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

Kabura L, Ilibagiza D, Menten J, Van den Ende J

CRD summary
The review assessed the efficacy of intrathecal therapy with antitetanus serum (ATS) in neonates and adults. The authors concluded that intrathecal administration of ATS or human immunoglobulin was more beneficial than intramuscular administration in the treatment of tetanus. Summary estimates and variation between the studies were not reported, thereby limiting the reader’s interpretation of the results presented. The authors’ conclusions should be interpreted with caution.

Authors’ objectives
To determine the efficacy of intrathecal therapy with antitetanus serum (ATS) in neonates and adults.

Searching
MEDLINE, the Cochrane Library and Current Contents were searched for relevant papers published in English or French; the search terms were reported. The authors also reported that other electronic data providers were searched, but did not specify what these were.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared intrathecal (ITS) and intramuscular (IMS) administration of ATS were eligible for inclusion. Human immunoglobulin (TIG) and equine antitoxin were included in the review. The doses ranged from 50 to 1,500 IU in the ITS arm and from 250 to 40,000 IU in the IMS arm. Two studies also considered the use of steroids.

Participants included in the review
Adults and neonates with tetanus were eligible for inclusion. Half of the included studies were conducted in adults and half in neonates.

Outcomes assessed in the review
The primary outcome was the mortality rate. Other outcomes included adverse events and length of hospital stay.

How were decisions on the relevance of primary studies made?
The authors did not state how papers were selected for the review, or how many reviewers performed the selection. Papers were required to provide the following information: intervention and outcome data, country in which trial was conducted, year of publication, sample size, age of the participants and dosage.

Assessment of study quality
The methodological quality of the included studies does not appear to have been formally assessed. However, the authors did report elements of methodological quality (blinding and stratification before randomisation) in their discussion.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data
Relative risks (RRs) with 95% confidence intervals (CIs) were calculated for mortality.

**Methods of synthesis**

**How were the studies combined?**
The studies were combined, and pooled RRs with 95% CIs were calculated using the Mantel-Haenszel method.

**How were differences between studies investigated?**
Meta-regression was used to assess the effects of possible predictors on treatment differences. Subgroup analyses were performed for mortality: adults versus neonates, high versus low serum doses, human TIG versus country (India versus outside India), sample size (<80 versus at least 80), overall mortality rate (<50% versus at least 50%) and type of serum (horse versus human). The Cochran Q test, I-squared test and Galbraith plot were used to assess statistical heterogeneity. Pooled effect sizes from random-effects and fixed-effect analyses were compared for consistency.

**Results of the review**
Twelve trials (n=942) were included in the review. The majority of the trials were conducted in developing countries.

The authors reported that none of the trials were blinded; that stratification before randomisation according to severity score was not always systematic; and that dosages were different across the studies.

A beneficial effect of ITS compared with IMS was found for mortality (0.71, 95% CI: 0.62, 0.81), based on 12 studies. A significant reduction in mortality was found with ITS in studies using high-dose ITS compared with low-dose ITS (p=0.037), based on 3 studies; the estimates were not reported. The authors reported that other factors did not show a significant difference in mortality between ITS and IMS. Heterogeneity was not reported.

**Authors’ conclusions**
ITS administration of ATS or TIG was more beneficial than IMS administration in the treatment of tetanus. This difference was slightly greater in adults and significantly greater when using high-dose ITS.

**CRD commentary**
The review question was supported by clear inclusion criteria. Appropriate databases were searched, although the search was restricted by language (French and English) and it was unclear whether attempts were made to locate unpublished data; this may mean that some studies were missed. The methods of the review were poorly reported, so it was unclear whether appropriate steps were taken to reduce the risk of error and bias during the study selection and data extraction processes. Although the validity of the primary studies does not appear to have been systematically evaluated, some elements of study quality were discussed. Attempts to assess and investigate study heterogeneity were made; however, summary estimates and heterogeneity were not always reported, thereby limiting the reader's interpretation of the results. Given these limitations, the authors' conclusions should be interpreted with caution.

**Implications of the review for practice and research**
Practice: The authors stated that ITS serotherapy should be used in preference to IMS serotherapy when tetanus is suspected.

Research: The authors did not state any implications for further research.

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