

Freedom from reintervention is likely to be a powerful indicator of overall performance, but several years' data will be required before our capability to track reintervention can be put to use.

Conclusions

Independent validation of data is essential for accurate survival analysis. One year survival statistics give a more realistic view of outcome than traditional perioperative mortality. At present survival is no different between any of the 13 UK tertiary centres for congenital heart disease, but confidence intervals are wide, limiting our power to detect underperformance from analysis of a single year's data. Appropriately resourced, focused, national audit is capable of accurate data collection on which nationwide, long term, quality control can be based.

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Randomised controlled trial of tetanus treatment with antitetanus immunoglobulin by the intrathecal or intramuscular route

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Abstract

Objective To evaluate the effect of intrathecal therapy with human antitetanus immunoglobulin on clinical progression of and mortality from tetanus.

Design Randomised controlled trial.

Setting Intensive care unit of a university hospital, Pernambuco, Brazil.

Participants 120 patients with tetanus allocated to antitetanus immunoglobulin by either the intrathecal and intramuscular route (n = 58) or the intramuscular route (n = 62; control group).

Main outcome measures Clinical progression of disease, duration of hospital stay, duration of occurrence of spasms, complications, respiratory infection, respiratory failure or mechanical ventilation, duration of respiratory assistance, and mortality.

Results Patients in the treatment group showed a better clinical progression than those in the control group (χ^2 for trend 7.752, $P = 0.005$; difference in proportion of patients with improvement 20%, 95% confidence interval 4% to 35%). The duration of

occurrence of spasms, hospital stay, and respiratory assistance were all shorter in patients in the treatment group: respectively, 14.96, 0.0001 (difference in proportion of patients with spasms lasting ≤ 10 days 36%, 18% to 55%); 4.56, 0.03; and 6.56, 0.01 (proportion of patients who needed assistance for ≤ 10 days 69.2% in the treatment group and 30.8% in the control group (difference 38%, 12% to 65%).

Conclusion Patients treated with antitetanus immunoglobulin by the intrathecal route show better clinical progression than those treated by the intramuscular route.

Introduction

Treating tetanus by neutralising the toxin is still controversial, especially dosage and route of administration.¹⁻¹¹ A meta-analysis of intrathecal

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Table 1 Clinical progression of patients treated for tetanus by the intramuscular route (control group) or intrathecal route

Clinical progression	No (%) in control group (n=60)	No (%) in study (n=58)	P value*
Improvement	10 (17)	21 (36)	$\chi^2=7.752$; 0.005
Stabilisation and improvement	13 (22)	15 (26)	
Deterioration†	37 (62)	22 (38)	

* χ^2 for linear trend.

†Smaller risk of deterioration or death within first 10 days in study group (relative risk 0.6, 95% confidence interval 0.4 to 0.9).

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therapy was inconclusive in adults.¹² We evaluated the effect of such therapy on clinical progression of and mortality from tetanus.

Methods

Our study sample was patients with tetanus admitted to the intensive care unit of the Oswaldo Cruz University Hospital, Recife, Brazil. Potential participants were aged 12 or over and had secondary sex characteristics. They were randomised to receive antitetanus immunoglobulin by either the intrathecal and intramuscular routes (treatment group) or the intramuscular route (control group).

Our two outcomes were disease progression and mortality.¹³ In the past 15 years, mortality from tetanus at our hospital has been up to 35%.¹⁴ Taking previous studies as reference, we estimated a reduction in mortality to 18%.^{1 3 4}

After obtaining written informed consent, we randomised participants to the treatment group or control group. Randomisation was based on blocks of 20, and treatment allocation was concealed in sealed envelopes. We classified tetanus as grade 1, trismus, dysphagia, and generalised rigidity with no spasms; grade 2, mild and occasional spasms; grade 3, severe and recurrent spasms—usually triggered by minor or imperceptible stimuli; and grade 4, features of grade 3 and overactivity of the sympathetic nervous system.¹⁵ The grade was recorded on admission.^{16 17} We collected data on clinical progression, outcomes, re-evaluations as outpatients, and the occurrence of spasms.

To minimise observation bias, we used several approaches: doctors classifying the disease were rotated on alternate days for 10 days after patients were

admitted; the clinical stage was recorded on a form devoid of information on treatment or previous classifications; treatment allocation was known only by certain members of the research team; and regular meetings were held to discuss problems.

For intrathecal therapy, we used 1000 IU of a lyophilised human immunoglobulin, free of preservatives to avoid irritating the meninges. Both groups received 3000 IU of immunoglobulin with preservative by the intramuscular route.

We used EPI INFO 6.0 for analyses. Participants who failed to undergo the therapeutic procedure were analysed according to the group to which they were allocated.

Results

From July 1997 to July 2001 we recruited 120 patients; 58 were allocated to the treatment group and 62 to the control group. Potential confounders were similarly distributed between the groups (see [bmj.com](#)).

Three patients refused to participate, and in two it proved difficult to achieve suboccipital or lumbar puncture; they received treatment by the intramuscular route only but for analyses were considered in the intrathecal group. We excluded one patient randomised to each group owing to misclassification of diagnosis.

The treatment group showed better clinical progression than the control group (table 1). Up to 10 days after admission most patients in the treatment group had grade I or II disease and most patients in the control group had grade III or IV disease (see [bmj.com](#)).

We excluded 23 patients on the basis of spasms. The study group had shorter duration of occurrence of spasms (table 2). Among the 106 patients who survived, duration of hospital stay varied from 2 to 80 days. The treatment group had a shorter duration of hospital stay (table 2); a smaller proportion had complications during this time, although the difference was not significant (see [bmj.com](#)).

Respiratory infection was the most common complication. The relative risk of patients developing respiratory failure that required artificial respiration was smaller in the treatment group than in the control group, but the difference was not significant (see [bmj.com](#)). However, the difference in the duration of respiratory assistance among 50 patients in both groups (six died during respiratory assistance) was significant (see table 2).

Five patients had mild headache during the intrathecal procedure, but we observed no meningeal irritation or meningitis. Among the 106 patients who were discharged, 64 returned for a check up, in accordance with the study protocol. Of these, 37 belonged to the treatment group; they had no side effects.

Fourteen patients died during the study. The cause of death was not determined in seven. Half of these patients died within 10 days of admission. The others died between days 16 and 89. No particular pattern was observed.

Table 2 Duration of occurrence of spasms and hospital stay and need for respiratory assistance in patients treated for tetanus by the intramuscular route (control group) or intrathecal route

Duration (days) of outcome	Control group	Study group	P value*
Permanence of spasms:	n=51	n=46	
≤10	14 (32)	30 (68)	14.96;0.0001†
11-20	18 (62)	11 (38)	
>20	19 (80)	5 (21)	
Hospital stay:	n=52	n=54	
≤15	14 (27)	23 (43)	4.56;0.03‡
16-30	17 (33)	19 (35)	
>30	21 (40)	12 (22)	
Respiratory assistance:	n=30	n=20	
≤10	4 (31)	9 (70)	6.56;0.01§
11-20	12 (63)	7 (37)	
>20	14 (78)	4 (22)	

* χ^2 for linear trend.

†P=0.001 (t test).

‡P=0.13 (t test).

§P=0.01 (t test).

What is already known on this topic

Neutralisation of tetanus toxin as part of tetanus therapy is still controversial, especially the dosage and route of administration

A meta-analysis of intrathecal therapy with antitetanus immunoglobulin was inconclusive in adults

What this study adds

Giving antitetanus immunoglobulin by the intrathecal route shows several clinical benefits

Patients treated by the intrathecal route had a better disease progression than those treated by the intramuscular route

Discussion

Patients treated for tetanus with human antitetanus immunoglobulin by the intrathecal route show better clinical progression than patients treated by the intramuscular route. They also showed fewer complications, particularly respiratory ones, and needed less intervention if they did.

We monitored disease progression by grade of tetanus.¹⁵ Grade I and II predominated in the treatment group and grade III and IV predominated in the control group. Such differences were perceptible in the early stages of hospital stay and may be attributed to intrathecal therapy.

Spasm is easily identified and a relatively reliable indicator. The duration of occurrence of spasms was shorter among patients in the treatment group. Duration of hospital stay was also shorter in the treatment group.

Complications from tetanus, especially respiratory ones, are often followed by death.^{17,18} Over half of the patients in our study had some type of complication, such as respiratory infection or respiratory failure, most often in the control group. Although the differences were not statistically significant, in both cases the probability was close to the cut-off point. Patients in the treatment group who did require artificial respiration needed less assistance than those in the control group. The difference was statistically significant.

To calculate our sample size we chose the outcome of reduction in mortality. During the early stage of data

collection the intensive care unit was created and mortality from tetanus decreased from 35% to almost 12%. This may have had made it more difficult to show a statistically significant difference between the groups.

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