

Intrathecal vs. intramuscular administration of human antitetanus immunoglobulin or equine tetanus antitoxin in the treatment of tetanus: a meta-analysis

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Summary

BACKGROUND Mortality caused by tetanus is still a serious health problem in developing countries. Apart from immunization, early treatment with equine antitetanus serum (ATS) or human tetanus immunoglobulin (TIG) is the real treatment that can avoid death. On pathophysiological grounds intrathecal administration would be preferred because of high concentrations of the antiserum in cerebrospinal fluid and thus around the nerve roots. Many studies concluded on its effectiveness whereas others did not find any superiority of this method. However, most of those studies were not random and/or had no sufficient weight.

OBJECTIVE To assess the efficacy of intrathecal therapy with ATS in neonates and adults.

METHODS Meta-analysis: Clinical trials were identified by searching Medline, the Cochrane library and Current Contents. Published randomized studies in English or French comparing intrathecal therapy and intramuscular therapy (IMS) were analysed with Revman, R, and Stata software. Treatment effects were evaluated by relative risk (RR) between intrathecal *vs.* intramuscular administration.

RESULTS A total of 942 patients were included in 12 trials, 484 in the intrathecal group and 458 in the intramuscular one. The combined RR of mortality for intrathecal *vs.* IMS was 0.71 (95% CI, 0.62–0.81). The superiority of intrathecal therapy also emerged when the analysis was performed in subcategories of both adults and neonates and for high and low dose of intrathecal serotherapy.

CONCLUSION Intrathecal administration of ATS or TIG is more beneficial than intramuscular administration in the treatment of tetanus.

keywords tetanus, intrathecal, equine tetanus antitoxin, human antitetanus immunoglobulin

Introduction

Since Ildirim's study in 1967, which stated the efficacy of intrathecal immunotherapy (ITS), many other studies have been published evaluating its efficacy. He demonstrated that the plasmatic level of antitetanus serum (ATS) was <0.008 IU/ml after intramuscular administration of 6000 IU of human ATS whereas this level reached 1024 IU/ml when administered intrathecally (Ildirim 1967). In addition, when ATS is administered systemically, the large protein molecule cannot readily cross the blood brain barrier and neutralise the unfixed toxin already present in the central nerve system (Gupta *et al.* 1980). In 1979 Sedaghatian found that the mortality rate and duration of hospital stay were not significantly different in a group of intrathecal therapy *vs.* a group with intramuscular therapy (IMS) (Sedaghatian

1979). A study comparing i.v. and intrathecal serotherapy was also interrupted by Vakil in 1979 because no significant difference was found between the two groups (Vakil *et al.* 1979). On the other hand, Bandari showed that intrathecal serotherapy leads to higher mortality than IMS (Bhandari *et al.* 1980). Seven years later, Mongi concluded that ITS was superior to IMS in the treatment of neonatal tetanus (Mongi *et al.* 1987). Recently, Menon confirmed this statement (Menon & Mathews 2002).

In 1991 Abrutyn tried to settle these two opinions by conducting a meta-analysis and concluded that there was no superiority of intrathecal serotherapy over the other methods (Abrutyn & Berlin 1991). Unfortunately all clinical trials in this meta-analysis were not randomized. Moreover, there was an important heterogeneity between the studies so that caution must be taken.

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Most of the time, the intramuscular way is preferred probably because of comfort and convenience for administration. Meanwhile, tetanus continues to kill in developing countries. For example one estimate suggests that the annual incidence is near 15 per 100 000 in Sub-Saharan Africa and 40–60 per 100 000 in India (Ribero & Gayon 2000). This information is of great public health importance because the worldwide burden of the disease is still large. To assess the efficacy of intrathecal therapy, we conducted a meta-analysis of randomized-controlled trials comparing intrathecal and intramuscular administration in the treatment of tetanus.

Methods

Trials were identified by searching the Medline database, the Cochrane library and the Current contents and other electronic data providers using following keywords: intrathecal tetanus antitoxin; intramuscular tetanus antitoxin; tetanus immunoglobulin (TIG). All articles published or translated in French or in English and matching our keywords were identified.

Next we selected only randomized trials focusing the comparison of intrathecal *vs.* intramuscular routes. Necessary data were: the country in which the trial was conducted; the year of publication; the sample size; in both two arms the age of the subjects, the dosage, the type of intervention and the mortality. Other criteria like the length of hospital stay, side effects of the treatment, length of follow-up were also identified but they did not contribute to exclude the trials.

The principal end point of our study was the evaluation of the efficacy of ITS *vs.* IMS by calculating the mortality rate within the two groups. The secondary end point consisted in calculating the mortality rate in subcategories: adult *vs.* neonates; low doses *vs.* high doses; serum (horse) *vs.* human TIG.

We used Revman 4.2 software to record and to analyse data, further analyses were performed using the statistical software packages R 2.1 and Stata 8.2. Combining trials was performed using the Mantel–Haenszel method, the heterogeneity statistic being given by Cochrane Q as:

$$Q = \sum \omega_i (\theta_i - \theta_{MH})^2,$$

where the size of each trial θ_i is given the weight ω_i in the analysis.

θ_{MH} is the overall estimate of the pooled effect, and it is given by: $\theta_{MH} = \sum \omega_i \theta_i / \sum \omega_i$, θ is the log relative risk (RR) or risk difference and the ω_i are the weights calculated as $1/SE(\theta_i)^2$ under the null hypothesis that there are no differences in treatment effect between trials. This follows

a chi-squared distribution on $k-1$ degrees of freedom (where k is the number of studies contributing to the meta-analysis) and standard error (SE).

The statistic I^2 was also calculated as $I^2 = (Q - (k - 1) \times 100) / Q$. This measures the extent of inconsistency among the studies' results, and is interpreted as approximately the proportion of total variation in study estimates, i.e. because of heterogeneity rather than sampling error. The Z -test was also performed to assess the difference between the groups with significance level at 1.96. The null hypothesis of homogeneity was rejected at significance level of 0.05. Heterogeneity was also assessed using the Galbraith plot as suggested by Devillé, the standardized RR being given by \ln_{RR}/SE (y -axis) against the inverse of SE (x -axis) (Deville *et al.* 2002). The efficacy of the treatment was determined by calculating the RR. The impact of possible predictors on the treatment difference between intrathecal and intramuscular serotherapy was assessed using metaregression (van Houwelingen *et al.* 2002).

Results

In this meta-analysis, 12 clinical trials were selected involving 942 patients. Most of the trials were conducted in developing countries. Six trials involved adult subjects and six were conducted in neonates. The characteristics of the trials are shown in Tables 1 and 2. The dose in the ITS group was ranging between 50 and 1500 IU and between 250 and 40 000 IU in the IMS group. Figure 1 shows the Galbraith plot of the 12 studies. All the studies are within the 95% boundaries, meaning that there is homogeneity between studies. Figure 2 shows the RR for intrathecal serotherapy in individual trials and overall. The RR was below 1 in 11 out of the 12 trials and the overall RR was 0.71 (95% CI, 0.62–0.81, P -value < 0.001) meaning that the mortality rate was significantly lower for the intrathecal treatment.

Figure 3 presents a sensitivity analysis of the meta-analysis. Results from a random effects meta-analysis were consistent with those from the fixed effects model. In all subgroups, defined by the subject age, serum/Ig type, IT dose, geographical location, study size, and overall mortality rate, the intrathecal route showed a significantly lower mortality rate than the intramuscular route. There was a significantly ($P = 0.037$) higher reduction in mortality, compared with intramuscular administration, in studies using high dose ITS (>250 units) than in studies using low dose ITS (≤ 250 units). However, these results should be interpreted with care as only three studies used high dose ITS. Other factors did not show a significant effect on the difference in mortality between intrathecal

L. Kabura *et al.* Intrathecal antitetanus immunoglobulin**Table 1** Study characteristics of randomized trials comparing intrathecal with intramuscular administration of human immunoglobulin or equine antitoxin in the treatment of tetanus

Authors	Country	Year	Age	Score	Serum	Steroids	Mortality/sample size			Dose		Methods
							Total	ITS	IMS	ITS	IMS	Study type
Agarwal	India	1998	Adults	1,3	Human	No	14/36	7/18	7/18	250	750	SRDB
Arun	India	1980	Neonates	2,3	Equine	Yes	54/99	20/49	34/50	50–100	10 000	SRSB
Asim	Turkey	1980	Neonates	1,2,3	Equine	No	19/41	8/21	11/20	250	500	RT
Chugh	India	1985	Neonates	1,2,3	Human	No	81/106	41/55	40/51	250	250	RT
Gupta	India	1980	Adults	1,2,3	Human	No	32/97	1/49	10/48	250	1000	RT
Keswani	India	1980	Adults	1,2,3	Equine	No	49/118	22/70	27/48	200	10 000	RT
Mbise	Tanzania	1984	Adults	1,2,3	Equine	No	23/36	8/18	15/18	1500	10 000	RT
Miranda Filho	Brazil	2004	Adults	1,2,3	Human	No	14/120	4/58	10/62	1000	3000	RT
Mongi	Tanzania	1987	Neonates	1,2,3	Equine	No	42/66	15/33	27/33	1500	10 000	RT
Paul	India	1984	Neonates	1,2,3	Equine	No	64/87	32/45	32/42	250	250	RT
Sanders	England	1977	Adults	1,2,3	Equine	Yes	35/76	16/38	19/38	200	1500	RT
Sedhagatian	Turkey	1979	Neonates	1,2,3	Human	No	28/60	13/30	15/30	150	40 000	RT

RT, randomized trial; SRSB, stratified randomized single blind; SRDB, stratified randomized double blind trial; ITS, intrathecal immunotherapy; IMS, intramuscular therapy; score, the Dakar score represents a scale of morbidity – 1 few symptoms, 2 moderate, 3 serious.

Table 2 Outcome, duration of hospital stay and follow-up in randomized trials comparing intrathecal with intramuscular administration of human immunoglobulin or equine antitoxin in the treatment of tetanus

Authors	Outcome	Hospital stay	Follow-up duration
Agarwal	All mild tetanus in control group: evolution to severe tetanus	Significant difference in mild tetanus for hospital duration in favour of IT group (12.3 days) <i>vs.</i> IM group (24.1 days)	Period of hospitalization
Arun	No difference in mortality rate according to the dose	Hospital stay 7.4 days in IT group; 10.4 IM group	Period of hospitalization
Asim	Mortality: 38% in treated group, 55% in control group	Follow-up: 6 months duration of therapy: 19.7 days in ITS and 20.4 days in control group	Period of hospitalization
Chugh	Mortality: higher in control group than in IM and IT group	Duration in hospital: 3.34 days IT IM group, 3.31 days control group: 2.63 days	Period of hospitalization
Gupta	Mortality: higher IM group more progression to severe tetanus observed in IM group	Duration in hospital not reported	2–3 months
Keswani	Mortality: higher in control group than IT group	Duration in hospital not reported	Period of hospitalization
Mbise	Mortality higher in control group (IM) than IT group	Duration in hospital not reported	Period of hospitalization
Miranda Milho	Better clinical outcome on 10th day in IT group, difference in recurrence of spasms or in hospital duration	Shorter duration of hospital stay in ITS group	Period of hospitalization
Mongi	Mortality rate: intrathecal group = 45%, IM group = 82%	19.3 days in IT group, 28.7 in IM group	Period of hospitalization
Paul	Mortality rate: 71% in IT group, 76% in IM group	Duration in hospital not reported	Period of hospitalization
Sanders	Mortality: no significant difference observed	Duration of hospital stay not reported	Period of hospitalization
Sedhagatian	Mortality rate: no difference	Days in hospital: no difference, days in sedation: no difference	Period of hospitalization

ITS, intrathecal immunotherapy.

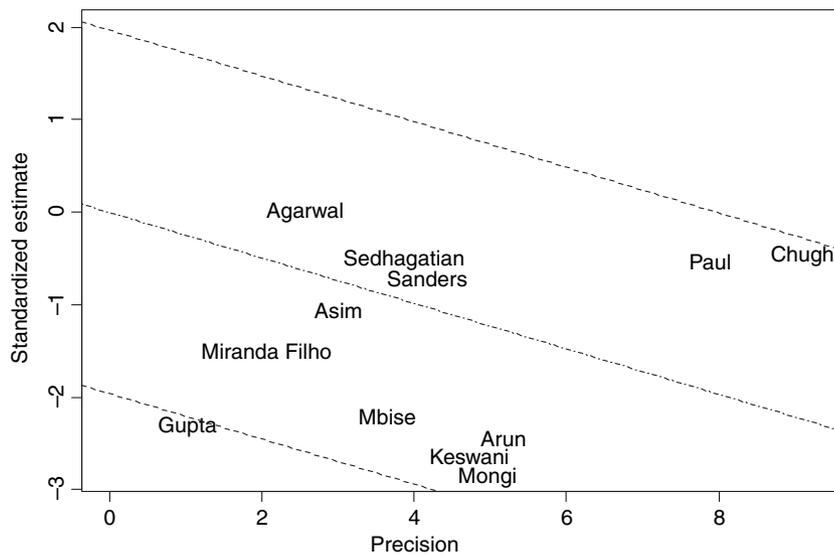


Figure 1 Galbraith plot showing standardised treatment effect estimate [log relative risk divided by standard error (SE)] *vs.* precision (inverse of SE) of randomized trials comparing intrathecal with intramuscular administration of human immunoglobulin or equine antitoxin in the treatment of tetanus.

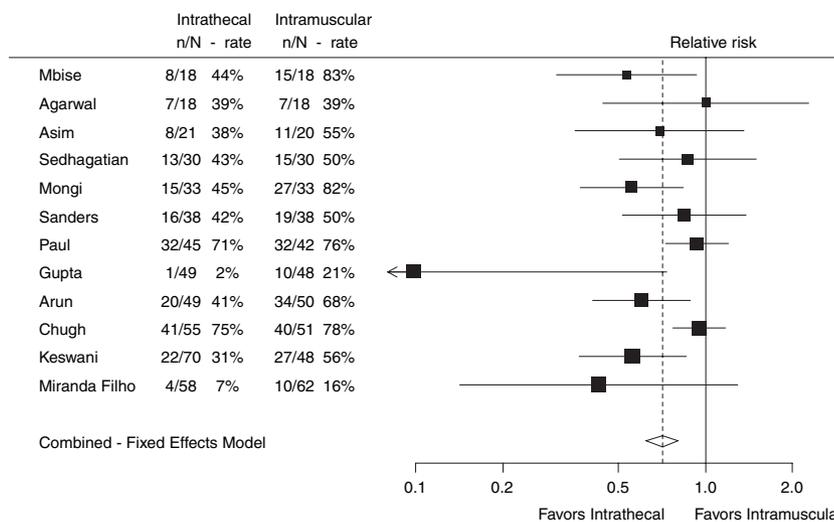


Figure 2 Treatment effects expressed as relative risks of individual randomized trials and all trials combined comparing intrathecal with intramuscular administration of immunoglobulin or equine antitoxin in the treatment of tetanus (studies are ordered according to sample size).

and intramuscular route. The treatment difference appeared to be smaller in neonates, compared with adults. This difference was not statistically significant ($P = 0.194$), but could not be explained by confounding with ITS dosage, type of serotherapy, or overall mortality rate (Figure 4).

Discussion

In this meta-analysis we found out that ITS was more effective than IMS. To minimize bias we selected only randomized trials as suggested by Cucherat *et al.* (1997).

This contributed certainly to an increased strength of our study but some weaknesses should be pointed out: trials were not blinded (which is impossible with this type of treatment comparison), stratification before randomization according to the score of severity was not systematic in all trials, and dosage was different among trials. Moreover, some trials added corticotherapy to the serotherapy whereas others did not. These factors contributed probably to the reduction of homogeneity. The limitation of studies published in French or English was indicated by practical reasons, and probably did not affect the representativity of this meta-analysis. For studies in other languages with an

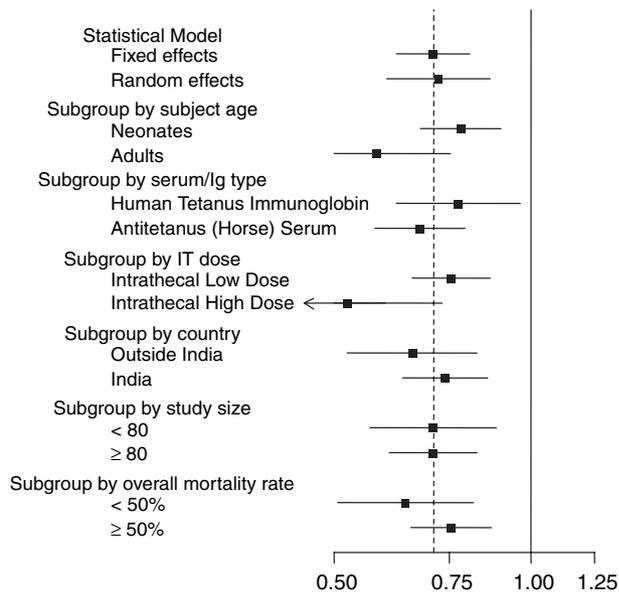
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Figure 3 Treatment effects of randomized trials comparing intrathecal with intramuscular administration of immunoglobulin or equine antitoxin in the treatment of tetanus, according to selected study characteristics (age, serum type, dose ...).

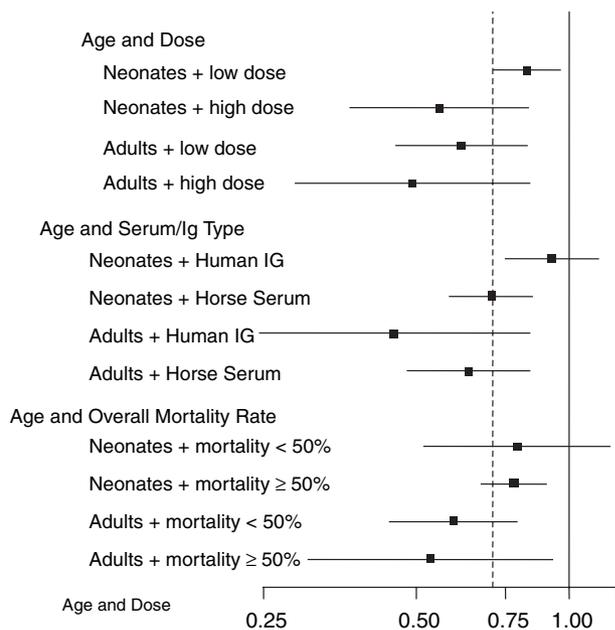


Figure 4 Treatment effects of randomized trials comparing intrathecal with intramuscular administration of immunoglobulin or equine antitoxin in the treatment of tetanus, combining age with dose, serum type and overall mortality rate.

abstract in English, only one met the inclusion criteria (Levin *et al.* 1987). All the studies were conducted in neonates and adults. No trial was performed in young children. This is probably because of the rarity of tetanus in this subcategory because of generalized worldwide programs of immunization at this age.

Several authors state that high doses of ITS could lead to better results than low doses (Mbise *et al.* 1984; Chopra *et al.* 1986; Mongi *et al.* 1987). Our analysis confirms this trend, although few studies used a high dose.

Results were not stratified by the severity of the disease because most of the trials included all stages of the tetanus without randomization for severity. However, without an effective treatment a mild tetanus can switch to severe tetanus and vice versa. Agarwal showed that intrathecal therapy reduces the progression of minor tetanus to severe tetanus whereas 50% of patients with minor tetanus who received intramuscular serotherapy developed severe tetanus within 24 h and 70% within 48 h (Agarwal *et al.* 1998).

We did not compare the duration of hospitalization between the groups because in several trials this item was lacking, and for the remainder it was often not possible to know if the duration in hospital was calculated in all patients or in survivors only.

Singh *et al.* showed that ITS was more effective than IMS when the serum is given within 24 h of onset of the convulsions (Singh *et al.* 1980). Many other authors confirmed this (Sanders *et al.* 1977; Singh *et al.* 1980; Mbise *et al.* 1984; Robert *et al.* 1984; Chopra *et al.* 1986; Mongi *et al.* 1987). Intrathecal immunotherapy could be difficult to perform but Gupta did not find any problem, patients being relaxed after i.v. diazepam (Gupta *et al.* 1980).

No neurological side effects of the intrathecal route were reported. However, in most of the trials the follow-up did not extend over the period of hospitalization. In fact, many authors claim that the intrathecal route for serotherapy is innocuous (Diop-Mar *et al.* 1975). Gupta did not find any definite neurological deficit after ITS during 3 months of follow-up (Gupta *et al.* 1980). On the other hand Robert *et al.* reported reversible paraplegia after high dose of intrathecal human immunoglobulin (Robert *et al.* 1984). This complication had been attributed to either the high dose of immunoglobulin or to drug preservatives.

Do other aspects of management of tetanus play an important role in the prognosis? Recent advances in intensive care especially those concerning spasms and neurovegetative manifestations and respiratory distress management should probably explain the reduction of mortality observed in recent trials like in the Miranda study but not in old ones like the Gupta study (Sutton *et al.*

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1990; Attygalle & Rodrigo 2002, 2004; Reddy 2002; Thwaites *et al.* 2004). However, other studies showed that even in well-equipped intensive care units the mortality because of the tetanus remains very high (Attygalle & Rodrigo 2004). Hyperbaric oxygen is commonly and successfully used in the treatment of *Clostridium perfringens* infections. We did not find any trial in English or in French stating that this treatment was effective in tetanus cases. It might be that authors did not find any benefit in this method, or that a randomized trial was judged unethical.

Conclusion

We conclude that intrathecal serotherapy is more effective than intramuscular serotherapy and should be preferred whenever tetanus is suspected. The difference is slightly higher in adult subjects and significantly higher when using high dose ITS (dosage >250 units).

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Administration intrathécale versus intramusculaire d'immunoglobulines antitétaniques humaines ou d'antitoxines antitétaniques équines dans le traitement du tétanos: une méta-analyse

INTRODUCTION La mortalité liée au tétanos continue d'être un sérieux problème de santé publique dans les pays en voie de développement. Hormis la vaccination, le traitement précoce par du sérum antitétanique équin ou par des immunoglobulines tétaniques humaines reste le traitement approprié pour éviter le décès. Du point de vue physiopathologique, l'administration intrathécale est préférable car celle-ci permet d'obtenir des concentrations élevées d'antitoxines dans le liquide céphalorachidien, donc à proximité des racines nerveuses. Plusieurs études ont démontré l'efficacité de ce type de traitement alors que d'autres n'y ont trouvé aucun avantage par rapport à l'administration intramusculaire. Cependant, la plupart des études n'étaient pas randomisées et/ou manquaient de puissance.

OBJECTIFS L'objectif de cette étude était d'évaluer l'efficacité de la thérapie intrathécale chez les nouveaux nés et les adultes par méta-analyse.

MÉTHODES Les essais cliniques ont été identifiés en cherchant dans Medline, dans la librairie Cochrane, ainsi que dans Current Contents. Les études randomisées, publiées en Anglais ou en Français et comparant les thérapies intrathécales et intramusculaires ont été analysées en utilisant les logiciels Revman et Stata. Les effets des traitements ont été évalués par analyse de la différence en risque relatif.

RÉSULTATS 942 patients ont été inclus dans 12 essais cliniques: 484 dans le groupe intrathécal et 458 dans le groupe intramusculaire. Le risque relatif global de mortalité entre la thérapie intrathécale et la thérapie intramusculaire était de 0,71, en faveur de la thérapie intrathécale (IC95%: 0,62–0,81). La supériorité de la thérapie intrathécale a également été démontrée lors de l'analyse de sous catégories d'âge et de doses.

CONCLUSION L'administration intrathécale d'immunoglobulines antitétaniques humaines ou d'antitoxines antitétaniques équines est supérieure à l'administration intramusculaire dans le traitement du tétanos.

mots clés tétanos, intrathécal, immunoglobulines antitétaniques humaines, antitoxines antitétaniques équines

Administración intratecal versus intramuscular de la inmunoglobulina humana antitetánica o la antitoxina equina en el tratamiento del tétano: un meta-análisis

ANTECEDENTES La mortalidad por tétano continua siendo un problema de salud serio en países en vías de desarrollo. Aparte de la inmunización, el tratamiento temprano con suero equino antitetánico (SAT) o con inmunoglobulina humana antitetánica (IGT) es la intervención que puede evitar la muerte. En términos patofisiológicos, la administración intratecal es preferible, puesto que resulta en una alta concentración del antisuero en el líquido cefaloraquídeo (LCR), y por lo tanto alrededor de las raíces nerviosas. Muchos estudios concluyen sobre su efectividad, mientras que otros no han encontrado ninguna superioridad en este método. Sin embargo, la mayoría de estos estudios no estaban aleatorizados y/o no tenían suficiente peso.

OBJETIVO Evaluar la eficacia de la terapia intratecal con suero antitetánico en neonatos y adultos.

MÉTODOS Metanálisis. Se identificaron ensayos clínicos mediante búsquedas en *Medline*, la *Cochrane library* y *Current Contents*. Se analizaron los estudios aleatorizados publicados en inglés o francés, que comparasen la terapia intratecal con la intramuscular, utilizando los paquetes informáticos de Revman, R y Stata. Los efectos del tratamiento se evaluaron por el riesgo relativo entre la administración intratecal vs. intramuscular.

RESULTADOS Se incluyeron un total de 942 pacientes provenientes de 12 ensayos, 484 en el grupo intratecal y 458 en el intramuscular. El riesgo relativo combinado de mortalidad para la terapia intratecal vs. intramuscular fue de 0.71 [95% CI, 0.62–0.81]. La superioridad de la terapia intratecal también fue patente cuando se realizó el análisis por subcategorías, tanto de adultos y de neonatos, como para dosis elevadas y bajas de seroterapia intratecal.

CONCLUSIÓN La administración intratecal de IGT o LCR es más beneficiosa que la administración intramuscular en el tratamiento del tétano.

palabras clave tetanus, intratecal, antitoxina equina de tétano, inmunoglobulina humana antitetánica