Failure of intrathecal antitetanus serum to improve survival in neonatal tetanus

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SUMMARY In a prospective study, 161 infants with neonatal tetanus were randomised to receive (a) standard treatment, or (b) standard treatment together with intrathecal equine antitetanus serum, or (c) intrathecal antitetanus serum with systemic betamethasone. There was no difference in survival between the three treatment groups in infants with severe tetanus, but in mild tetanus those who received standard treatment alone had an improved survival rate. Parenteral intramuscular diazepam as a sedative was found to be preferable to paraldehyde, as the latter was associated with a higher incidence of secondary infections.

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%.¹ Management in many such countries consists of administration of equine antitetanus serum (ATS) or human tetanus hyperimmune globulin (TIGH) in combination with sedatives and antibiotics, as resources and staff are generally not available for mechanical respiratory support.

In recent years there has been a revival of interest in the use of intrathecally-administered ATS. Its use was abandoned in the 1940s owing to the high incidence of complications,² but recent reports have shown that combined with steroids it can be given safely. Initial studies reported favourably on the use of either intrathecal ATS or TIGH.³⁻⁴ In an effort to reduce the high mortality rate associated with neonatal tetanus, we decided to evaluate intrathecal ATS as an adjunct to our standard treatment in a controlled study. We hoped that this might be a useful and easy adjunct to treatment, even in small rural hospitals.

Patients and methods

Between April 1979 and January 1981, 161 neonates with clinical tetanus were admitted to the neonatal tetanus unit of the Korle Bu Teaching Hospital in Accra. On admission, the severity of the disease was graded. A case of risus sardonicus, generalised rigidity with or without occasional short spasms on stimulation, was graded as mild to moderate. The addition of repetitive spontaneous spasms on admission was graded as severe.

All patients received a standard treatment which consisted of ATS 750 IU administered intramuscularly on admission. Parenteral crystalline penicillin and kanamycin in appropriate doses were administered for the first week of admission. A nasogastric tube was passed for feeding with expressed breast milk and for oral sedation. Sedation was by phenobarbitone 10 mg 6 hourly and chlorpromazine 7.5 mg 6 hourly, both given by nasogastric tube. If spasms were still uncontrolled diazepam 2.5 mg was given 4 to 6 hourly in addition, and during part of the study period when diazepam was unavailable, parenteral paraldehyde 1 ml 4 to 6 hourly as necessary, was used instead. General nursing care included attention to maintenance of the airways by suction and posture, and the prevention of bed sores. No patient had assisted ventilation.

On admission each patient was allocated to one treatment group. This was done on a prearranged sequential basis and was carried out by the admitting nurse by reference to a written chart. Group A (57 patients) received only the standard treatment; group B (60 patients) received, in addition to the standard treatment, intrathecal ATS, 250 IU mixed with 10 mg hydrocortisone to a volume of 6 ml and injected slowly by the lumbar route. Group C (44 patients) received the standard treatment, intrathecal ATS with hydrocortisone and systemic betamethasone 1 mg intramuscularly 8 hourly for a duration of 7 days.

Intrathecal ATS administration was unsuccessful in 4 infants owing to technical problems, and these 4 were eliminated from the study.

Results

Each neonate was allocated sequentially to a treatment group—A, B, or C. The mean age on admission was 8.6 days in group A, 7.4 days in group B, and 8.2 days in group C. The mean weights on admission were 3.2 kg in group A, 3.5 kg in group B, and 3.1 kg in group C. There was no difference in the distribution of genders. The incubation period was measured as the time from the cutting of the umbilical cord until the time of the first symptoms, and was 6.6 days in group A, 6.4 days in group B, and 7.0 days in group C. Thus the patients in each group were similar with regard to age on admission, weight, gender, and incubation period of the disease. The time between the onset of symptoms and admission to hospital also showed no difference between the groups. In group A this was 1.6 days, in group B 1.3 days, and in group C 1.5 days.

Of the 161 neonates with tetanus 120 (74.5%) were clinically classified as severe and 41 (25.5%) as mild to moderate. The overall survival of both severely and mildly affected groups was 35.4%. However, the survival rate in the severely affected neonates was low, 16.2% in group A, 21.5% in group B, and 15.6% in group C. The difference in survival between the three groups was not statistically significant (Table 1).

In the neonates presenting with mild to moderate tetanus, survival of those who received the standard treatment alone (group A) was significantly better (94.7%) than that of those in group B, which was 70% ($P < 0.05$). Survival of group A patients was also better than that of patients in group C (83.3%) but the difference was not significant (Table 2). Of

the 6 babies with mild to moderate tetanus who died, 3 had progression of the disease to a severe form. They comprised one from group A and two from group B. One infant from group B died unexpectedly and suddenly one hour after receiving the intrathecal ATS. The two deaths in group C were both from overwhelming infection, one from *Klebsiella* septicaemia and one from pneumonia and complicating empyema thoracis.

Of the patients with severe tetanus requiring additional parenteral sedation, 63 received diazepam, and 49 paraldehyde. The percentage survival for those receiving diazepam (20.6%) was better than that for those receiving paraldehyde (12.2%) but not significantly so. The incidence of deep injection necrosis and of septicaemia was increased in infants who received paraldehyde. Five infants in the paraldehyde group died of septicaemia proved by positive blood culture, compared with none in the diazepam group.

Discussion

The overall survival rate for neonatal tetanus in our series was 35.4%. This seemingly poor outcome was most likely owing to the high proportion (74.5%) of infants who presented with severe tetanus, and for whom survival was extremely poor compared with those whose disease on admission was clinically classified as mild to moderate. No significant improvement in survival was observed with the use of intrathecal ATS.

Ildirim, in Yugoslavia, reported a markedly reduced mortality rate in neonatal tetanus, using either ATS (14.8% mortality) or TIGH (20.5% mortality) intrathecally, without assisted ventilation.³ Subsequently Sanders *et al.* reported favourably on the use of 200 IU of ATS given intrathecally to cases of non-neonatal tetanus. They also used systemic betamethasone in addition to standard treatment including systemic ATS. They were able to demonstrate separate beneficial effects both of systemic betamethasone and intrathecal ATS.^{4,5} In our series however, we did not find any benefit from the use of systemic betamethasone in neonatal tetanus, and its use may have contributed to the deaths of two infants from overwhelming infection in the mild to moderate group.

More recently other workers have reported on the use of intrathecal ATS and TIGH in tetanus, but with conflicting results. Singh *et al.* reported decreased mortality associated with the use of intrathecal ATS, the former group in neonates, and the latter in older patients.⁶⁻⁷ However, Vakil *et al.* found no difference in mortality using intrathecal TIGH in older patients, and Bhandari *et al.* also

Table 1 Survival in 120 neonates with severe tetanus

	Group		
	A (n=37)	B (n=51)	C (n=32)
Number of patients			
Who survived	6	11	5
Who died	31	40	27
Survival (%)	16	22	16

Table 2 Survival in 41 neonates with mild to moderate tetanus

	Group		
	A (n=19)	B (n=10)	C (n=12)
Number of patients			
Who survived	18	7	10
Who died	1	3	2
Survival (%)	95	70	83

found no beneficial effect in neonates using a much larger dose of ATS intrathecally.⁸⁻⁹ Gupta *et al.* also initially found no difference in patients with severe tetanus, but in a more recent series using TIGH they were able to show a decreased incidence in the progression of the disease to a severe form, and a decreased mortality in patients who presented with mild or moderate tetanus.¹⁰⁻¹¹ The theoretical basis for the intrathecal administration of tetanus antitoxin is that when it is given systemically, the large molecule cannot cross the blood brain barrier readily, and so cannot neutralise unfixed toxin already present in the central nervous system.¹² In severe tetanus, where a fairly large amount of toxin is already fixed, the intrathecal administration of antitoxin may not influence the course of the already established disease process. In mild tetanus it could conceivably neutralise unfixed antitoxin present in the central nervous system and prevent progression of the disease to a severe form. In our series we did not demonstrate any beneficial effect of intrathecal ATS in either severe or mild to moderate cases. In our mild to moderate cases, the prognosis was in any case so good (94.6% survival) that any additional measures are probably not necessary.

Severe neonatal tetanus however, remains a major management problem. The high mortality associated with this form of tetanus remains apparently uninfluenced by conservative management. Unfortunately, in many third world countries where severe neonatal tetanus is the more common form of presentation, facilities for controlled or mechanical respiratory support are generally not available. Only such support has been clearly documented to improve survival in severely affected neonates.¹³

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