ORIGINAL ARTICLE

High Dosage Diazepam as Single Antispasmodic Agent in the Treatment of Neonatal Tetanus

by

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Abstract

An evaluation of diazepam as a single antispasmodic drug in the treatment of neonatal tetanus was made on 30 neonates, who were admitted to the Dept. of Child Health, General Hospital, Denpasar. Diazepam (Valium) was given with the dose of 2,5 mg intravenously at 2 hours intervals. It can be increased in very severe cases, to a maximal dose of 40 mg/kg.bw/day.

The overall mortality of this study was 20%. Almost all deaths occurred within the first 5 days. Incubation period of less than 7 days, period of onset of less than 48 hours, age on admission of less than 5 days and spontaneous paroxysmal spasm were important factors to contribute to the high mortality. The mortality also rose in proportion to the severity according to Patel and Joag criteria.

Received 20 August. 1982

Introduction

Tetanus as a preventable disease is still a major public health problem in developing countries. The incidence of this disease is still high. Geographic, social, cultural and economic factors interrelate to form an important background for the prevalence of this disease. Lack of education, inadequate medical care and ignorance are also important factors to contribute to the high incidence of this disease. (Athavale and Pai, 1964; Stoll, 1979).

Furthermore, treatment of neonatal tetanus is still a major challenge to the pediatrician in the developing countries. Various forms of treatment have been tried (Adam et al, 1979; Bhat et al, 1979; Khoo and Lee, 1978; Liem Wie Tjoen et al, 1970; Sedhagatian, 1979; Sing et al, 1980), but the result was still very controversial. For sedation, and control of spasms the commonly used drugs are phenobarbitone and chlorpromazine (Gupta et al, 1979). However in higher doses serious side effects like depression of respiration, hypotension and hypothermia frequently appear. It would be desirable to have some drugs which would have similar good spasms controlling properties and yet be free of these serious side effects. Diazepam has been used in some centres and proclaimed to be effective (Femi Pearse, 1966; Ismudijanto et al, 1981; Khoo and Lee, 1978; Taslim S. Soetomenggolo et al, 1981).

The purpose of this study is to evaluate the result of high dosage diazepam with the maximal dosage of 40 mg/kg bw/day as a single antispasmotic drug in treating patients with neonatal tetanus, and to find out the factors which might contribute to the mortality of the disease.

Material and Methods

The 30 cases of neonatal tetanus who were admitted to the Department of Child Health at the General Hospital of Denpasar from July 1981 to June 1982 were taken for this study. The age, sex, birth place, mortality, period of onset, incubation period, duration of hospital stay were analysed. All cases were classified into 5 grades of severity according to the criteria of Patel and Joag (reviewed by Athavale, 1964). After admission, treatment were given as follows:

a. Intravenous fluid drip (IVFD) with 10% dextrose was started and continued till spasms were adequately controlled (Adam et al, 1979; Gupta et al, 1979). After 48-72 hours of admission, gastric feeding were introduced (Taslim S. Soetomenggolo et al, 1981).
b. Anti tetanus serum (ATS) 5000 units were given intravenously on admission and the next day.
c. Antibiotics used were ampicillin 125 mg intravenously at six hours interval for five days and ampicillin in the same dose orally for the next five days. Additional antibiotics were used if secondary complication set in.
d. Diazepam (Valium) of 2,5 mg was given intravenously at 2 hours intervals. In cases where spasms were not adequately controlled, the dosage should be increased gradually to a maximal dose of 40 mg/kg bw/day (Ismudijanto et al. 1981; Khoo and Lee, 1978; Taslim S. Soetomenggolo et al, 1981). After spasms could be controlled, the drug was withdrawn gradually. If there were no spasms for 3 days, sedation was stopped (Sutanto Dibyosubroto, 1980).
e. Treatment of the umbilical cord was restricted to cleaning of the stump with 95% alcohol or 10% betadine solution.
f. Especially stern measures were taken to clean the respiratory tract during and after the spasms.
g. Oxygen was given as needed.

Result

A. Age and sex incidence

Table 1 lists the age on admission, sex incidence and the mortality. Of the 4 patients aged 5 days or less, only 1 patient recovered and 3 died (75%). Of those between 6-10 days old, 10 recovered and 11 died (52.38%), while the 5 patients older than 10 days, 1 (20%) died and 4 recovered. The overall mortality of the 30 patients was 50%.

From this table we can see also that of the 30 patients, 18 were males and 12 were females. Thus the sex ratio was 3:2. Male to female ratio of the dead patients were 11:4, while in the recovered patients 7:8.

TABLE 1: No. of cases and sex incidence in relation to prognosis,

Age on admission	No. of Cases	Died		Recovered		Mort. (%)
		Males	Females	Males	Females	
⩽ 5 days	4	2	1	—	1	75.00
6-10 days	21	8	3	6	4	52.38
> 10 days	5	1	—	1	3	20.00
Total	30	11	4	7	8	50.00

B. Factors affecting the mortality

Table 2 shows the comparison between the mortality of the patients who were delivered by the "dukun", their family or the midwife. From this table we can see that of 6 patients who were delivered by the "family", 4 died (66.67%), while the 15 patients who were delivered by the "dukun" (traditional birth attendant), 8 died (53,33%), and only 3 patiants died (33.33%) who were delivered by the midwife.

TABLE 2: *Mortality rate according to birth place.*

Birth place	No. of Cases	Died	Recovered	Mort. (%)
At home by "family"	6	4	2	66.67
At home by "dukun"	15	8	7	53.33
Maternity clinic by midwife	9	3	6	33.33

From table 3 we can see the relation of incubation period and the prognosis.It is seen that the majority of the patients with an incubation period of 7 days or less died (58.33%), while of the six patients with an incubation period of more than 7 days only one patient (16.67%) died.

It seems that the mortality decreased with the prolongation of the incubation period.

TABLE 3: *Relationship between incubation period and mortality.*

Incubation period	No. of Cases	Died	Recovered	Mort. (%)
< 7 days	24	14	10	58.33
> 7 days	6	1	5	16.67

Table 4 shows the relationship of the period of onset and the prognosis in our series. The period of onset of 48 hours or less was found in 86.67% patients, with the mortality rate 57.69%. None of the 4 patients with the period of onset of more than 48 hours died.

TABLE 4: *Mortality in relation to period of onset.*

Period of onset	No. of Cases	Died	Recovered	Mort. (%)
⩽ 48 hours	26	15	11	57.69
> 48 hours	4	0	4	0.00

Almost all deaths occurred whitin the first 5 days (table 5). The duration of hospitalization for those who recovered varied from 13 to 53 days with a mean of 24.73 days.

Table 6, shows the temperature on admission. Each of the 3 group: Sub febrile, febrile and hyperpyrexia had the mortality rate: 31.25%, 80% and 66.67 respectively.

TABLE 5: Mortality in relation to days of hospitalization.

Hospitalization	No. of Cases	Died	Recovered	Mort. (%)
- 5 days	12	4	0	100.00
6-10 days	12	13	0	100.00
11-15 days	1	1*	3	25.00
> 15 days	1	1*	12	7.69

* = This patient also had aspiration pneumonia as complication

From our 25 patients who had spontaneous paroxysmal spasms, 14 (56%) died while of the 5 patients who had induced spasms, 1 (20%) died. The mortality in relation to convulsion and age on admission is listed on table 7.

Scoring was done on the first day of admission, when signs and symptoms are usually positive. When this system is applied to our 30 patients, a direct relationship can be seen between the severity of the disease and the mortality rate (table 8). The majority of our patients were

TABLE 6: *Mortality in relation to body temperature on admission*

Body temprature	No. of Cases	Died	Recovered	Most. (%)
<38°C	16	5	11	31.25
38-39°C	5	4	1	80.00
>39°C	5	6	3	66.67

TABLE 7: *Mortality in relation to type of convulsion and age on admission.*

Age on admission	No. of Cases	Spontaneous par. spasm	Induced spasm	Died	Recovered	Mort. (%)
⩽ 5 days	4	3	0	3	0	100.00
		0	1	0	1	0.00
6-10 days	21	18	0	10*	8	55.56
		0	3	1	2	33.33
> 10 days	5	4	0	1	3	22.00
		0	1	0	1	0.00

* = *2 patients also had a complication of aspiration pneumonia and died 11 days and 16 days after admission.*

TABLE 8: *Mortality rate in relation to severity.*

Severity	No. of Cases	Died	Recovered	Mort. (%)
Grade I	0	0	0	0.00
Grade II	1	0	1	0.00
Grade III	6	1	5	16.67
Grade IV	11	4	7	36.36
Grade V	12	10	2	83.33

grade IV and V. There was only one pateient with grade II.

Discussion

Treatment of established tetanus includes: therapy with antitoxin, antibiotics, care of wounds and supportive measures (Stoll, 1979). Toxin has usually been fixed and cannot be neutralized (Kerr, 1979; Krugman and Katz, 1981). However antitoxin may modify the disease if it is given during the incubation period or very early in the course of the illness.

Antibiotics are recommended to eleminate the vegetative form of C. tetani and to control secondary infection.

Supportive therapy and good nursing care are of utmost importance. Various agents have been used to decrease the frequency and severity of muscle spasms. Diazepam (Valium is proven to be a very valuable drug because it effectively controls spasms and yet is free of significant side effects (Agurell et al, 1975; Krugman and Katz, 1981). Hendrickse and Sherman (1966) first reported the use of oral diazepam in a controlled study of 104 cases of neonatal tetanus. They concluded that though the mortality rate was 55%, it was of value in relaxing tonic muscle spasms; moreover it was relatively free of unpleasant side effects or toxicity. Gupta et al. (1979) added the diazepam schedule and on comparison mortality in the diazepam group was found lower than the non diazepam group through it was statistically not significant ($p>0.05$).

Diazepam as a single agent to control spasms were reported by Tjandra Husada et al, (1976) and Taslim S. Soetomenggolo et al, (1981). They had mortality rates of 50%. Their experience showed that diazepam (Valium) with the total dose of 8-10 mg/kgbw/day, was not enough to overcome the attack of convulsion.

The use of high dose diazepam were reported by Femi Pearse (1966) and Khoo and Lee (1978). Femi Pearse gave 40mg/kgbw/day for neonates weighing 3 kg for 3 days and then the dose was decreased with the total duration of diazepam administration of 3 weeks. While Khoo and Lee gave 20-40 mg/kgbw/day combined with phenobarbitone 10-15 mg/kgbw/day This regimen adequately controlled spasms in 12 patients and failed in 7 patients who subsequently received total paralysis and IPPV. The overall mortality was 11%.

In the present series we gave diazepam (valium) of 2.5 mg intravenously at 2 hours interval and should be increased in severe cases. The mortality of our cases (50%) is still high (table I), but if we compare with the cases of Bhat, et al, (1979, 72%), Athavale and Pai (1965, 73%), Medical record data from the Dept. of Child Health Cipto Mangunkusumo, Jakarta 1979 (62.5%) (Cited by Rusepno Hasan, 1982). this figure is much lower.

From table 3 we can see that the age on admission and also the incubation period are important factors which contribute to the severity of the disease. Because the contamination generally occurr at the time of cutting the umbilical cord or putting traditional medicine to the umbilical stump, this age is about the same with the incubation period. In our series it was observed that the younger the age on admission or the shorter the incubation period, the higher was the mortality rate. This means that the younger the age or the shorter the incubation period, the more severe the disease. This is also the opinion of many authors (Athavale and Pai, 1964; 1965; Taslim S. Soetomenggolo et al, 1981; Tjandra Husada et al, 1976).

From table 1 we can also see the sex incidence and its prognosis. The male babies were more in number than the female. Previous investigators noted a similar figure (Athavale and Pai 1964;

1965; Bhat et al, 1979; Gupta et al, 1979). According to table 2 21 (70%) patients were delivered at home. Between them, 15 (71.42%) were assisted by the "dukun", 6 (28.58%) by their family. The lower mortality rate of patients delivered by "dukun" proved that the existing health services function properly and develop proportionately including adequate tra ining for "dukun". Marwoto and Achmad Surjono (1976), reported that 27 (92%) cases having home diliveries were asissted by "traditional midwifes", while Dibjosubroto et al, (1978) found that 40 (90.9%) of neonates were delivered by "peraji".

Table 4 shows the relationship of period of onset and prognosis of our series. The period of onset was less than 48 hours in 86.67%, with mortality rate 57.69% Athavale and Pai (1964) found a period of onset less than 48 hours in 13.2% of newborn infants, with the mortality rate 77.7% for period of onset less than 24 hours and 73.6% if the period of onset was 24-48 hours. They concluded that the shorter the period of onset, the worse was the prognosis.

From table 5 we can see that 12 of 15 (80%) patients died during the first 5 days of hospitalization. Of these patients 4 died on the first day, 4 on the second day, 3 on the third day and one on the fourth day. If these patients are classified to the criteria of Patel and Joag, 7 patients were grade V, 4 patients were grade IV and only one patient was grade II. In our observation all but two, death was due to respiratory failure.

The body temperature on admission did not have much effect on the mortality (Tjandra Husada et al, 1976). Other authors (review by Tjandrahusada, 1976) however believed that very high temperatures (more than 39°C) would have deterious influence. In our series the mortality rate was 66.67% for temperature more than 39°C and 42.86% for temperature 39°C or less (table 6).

From our patients who had spontaneous paroxysmal spasms, 14 (56%) died, while of the 5 patients who had induced spasms only one (20%) died. We considered that spontaneous paroxysmal spasms would certainly influence the outcome unfavourably (table 5). Many investigators also considered spasms as an important factor for severity (Athavale and Pai, 1964; 1965; Ismudijanto et al, 1981; Tjandra Husada et al, 1976).

Table 8 gives the relation of severity of the disease as expressed in grades and mortality in our series. The mortality as shown above, rises in proportion to the severity of the grading.

Rusepno Hassan (1982) reported that there were no deaths among 2 cases treated with valium, penthotal and intermittent Mandatory Ventilation. Ellis (1963) reported that there were no deaths among 34 cases treated with curare and IPPV and Smyth et al. (1964) treating 186 and 97 cases with tubocurarin and IPPV, had a mortality of 21% and 10% respectively (reviewed by Taslim S. Soetomenggolo et al, 1981).

Such a method of treatment is beyond the scope of most hospitals in Indonesia, due to the shortages of equipment and experts medical personel. Resent investigations revealed that diazepam (valium as a relaxant in tetanus neonatorum) gave good result. However some authors still found different results in their trials. The method is very simple and can be done in most hospitals in Indonesia.

However we thought that it might be more practical to immunize pregnant women with tetanus toxoid, in the hope that sufficient high tetanus antibodies might remain for the protection of their babies in subsequent pregnancy. To be economical, protection should be effective for periods of at least 3 to 5 years.

Newell et al. (1966), reported that the immunization of a group of woman volunteers with (or 3) intramuscular injections of 1 ml of aluminium phosphate adsorbed tetanus toxoid resulted in the complete absence of tetanus neonatorum from their babies born in subsequent pregnancies, for a period of more than four years.

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