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TO EVALUATE THE ROLE OF INTRATHECAL HATG AND ITS COMPARISON WITH INTRAVENOUS AND INTRAMUSCULAR HATG IN TREATMENT OF TETANUS

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Abstract
Background: Tetanus is a vaccine-preventable disease that continues to occur despite several decades of sustained global health programs. Recently outbreaks of tetanus have been reported after natural disasters such as tsunamis and earthquakes.
Methods: The present study was carried out among 30 patients of tetanus irrespective of age, sex and severity, admitted in P.B.M. Hospital, Bikaner.
Results: Overall mortality was 30% in present study. Out of 10 patients in each group one in group I, 4 in group II and 4 in group III expired respectively. So the mortality was 10% in group I, 40% in group II & III. In mild tetanus mortality was nil in all groups. In moderate tetanus mortality was 9.9%. All patients of moderate tetanus in group I and II survived. In group III mortality in moderate tetanus patients was 20%. In severe tetanus patients over all mortality was 53.3%, in group I 25%, in group II and 50% and in group 10% respectively.
Conclusion- Intrathecal HTAT is safe and effective treatment.
Keywords: Intrathecal, Intravenous, Mortality, HTAT.

INTRODUCTION

The earliest record of tetanus is in Edwin Smith Surgical Papyurs, supposed to be dated 19th 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 paralysing effect of crude curare preparations from South America. Sir Benjamin Collins Brodie showed that artificial respiration and bellows preserved the life of curarised animals.[1] 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.[2] Von Bellin and Kitasato did successful immunization against tetanus.[3] 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).[4]

Material and methods

The present study was carried out among 30 patients of tetanus irrespective of age, sex and severity, admitted in P.B.M. Hospital, Bikaner.

Patients were graded as mild, moderate and severe tetanus.

Mild : Trismus, dysphagia, localized rigidity but no spasm.

Moderate : trismus, dysphagia, localized rigidity and occasional spasm.

Severe : Trismus, dysphagia generalized rigidity reflex spasms at hourly interval or more frequently.

A detailed history was recorded with complaints and duration. The thorough general physical and local examination was carried out. Presenting signs of tetanus in form of Trismus (Lockjaw), neck rigidity, limb rigidity, dysphagia, abdominal muscle rigidity, frequency of spasms, reflex spasms and opisthotonus were noted.

Routine investigations i.e. blood (Hb, BT, CT, TDLC) urine (Alb, Sugar and Microscopic) was done. Grading of patients were done as mild, moderate and severe according to frequency of spasms.

Patients were divided into three groups; and HATG was given to all patients by different routes in different groups.

Group I : 10 cases were kept in group I and given intrathecal HATG 250 IU.

Group II : 10 patients were kept in group II and given intravenous HATG 1000 IU.

Group III : 10 patients were kept in group III and given intramuscular HATG 1000 IU.

Technique

1. Intrathecal :

Lumbar puncture was done with aseptic precautions in between 3rd and 4th lumber vertebrae. When there was free flow of C.S.F. than 250 IU of HATG was injected intrathecally slowly.

2. Intravenous :

1000 IU of HATG was dissolved in 200 cc of normal saline and it was given by IV infusion 20 drops per minute.

3. Intramuscular

1000 IU of HATG was given IM stat.

Conventional treatment in all patients was same and given as follow –

(1) ATS :

Inj. ATS 1 lacs IU in patients above 12 years and 50000 IU in patients below 12 years.

Half dose of ATS was given IV and half was given by IM routes after doing sensitivity test.

(2) Antibiotics

In adult patients Inj. C.P. 10 lacs IU was given by IV / IM 6 hourly after doing sensitivity test and in children C.P. 5 lacs was given IV/IM 6 hourly AST for the period of 10 to 14 days. In some patients Inj. C.P. was given with combination of other antibiotics i.e. chloramphenicol, gentamycin, cephexin and metrogly etc. whenever chest complication or other complication occurs.

(3) Sedatives

OBSERVATIONS

The total patients studied under this dissertation were 30, out of which 10 were in group I (intrathecal HATG), 10 in group II (intravenous HATG) and 10 in group III (intramuscular HATG).

Table 1: Shows male and female ratio in different age group

Age in years	Total				Total	
	Survived		Expired		Male	Female
	Male	Female	Male	Female		
0-5	1	3	1	1	2	4
6-10	4	1	-	-	4	1
11-20	2	4	-	4	2	8
21-30	1	1	-	1	1	2
31-40	-	-	-	1	-	1
41-50	1	2	-	1	1	3
Above	1	-	-	-	1	-
Total	10	11	1	8	11	19

The tables no. 1 shows the male, female ratio in different age groups. Among the 30 cases studied, 11 patients were male and 19 were female giving a ratio of 1:1.7. Maximum number of patients of both sexes were seen in first and second decade of life.

Table 2: Showing various sources of infection

Source of infection	Group I		Group II		Group III		Total		Total
	Survived	Expired	Survived	Expired	Survived	Expired	Survived	Expired	
Trauma	-	-	3	1	2	2	5	3	8
Puerperium	-	-	1	2	1	2	2	4	6
CSOM	3	-	-	-	-	-	3	-	3
Post Inj.	-	-	-	-	1	-	1	-	1
Post Op.	-	-	-	-	1	-	1	-	1
Unknown	6	1	2	-	1	-	9	1	10
Multiple TB sinuses	-	-	-	1	-	-	1	-	1

The source of infection was unknown in 10 (33%) patients out of whom one expired.

Table 3: Showing incubation period

Incubation period	Group I		Group II		Group III		Total		Total
	Survived	Expired	Survived	Expired	Survived	Expired	Survived	Expired	
Less than 10 days	1	-	1	3	3	3	5	6	11
11-30 days	2	-	3	-	1	1	6	1	7
More than 30 days	1	-	-	-	1	-	2	-	2
Unknown	5	1	2	1	1	-	8	2	10

Incubation period was unknown in 10 patients. Out of them 2 expired. Incubation period upto 10 days was seen in 11 patients, out of them 7 expired. In 7 patients incubation period was ranging from 11 to 30 days out of them one expired. In two (2) patients incubation period was more than one month, both survived. Incubation period does not show any significant relation with mortality

Table 4: Showing period of onset in different groups

Period of onset	Group I		Group II		Group III		Total		Total
	Survived	Expired	Survived	Expired	Survived	Expired	Survived	Expired	
Nil	1	-	1	-	1	-	3	-	3
Less than 48 hours	7	1	4	4	3	4	14	9	23
2-5 days	1	-	1	-	1	-	3	-	3
More than 5 days	-	-	-	-	1	-	1	-	1

The period of onset was less than 48 hours in 23 patients, out of them 9 (39.5%) expired. The period of onset ranging from 2-5 days was observed in 3 patients ; more than 5 days in one patient, all survived. The maximum number of patients (23) were having period of onset less than 48 hours, showing maximum mortality (39.5%).

Table 5: Showing grade of tetanus and progress towards severity

Grade of tetanus	Group I			Group II			Group III			Total		Total
	Survived	Expired	Progress	Survived	Expired	Progress	Survived	Expired	Progress	Survived	Expired	
Mild	1	-	-	1	-	-	2	-	1	4	-	4
Moderate	5	-	-	1	-	-	5	1	4	1	10	11
Severe	3	1	-	4	4	-	-	3	-	7	8	15

The total no. of patients of mild tetanus were 4 in all groups. All of them survived, 1 patient in group I, one patient in group II and 2 patients in group III. One patient in group III progressed from mild to moderate tetanus inspite of starting the treatment.

The patients of moderate tetanus in all groups were 11 out of them one expired. In group I there were 5 patients & all survived and did not progress towards severity, in group II there was one patient who survived and did not progressed to severe tetanus. There were 5 patients in group III. Out of them 4 progressed to severe tetanus and one expired.

There were 15 patients of severe tetanus in all groups. Out of them 8 expired. The mortality in severe patients was 53.3%. There were 4 patients in group I, 8 patients in group II and 3 patients in group III. One patient in group I, 4 patients in group II and all three patients in group II expired.

Table 6: Showing various complications

Complications	Group I		Group II		Group III		Total		Total
	Survived	Expired	Survived	Expired	Survived	Expired	Survived	Expired	
Bronchopneumonia	2	-	3	-	1	1	6	1	7
Bedsore	-	-	1	-	1	-	1	-	1
Anaphylaxis	-	-	-	1	-	-	-	1	1

The bronchopneumonia developed in 7 patients, out of them 2 patients in group I, 3 patients in group II and 2 patients in group III, one patient in group III expired.

Bed sores developed in one patient of group III who survived. One patient in group II expired due to anaphylactic reaction with ATS.

Table 7: Showing average duration of control of reflex spasm in various groups

Grade of tetanus	Group I		Group II		Group III		Total		Total
	Survived	Expired	Survived	Expired	Survived	Expired	Survived	Expired	
Mild	No spasm	-	No spasm	-	0-7 days	-	0-7 days	-	-
Moderate	5 days	-	5 days	-	10 days	5 days	6.6 days	5 days	-
Severe	8.3 days	2 days	9 days	2 days	-	27 days	8.6 days	2.2 days	
Total	6.6	5 days	4.6 days	2 days	8.8 days	3.8 days	6.6 days	3.6 days	-

In group I there was one patient of mild tetanus who never developed reflex spasms. Average duration of control of reflex was 5 days in moderate tetanus and 8.3 days in severe tetanus. One patient of severe tetanus expired on second day.

In group II there was one patient of mild tetanus who has no reflex spasms. In moderate and severe tetanus average duration of control of reflex spasm was 5 days and 9 days respectively.

In group III there were two cases of mild tetanus one never developed reflex spasms and another one progressed in moderate tetanus in which reflex spasms were controlled on 7^{th} day, in moderate tetanus average duration of control of reflex spasm was 10 days. All patients of severe tetanus expired on 2.7^{th} days.

Table 8: Showing average stay of patients in days in hospital

Grade of tetanus	Group I		Group II		Group III		Total	
	Survived	Expired	Survived	Expired	Survived	Expired	Survived	Expired
Mild	13	-	10	-	9.5	-	10.83	-
Moderate	9.1	-	20	-	16.5	5	15.2	5
Severe	11.7	2	20	2	-	2.7	15.85	2.2
Total	11.2	2	16.6	2	13	3.8	13.96	3.6

The average stay in hospital was 13.96 days in survived patients, 11.2 days in group I, 16.6 days in group II and 13 days in group III. Minimum hospital stay was observed in group I.

Hospital stay in patients of mild tetanus was 13 days in group I, 10 days in group II and 9.5 days in group III almost equal in all groups.

In patients of moderate tetanus average stay in hospital was 15.2 days. 9.1 days in group I, 20 days in group II and 16.5 days in group III. Minimum hospital stay was in group I. The average stay of severe tetanus patients in hospital was 15.85 days. 11.7 days in group I, 20 days I group II and all patients in group III expired on 2.7 days.

Table 9: Showing mortality in various groups

Grade of tetanus	Group I		Group II		Group III		Total	
	Survived	Expired	Survived	Expired	Survived	Expired	Survived	Expired
Mild	1	-	1	-	2	-	4	-
Moderate	5	-	1	-	4	1	10	1
Severe	3	1	4	4	-	3	7	8
Total	9	1	6	4	6	4	21	9

Overall mortality was 30% in present study. Out of 10 patients in each group one in group I, 4 in group II and 4 in group III expired respectively. So the mortality was 10% in group I, 40% in group II & III.

In mild tetanus mortality was nil in all groups. In moderate tetanus mortality was 9.9%. All patients of moderate tetanus in group I and II survived. In group III mortality in moderate tetanus patients was 20%. In severe tetanus patients over all mortality was 53.3%, in group I 25%, in group II and 50% and in group 10% respectively.

Discussion

Risk of intramuscular injection are minimal. All tetanus patients currently receive intramuscular injection of antitoxin; therefore there is no additional risk associated with participating in this study. Intramuscular injection of human antitoxin is reported to be associated with fewer adverse reactions than the current standard equine antitoxin.

The intrathecal intervention group will have the additional risk of lumbar puncture. The most serious complication that may be linked to lumbar puncture is cerebral herniation. This has never been reported in patients treated with intrathecal antitoxin in tetanus. This event is argued to be a result of associated raised intracranial pressure not the lumbar puncture procedure and as raised intracranial pressure does not occur in tetanus the risk of this event is extremely low (<0.001%). No lumbar punctures will be performed if the patient is suspected of having raised intracranial pressure or has a contra-indication to lumbar puncture. Other risks of lumbar puncture include infection (rare and currently < 0.1% at Hospital for Tropical Diseases), headache and venous puncture. Staff who will be performing the lumbar puncture are highly experienced clinicians who have performed this procedure >500 times.

Studies using intrathecal antitoxin report a low incidence of AEs. Most older studies used either equine antitoxin or human antitoxin preparations containing thimerosal preservative, which has been suggested to be responsible for many of the side effects. Only 1 published study of human tetanus immunoglobulin has reported the exact formulation used. In this study by Menon *et al.*, 41 patients were treated with TetGlob, a product containing thimerosal. One patient was reported to have mild learning difficulties and cerebral palsy on long-term follow up; a child aged of 11 months at the time of treatment, the authors felt this was most likely due to the age of the child and severity of disease. Studies in Africa have reported incidence of learning difficulties and cerebral palsy to be 20–40% in survivors of neonatal tetanus treated without intrathecal antitoxin.[5,6]

Conclusion

Intrathecal HTAT is safe and effective treatment.

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