001

**Table 3: Comparison of shift to oral therapy (in days).**

	Study group	Control group	p value
Mild	5.08 ± 3.23	7.21 ± 2.76	0.034
Moderate	5.9 ± 2.91	7.5 ± 1.71	0.044
Severe	8.61 ± 3.04	10.41 ± 3.34	0.033

**Table 4: Mean duration of hospital stay (in days).**

	Study group	Control group	p value
Mild	10.92 ± 5.98	14.79 ± 5.32	0.04
Moderate	12.7 ± 3.77	15.06 ± 3.76	0.069
Severe	15.82 ± 3.55	18.82 ± 8.05	0.04

## DISCUSSION

The introduction of intrathecal therapy has considerably reduced mortality in tetanus and has now become standard therapy in many centres. Even after reduction, the mortality is considerable in severe tetanus. In the present study, mortality was nil in mild tetanus in both study and control groups while it was 9.09% & 5.26% respectively in moderate tetanus. In severe tetanus, the corresponding figures were 21.43% & 22.73%.

Agarwal M et al observed a mortality of 20% in mild tetanus and 62.5% in severe tetanus when they used 250

IU of intrathecal HTIg.<sup>16</sup> Miranda-Filho et al could decrease the mortality to 7% when they added a dose of 1000 IU of intrathecal HTIg to 3000 IU of intramuscular HTIg while comparing it with intramuscular dose only. In their group, most of the patients were having mild to moderate tetanus. In the present study, 1500 IU of intrathecal HTIg was used in patients over 10 years of age. The total mortality was 15.38% in the study group having a majority proportion of patients having severe tetanus. Thus the study reconfirms the mortality benefit of using higher doses of intrathecal HTIg.

The study found no survival benefit of adding intramuscular HTIg to intrathecal therapy. However, the benefit of adding intramuscular HTIg occurred in patients who survived and resulted in faster recovery. In these patients, intramuscular HTIg significantly reduced duration of spasms. The benefit of adding intramuscular therapy was seen in all subgroups as spasms lasted for a mean duration of 0.33, 1 & 1.45 days in mild, moderate & severe tetanus respectively. This translated into a benefit of more than 2 days in all subgroups as spasms were controlled 2.07, 2.67 & 2.31 days earlier in the mild, moderate & severe grades respectively of the study group.

Though spasm is a reliable indicator in tetanus, there is no published study which has documented the mean duration of spasms. However the study by Miranda-Filho et al (vide supra) has commented that in patients in whom spasms were controlled in less than 10 days, 68% were those receiving intrathecal plus intramuscular HTIg while 32% were those receiving intramuscular HTIg.

The benefit of adding intramuscular HTIg continued after control of spasms as it was possible to shift these patients to oral therapy earlier. It was possible to start oral therapy 2.13 days earlier in mild tetanus, 1.6 days earlier in moderate tetanus and 1.8 days earlier in severe tetanus with all the differences assuming significant value. ‘Shift to oral therapy’ was used as a novel marker in this study. It represents an approximate ‘midpoint’ of recovery

process occurring between control of spasms and discharge from hospital.

Ultimately, the earlier control of spasms and an earlier shift to oral therapy in the study group had an amplifying benefit on the duration of hospital stay. In the study group, patients with mild, moderate and severe tetanus had a mean duration of hospital stay of 10.92 days, 12.7 days and 15.82 days respectively. Patients in the study group with mild tetanus were discharged 3.87 days earlier while those with moderate and severe tetanus were discharged 2.36 days and 3 days earlier respectively.

The study by Agarwal M et al. (vide supra) reported a mean duration of 12.3 days in mild tetanus and 29 days in severe tetanus patients receiving intrathecal therapy though the study had only 8 & 3 patients respectively in the above groups. The study by Miranda-Filho et al. (vide supra) had observed a reduction in duration of hospital stay in patients receiving intrathecal therapy with 43% of patients being discharged within 15 days as compared to 27% of patients being discharged within 15 days in intramuscular group. The present study suggests a further reduction in hospital stay when intramuscular HTIg is added to intrathecal therapy.

In the present study, no side effects of HTIg were observed in either group. Most of the other clinical trials had also not reported any side effects of HTIg though Robert et al. reported reversible paraplegia after high dose of intrathecal human immunoglobulin.<sup>17</sup>

Thus the benefit of adding intramuscular HTIg was found in all three parameters observed. It causes faster recovery of the patients and thus reduces hospital burden. An explanation of the benefit may be suggested. While intrathecal HTIg neutralizes the tetanus toxin in the CSF, the intramuscular dose neutralizes it in the circulation before it is taken up by the nerves. Thus the combined administration neutralizes the toxins more effectively. However, in patients who succumb to the disease, most of the toxin is already fixed and cannot be neutralized. Hence addition of intramuscular therapy is not helpful in reducing mortality.

## CONCLUSIONS

The addition of intramuscular HTIg to intrathecal therapy in tetanus does not confer any survival benefit. However, the benefit of combined administration occurs in patients who survive and manifests by faster recovery. It causes earlier control of spasms, earlier shift to oral therapy, and reduced duration of hospital stay and is without any side effects.

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