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DOUBLE-BLIND TRIAL OF INTRAMUSCULAR AND INTRAMUSCULAR PLUS INTRATHECAL HUMAN TETANUS IMMUNOGLOBULIN AND INTRAMUSCULAR EQUINE TETANUS ANTITOXIN IN THE TREATMENT OF TETANUS NEONATORUM*

*Asım Gültekin MD***, Mehmet Y. Akarca MD****, Aynur Oğuz MD**
*Ayşe Gökalp MD***, Güler Kanra MD*****

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Tetanus, still a serious worldwide health problem, is one of the major causes of death in many developing countries[1-4]. The mortality rate is particularly high in neonates, calling for serious measures to be taken in all developing countries. According to some reports, the mortality due to neonatal tetanus may be as high as 69 to 79 percent[5-7].

The management of this disease in many developing countries consists of the administration of equine tetanus antitoxin (TAT) or human tetanus immunoglobulin (TIG) in combination with sedatives and antibiotics due to the lack of mechanical ventilation facilities[8-15]. Varying dosages of TAT and TIG have been used and different results have been reported[8-14]. It is believed that 10,000 units of TAT or 500 units of TIG yield optimal effects in the treatment of tetanus neonatorum[10,16]. The aim of this study is to compare the intramuscular and the intrathecal plus intramuscular administration of TIG with the intramuscular administration of TAT in the treatment of neonatal tetanus.

Material and Methods

One hundred and twenty-two cases of neonatal tetanus were admitted to Cumhuriyet University Hospital between 1979 and 1984. Of these, 81 cases were

* From the Department of Pediatrics, Cumhuriyet University Faculty of Medicine, Sivas.
** Associate Professor of Pediatrics, Cumhuriyet University Faculty of Medicine.
*** Resident in Pediatrics, Cumhuriyet University Faculty of Medicine.
**** Professor of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

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admitted between 1979-1982 and treated with 10,000 units TAT intramuscularly. The remaining 41 cases which were subdivided into two groups at random were admitted between 1983-1984 and were treated with TIG which was obtained from the Refik Saydam Central Institute of Hygiene[17]. Group A consisted of 21 cases treated with 500 units TIG intramuscularly plus 250 units intrathecally. Group B consisted of 20 cases treated with 500 units TIG intramuscularly. A clinical diagnosis was made and the age, sex, weight, incubation period, rectal temperature, clinical symptoms and signs were recorded for each infant at the time of admission. The time of death, days of sedation and mortality were also recorded. After clinical evaluation, the patients were graded according to the criteria of Patel and Joag[18] in which one point was assigned to each of the following symptoms: presence of lockjaw, presence of spasms, incubation period of seven days or less, period of onset of convulsions of 48 hours or less, axillary or rectal temperature of at least 37.5°C on admission or within 24 hours of admission. Patients with one or two symptoms were classified as mild, patients with three symptoms as moderate and those with more than three symptoms as severe. The patients were kept in a separate quiet ward, and disturbed as little as possible. The umbilical cord of each patient was cleaned as this was considered a possible portal of entry for infection. On admission a peripheral intravenous infusion of 5% dextrose in 0.18% saline was administered. Feeding was initiated as soon as a nasogastric tube could be inserted without causing any severe spasms. Intravenous hyperalimentation was not needed in any of the cases. Particular care was given to clearing the nasopharyngeal secretions.

Muscular relaxation and sedation were achieved by nasogastric or intravenous diazepam. In the cases with severe muscular spasms 2.5 mg diazepam was given intravenously at every half hour. As soon as a nasogastric tube could be used, diazepam 40 mg/kg/day every two hours was continued.

Crystalline penicillin was given in a dosage of 100,000 units/kg/day intramuscularly for ten days. In addition, gentamycin, in a dosage of 5-7 mg/kg intramuscularly, was administered according to the clinical condition of the patient.

Results

All infants were born at term and delivered at home with the help of unqualified midwives. The umbilical cords of some infants had been cut with unsterilized instruments such as knives, scissors or blades[5]. Trismus was one of the most commonly observed clinical signs. The main symptoms and signs of the cases on admission and the various characteristics of the groups are compared and shown in Tables I and II.

The most important complications encountered in the patients in our study were pulmonary infections and gastroenteritis. There were no adverse reactions attributable to the intrathecal administration of TIG.

The mortality rate was 58% in the TAT Group and 46% in the TIG Group. The mortality rate of TIG Group A was 38% and of TIG Group B 55% (Table III). These results were not considered to be significant from the statistical point of view ($p>0.05$).

TABLE I: Signs, Symptoms and Severity of Illness in Both Groups of Infants on Admission

	TIG Group		TAT Group
Signs and symptoms	A Group intrathecally plus intramuscularly (n: 21)	B Group intramuscularly (n: 20)	intramuscularly (n: 18)
Refusal to feed	21	20	80
Convulsion (tetanic spasms followed by clonic movement)	18	18	79
Trismus	21	20	81
Generalised rigidity on arrival	17	16	76
Irritability	16	17	78
Cyanosis	12	13	77
Respiratory distress	7	6	24
Opisthotonus on arrival	13	11	70
Risus sardonicus	15	18	76
Poor reflexes	8	7	70
Rectal temperature on admission			
≤ 37.5°C.	5	6	22
37.6°C - 39°C	9	11	45
≥ 39.1°C.	7	3	14
Severity of illness			
Grade I and II (mild)	1	1	5
Grade III (moderate)	2	3	12
Grade IV and V (severe)	18	16	64

TABLE II: Comparison of Various Characteristics of the Two Treatment Groups

Characteristics	TIG Group A Group (n: 21)	TIG Group B Group (n: 20)	TAT Group (n: 18)
Mortality	8 (38%)	11 (55%)	47 (58%)
Age on admission (days)	10.28 ± 9.3*	8.8 ± 5.52	9.2 ± 6.85
Sex			
Male	17 (81%)	16 (80%)	65 (80%)
Female	4 (19%)	4 (20%)	16 (20%)
Body weight (g)	3200 ± 706	3190 ± 797	3185 ± 750
Incubation periods			
≤7 days	12 (57%)	11 (55%)	44 (54%)
8 - 14 days	9 (42.9%)	9 (45%)	37 (46%)
Duration of therapy (days)	19.76 ± 14.0	20.44 ± 6.64	21.75 ± 14.20
Duration of sedation (days)	18.30 ± 4.71	20.33 ± 9.74	19.50 ± 6.60
Duration of nasogastric feeding (days)	16.92 ± 11.80	19.11 ± 9.66	17.86 ± 9.60

* Mean ± 2 SD.

TABLE III: Mortality Rates of TIG and TAT Groups

Cases	TIG Group A Group	TIG Group B Group	TAT Group
Survivors	13 (63%)	9 (45%)	34 (42%)
Deaths	8 (38%)	11 (55%)	47 (58%)
Total	21	20	81

Discussion

In developing countries, deliveries effected under septic conditions by unqualified midwives may be the reason for most cases of neonatal tetanus. In this study, most of the cases were likewise delivered at home. Some, in accordance with regional traditions were swaddled after specially prepared soil was placed between their legs, serving as a diaper. This custom contributed to the higher incidence of tetanus neonatorum in the region.

As shown in Table I the clinical signs of our cases conformed with those in the literature[9,13]. Although some authors reported a higher number of male patients

compared to female patients their findings were not as high as ours[19]. In our study this ratio was observed to be 4:1. This difference has been considered to arise from the excessive attention the parents in this region give to their male infants.

Since the nineteenth century, different dosages of antitoxic serum therapy have been used and different results have been reported[8-14]. It is a well-known fact that one of the most important problems of neonatal tetanus is delay in diagnosis. Profuse toxin may penetrate into the cerebral system by the time diagnosis is made. Sanders et al[20] suggested that the initial spasms resulted from freely circulating tetanus toxin available for neutralization and after 24 hours, when the toxin is presumed to be fixed to the anterior horn cells, intrathecal antitoxin ceases to have much effect. Patel et al[21] investigating the circulation of TAT have reported a very poor penetration of TAT into the cerebrospinal fluid when not administered intrathecally.

In a study carried out by McCracken et al[10] antitetanus serum was used only intramuscularly and the mortality rate was found to be 41 percent in the TAT Group and 40 percent in the TIG Group, whereas in Sedaghatian's[9] series, the mortality rate was found to be 50 percent in the TAT and 43 percent in those administered TIG intrathecally in addition to TAT. The difference in the mortality rate between the two groups was not significant. In a study carried out in our country between the years 1959 - 76, 229 cases of neonatal tetanus were treated with TAT by different routes of administration and the overall mortality rate was found to be 66 percent[22]. In that study, in which the mortality rate was 36 percent, the best results were obtained when TAT was administered intramuscularly and intrathecally. In our study, the overall mortality rate was found to be 58 percent in the TAT Group and 46 percent in the TIG Group. We obtained the best results with the administration of TIG intramuscularly and intrathecally, in which the mortality rate was 38 percent.

Although the mortality rate in our study is similar to the studies mentioned above, in some other studies, a lower mortality rate in comparison to that of ours, has been reported[12,15]. The reason for this high mortality rate in our study is due to the severity of illness and delay in consulting the physician. Unfortunately, 80% of our cases were in Grades IV and V of the disease, as shown in Table I. In studies carried out in children and adults, it was shown that when intrathecal serotherapy was used in the early stages of the disease, better results were obtained[13,14]. We believe that the mortality rate in our cases could have been reduced if the infants had been hospitalized and given intrathecal TIG therapy at an earlier stage.

In conclusion, we can say that if TIG is available, the administration of TIG intramuscularly and intrathecally is the best way to treat neonatal tetanus. However, in spite of the various treatment methods, the mortality rate is high.

Furthermore, the duration of treatment is long and costly. Therefore, preventive measures, especially vaccination of pregnant women are essential for the eradication of the disease.

Summary

One hundred and twenty-two cases diagnosed as neonatal tetanus were admitted to our hospital between 1979 and 1984. Of these, 81 cases were treated with equine tetanus antitoxin (TAT) and 41 with human tetanus immunoglobulin (TIG). The latter were subdivided into two groups at random, Group A and Group B. Group A consisting of 21 cases, were treated with TIG intramuscularly and intrathecally, whereas group B consisting of 20 cases had only intramuscular TIG therapy. The overall mortality rate was found to be 58% in the TAT Group and 46% in the TIG Group. Whereas the mortality rate of TIG Group A was 38% and that of Group B 55%. Although no significant statistical difference in the mortality rates of both the TIG and TAT Groups and Groups A and B was observed, it is consequently believed that the use of TIG intramuscularly and intrathecally with appropriate supportive therapy, may yield more successful results.

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