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Gangliosides for acute spinal cord injury.

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[Intervention Review]

Gangliosides for acute spinal cord injury

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ABSTRACT

Background

Spinal cord injury (SCI) results in loss of feeling and movement. The consequences can be devastating for the patient and his or her carers. Global estimates of the number of new cases annually range from 15 to 40 per million. Leading causes of acute SCI are road traffic injury, violence, and injuries sustained in sports and other recreational activities. Care for people with SCI has improved, leading to an increase in survival rates. Attempts to improve patients' feeling and movement have involved the use of a wide range of treatments. Gangliosides are compounds that occur naturally in cell membranes. Laboratory studies have suggested they may have protective effects on nerves and even help them to re-grow. Clinical trials have taken place using gangliosides (usually GM1 ganglioside) for a number of neurological conditions.

Objectives

To quantify the evidence for the effectiveness and safety of gangliosides when used to treat acute SCI.

Search methods

We searched the following databases to identify trials for inclusion: Cochrane Injuries Group's Specialised Register (searched 4 June 2008), CENTRAL (The Cochrane Library issue 2, 2008), MEDLINE to May (week 3) 2008, PUBMED (searched on 5 June 2008 (Limit: added to database in last 90 days), EMBASE to June 2008, Current Controlled Trials metaRegister (searched 5 June 2008), Web of Knowledge; Science Citation Index (searched 5 June 2008). We also searched web-based sources using the search engine Google.com. We approached the manufacturers of the most widely used ganglioside and researchers in this field to try to locate any unpublished data.

Selection criteria

Randomised controlled trials of any ganglioside versus controls, in patients with SCI. Outcome measures specified were: mortality, recovery of motor function, improvement in sensory measures, measures of functional activity, infections and any other adverse events.

Data collection and analysis

Data were extracted from published studies and authors were contacted for further information. All data found was dichotomous and odds ratios (with 95% CIs) were calculated. A fixed-effects model was assumed.

Gangliosides for acute spinal cord injury (Review)

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Main results

Two studies met the inclusion criteria. There were no deaths in one (n=37). In the other (n=760), there were slightly more deaths in the treatment group than in the control group; odds ratio 1.07 (0.57, 2.00 95%CI) - a result that can be explained by the play of chance. Methodological weaknesses regarding the collection and presentation of data from the two studies made it impossible to reach any conclusions regarding the effect of gangliosides on the other specified outcomes.

Authors' conclusions

The evidence available does not support the use of ganglioside treatment to reduce the death rate in SCI patients. No evidence has yet emerged that ganglioside treatment improves recovery or quality of life in survivors.

PLAIN LANGUAGE SUMMARY

No evidence that treatment with gangliosides reduces death rate or improves life for survivors after spinal cord injury

Injuries to the spinal cord are often devastating. Worldwide there are up to 40 million such injuries a year. People who survive often have severe disabilities. Gangliosides are substances that occur naturally in nerve cells. They can be manufactured and there have been studies to see whether they can be used to treat various conditions where nerves have been damaged. This review found two studies where a ganglioside had been used to treat people with spinal cord injury. The treatment did not produce a lower death rate and there was no evidence that movement, feeling or quality of life was improved for those who lived.

BACKGROUND

Description of the condition

Spinal cord injury (SCI) is damage to the spinal cord that results in loss of feeling and movement. The consequences can be devastating for the patient and his or her carers.

There is no accepted figure for the number of new cases of acute SCI globally; estimates range from 15 to 40 cases per million annually (Sekhon 2001). The Japanese Society of Paraplegia has estimated the annual incidence nationally to be 39.4 per million (Shingu 1994). In the USA, it has been estimated that the number of cases admitted to hospitals will increase from 11,500 in 1994 to 13,400 in 2010, and that the number of people living with the consequences of an acute SCI will increase from 207,000 to 247,000 over the same period (Lasfargues 1995). Those injured are often young; a US study found that average age at injury was 32 (Kirshblum 2002).

Leading causes of acute SCI are road traffic injury, violence, and injuries sustained in sports and other recreational activities (particularly diving and certain forms of football). The picture varies considerably between and within countries; thus traffic injury is the biggest cause in most developed countries (44.9% in Japan (Shingu 1994) but in south-eastern Turkey the leading causes were

falls (37.3%), gunshot wounds (29.3%) and traffic injury (25.3%) (Karamehmetoglu 1997).

Care for people with acute SCI has improved, leading to an increase in survival rates (Sekhon 2001). Attempts to improve patients' feeling and movement have involved the use of a wide range of pharmacological and other treatments.

Description of the intervention

Gangliosides are compounds that occur naturally in cell membranes. They are particularly abundant in the membranes of the central nervous system. In vitro studies with gangliosides, dating back to the 1970s, suggested that gangliosides could promote axon growth (Roisen 1981). Animal studies have suggested that gangliosides may have protective effects on nerves and, in the longer-term, help them to re-grow (Ledeen 1984). The mechanisms of ganglioside action remain unclear (Blight 2002) but those proposed include anti-excitotoxic activity, apoptosis prevention, and potentiation of neuritic sprouting and the effects of nerve growth factors (Geisler 2001).

Clinical trials have taken place using gangliosides for a number of neurological conditions, most notably stroke (for which use

there has been a Cochrane systematic review (Candelise 2003) and Parkinson's disease (Schneider 1998). No major problem with adverse events has been detected, although sporadic cases of Guillain-Barré syndrome have been noted in stroke patients receiving gangliosides (Candelise 2003). The potential use of gangliosides for patients with SCI has attracted considerable attention within the medical community. In the USA there have also been articles in the popular media (Torg 1995). Research has focused on one ganglioside - GM1 ganglioside (monosialotetrahexosylganglioside GM1; Sygen®). Other gangliosides include GM2, GM3, GD1a and GD1b.

Why it is important to do this review

While the studies above suggest that these compounds may have properties worthy of some further investigation, gangliosides are not registered for use for people with SCI. The evidence for the effectiveness and safety of their use for this condition had not been ascertained. Hence we conducted a systematic review of randomised controlled trials.

OBJECTIVES

To quantify the evidence for the effectiveness and safety of gangliosides when used to treat acute SCI.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (including quasi-randomised), where controls received standard treatment or a placebo.

Types of participants

All patients with a diagnosis of acute SCI. The "acute" period was taken as within one week of the injury.

Types of interventions

All treatment with gangliosides, independently of duration, dosage and route of administration.

Types of outcome measures

The following outcome measures were included, as recorded after one year of follow-up (or the nearest date possible):

- recovery of motor function: e.g. improvement on a pre-specified validated scoring system, such as that of the American Spinal Injuries Association (ASIA)
- improvement in sensory measures (e.g. pinprick and light touch sensation)
- measures of functional activity / activities of daily living (ADL)
- infections and any other adverse events recorded in the study, including Guillain-Barré syndrome
- all-cause mortality
- GI bleeding, pneumonia, atelectasis and other problems specific to acute spinal cord injury.

Search methods for identification of studies

Searches were not restricted by date, language or publication status.

Electronic searches

We searched the following databases to identify trials for inclusion;

- CIG Specialised Register (searched 4 June 2008),
- CENTRAL (The Cochrane Library issue 2, 2008),
- MEDLINE to May (week 3) 2008PUBMED searched 5 June 2008 (Limit: added to database in last 90 days),
- EMBASE to June 2008,
- Current Controlled Trials metaRegister (searched 5 June 2008),
- WOK Science Citation Index (searched 5 June 2008),

The most recent searches were carried out in June 2008. Details of the full search strategies used can be found in [Appendix 1](#)

We searched the reference lists of all eligible studies and any review articles for further potentially eligible articles. We searched the Internet using the Google (www.google.com) search engine with selected terms from the search strategy, for any further unpublished or grey literature.

None of the search strategies were limited for date, language or publication status.

Searching other resources

Fidia Pharmaceuticals, who manufacture GM1 ganglioside as Sygen®, were contacted to enquire whether they had any unpublished data on clinical studies with this drug that they were willing to have included in this systematic review. No reply was received to our letter, sent in March 2003 to The Director, Research & Development, Fidia Pharmaceuticals Corporation, Washington DC, USA.

Researchers in this area were asked whether they knew of other published or unpublished data.

Data collection and analysis

Selection of studies

Abstracts of all studies identified were scanned independently by both reviewers and the full text of potentially relevant articles retrieved. The two reviewers independently assessed the identified studies for eligibility. Any disagreement was resolved by discussion. The quality of trials was assessed using methodology developed by Schultz and Chalmers (Schulz 1995). This considers whether the intervention was blinded, whether people evaluating outcome were blinded, how many subjects were followed up, and the quality of the randomisation process. Allocation concealment was rated: A - adequate, B - unclear and C - inadequate. The reviewers attempted to ascertain whether intention-to-treat analysis had been undertaken in the trials.

Data extraction and management

The following information was extracted from each trial: strategy for allocation concealment, number of randomised patients, duration of follow-up, loss to follow-up, blinding of outcome assessment and whether an intention-to-treat analysis was reported. Data was sought on the types of outcomes specified above. One reviewer extracted data and his extraction was then checked by the second reviewer. Authors were contacted for additional data.

Data synthesis

A fixed-effects model was to be used in the analysis. For dichotomous outcomes, odds ratios with 95% confidence intervals (95%CI) were to be calculated. For continuous data, weighted mean differences (WMD) were to be used. A standard heterogeneity test was planned to assist in decisions whether or not to produce typical estimates of effect. Sub-group analysis had been anticipated as follows: according to the quality of allocation concealment in trials, type of ganglioside, whether administration is "early" (within eight hours) or "late", and whether spinal injury is considered "complete" or "incomplete". Had there been heterogeneity in the length of follow-up, a sensitivity analysis would have been considered, data allowing.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#).

Results of the search

A total of 138 records have been retrieved in the search for studies to June 2008. All studies were screened independently by two review authors and 30 papers were obtained in full. Of these, one study, which was translated from Chinese to English Liu 2002, is still under investigation, three were potentially eligible, however one (Walker 1993) was excluded as patients suffered from chronic, not acute, SCI. Two studies met the inclusion criteria and were eligible for review.

Both studies had strict eligibility criteria and only a minority of the SCI patients screened were admitted to the studies. Thus the treatment was only tested on a sub-group of patients considered by the researchers to be suitable.

Included studies

The first study (Geisler 1991) involved 37 patients (of 351 screened) randomised to receive GM1 ganglioside (17 patients) or a placebo (20) but, for reasons described by the researchers as 'technical not therapeutic', only 34 completed treatment. Some heterogeneity was noted between patients in the treatment and control groups, for example with regard to the level of the injury. Follow-up assessment of patients took place after one year. The missing three patients (one in the treatment group and two in the placebo group) were not assessed neurologically though they were included in the analysis of adverse events. Six of the 34 patients who completed treatment were excluded from analysis of sensory function, because their grade, at entry, on the five-point Frankel system was in one of the highest two categories. (The researchers recorded the number of patients who improved by two or more grades and these six patients thus 'lacked room' to do this.)

The second study (Geisler 2001) involved 760 patients, of 3165 screened according to several eligibility criteria. Patients were required to have at least one lower extremity with a substantial motor deficit; patients with spinal cord transection or penetration were excluded, as were patients with a significant cauda equina. Patients were randomised to three groups: high-dose GM1 ganglioside, low-dose ganglioside and placebo. A further 37 patients were 'randomised in error' but no data is available on these patients. At the first interim analysis, an extramural monitoring committee recommended early discontinuation of the high-dose treatment group because, at that stage, there appeared to be greater mortality and lower efficacy in this group. Low-dose treatment was given to 331 patients (44%), high-dose to 99 (13%) and placebo to 330 (43%). Outcomes were: mortality, number of patients considered to have made 'marked recovery', motor and sensory scores, bowel and bladder function, safety. Follow-up regarding some outcomes ceased at six months; with others the final follow-up was at one year.

Risk of bias in included studies

Allocation

We rated both studies “A” in terms of allocation concealment.

Blinding

In [Geisler 1991](#) randomisation was performed by assigning each patient the next sequential pre-randomised drug-study number; and a similar method was apparently used in [Geisler 2001](#). Patients received either GM1 ganglioside or a placebo. Researchers assessing the patients’ progress were blinded as to the treatment given.

Other potential sources of bias

In [Geisler 1991](#) there was no loss to follow-up. However, as described above, treatment was discontinued in three of the 37 randomised patients and these three did not undergo neurological testing. Although data on American Spinal Injury Association (ASIA) motor scores are available on all 34 patients who completed treatment, we have not included this outcome in our analysis as, without data on the other three patients, the analysis would not be ‘intention-to-treat’. Likewise the approach used to assess sensory function, which excludes both the three patients who did not complete treatment and a further six patients who lacked ‘room to improve’, makes intention-to-treat analysis impossible. Data on adverse events are available for all 37 randomised patients and we have therefore included this in our analysis.

In [Geisler 2001](#) mortality data is available on all of 760 correctly randomised patients, i.e. there was no loss to follow-up. However, there are concerns regarding the exclusion of many of the patients from the researchers’ own analysis of most outcomes and the unavailability of data on the excluded patients. (This is discussed further under ‘Results’.) Intention-to-treat analysis is, therefore, only possible on the mortality data.

Effects of interventions

All-cause mortality (Table 01)

In [Geisler 1991](#), none of the 34 patients who completed treatment died. However, one of the three patients who did not complete treatment died. Thus in an intention-to-treat analysis, there is a mortality rate in the treatment group of 5.88% compared with none in the control group. The odds ratio is 3.73 (0.14, 97.64 95%CI) - a result that can be explained by the play of chance.

In [Geisler 2001](#), the mortality rate in the combined treatment groups (5.81%) was slightly higher than in the control group

(5.45%). The odds ratio is 1.07 (0.57, 2.00 95%CI), which can be explained by the play of chance.

Combining mortality in the two studies in a meta-analysis, the mortality rate in the treatment groups (6.04%) was higher than in the control groups (5.45%). The odds ratio is 1.13 (0.61, 2.07 95%CI), which can be explained by the play of chance.

Measures of recovery in surviving patients

As described above, the ASIA motor score and Frankel sensory grade data is not available for all randomised patients in [Geisler 1991](#) preventing an intention-to-treat analysis.

In [Geisler 2001](#), the authors recorded the number of patients considered to be making a ‘marked recovery’, this being assessed at 4, 8, 16 and 26 weeks after entry. This does not correspond with our inclusion criteria for outcome measures and we have not used the data in our analysis. Other data recorded in the study were: ASIA light touch, pinprick and motor scores; and number of patients with normal bowel and bladder function. The published paper presents summary graphs of this information but the data itself is not given. We contacted the researchers for missing data. We supplied them with a table wherein spaces were left blank for data we lacked. The researchers were unable to provide data in this form but kindly supplied us with data analysis print-outs. Unfortunately this still did not provide us with the information we needed to conduct an analysis on an intention-to-treat basis. We were therefore unable to analyse the data or draw any conclusions from it.

Adverse events (Table 02)

In [Geisler 1991](#), 16 GM1-treated patients had a total of 56 events of which 36 were urinary infections; comparable figures for the placebo group - 19 patients, 75 events, 49 urinary. For all adverse events combined, the odds of an event were slightly lower in the control group; OR 0.84 (0.05, 14.57 95%CI) - again a result that can be explained by the play of chance.

In [Geisler 2001](#) the authors considered that “The reported adverse events were typical for the acute SCI population, and there were no noteworthy differences among treatment groups in frequency or severity of events”. No data was, however, published and the authors have not been able to supply the reviewers with data for the events they recorded.

DISCUSSION

Both of the included studies have been extensively discussed in review articles by the authors and by others. The publication of the very small 1991 study led to optimism that GM1 ganglioside offered new hopes for the treatment of SCI. However, the results

of the 2001 study found no difference between treatment and control groups in terms of mortality. Although the presentation by authors of the studies of the data on other outcomes makes it difficult to conduct an analysis, no clear difference between treatment and control groups has emerged. No evidence of any harm from ganglioside treatment has been found, but we cannot exclude the possibility of rare adverse events that would only have been detected had much larger sample sizes been used.

Central to the approach adopted by the authors of the two studies is the notion that gangliosides may be effective with some but not other subgroups of patients, depending in particular on the exact site of the injury. This has influenced their presentation of the data but makes it hard to analyse the effects of gangliosides on SCI patients overall, while failing to identify any subgroup for whom the response to the treatment might be beneficial.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence for the use of gangliosides in the treatment

of acute SCI.

Implications for research

There is no evidence that ganglioside treatment reduces mortality in SCI patients. Further randomised trials of good quality would have to examine, as well as mortality, the improvement in sensory and motor scores of *all* recruited patients according to recognised motor and sensory scales.

ACKNOWLEDGEMENTS

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- Frances Bunn, an Editor of the Cochrane Injuries Group, has ably overseen the peer review process for this review and given much useful advice.
- Thanks to Cynthia To, Data Assistant, CRASH Trial, London School of Hygiene & Tropical Medicine for her valued assistance with translation.

REFERENCES

References to studies included in this review

Geisler 1991 *{published data only}*

Geisler FH, Dorsey FC, Coleman WP. Recovery of motor function after spinal-cord injury - a randomised placebo-controlled trial with GM-1 ganglioside. *New England Journal of Medicine* 1991;**324**(26):1829-38.

Geisler 2001 *{published data only}*

* Geisler FH, Coleman WP, Grieco G. The Sygen Multicenter Acute Spinal Cord Injury Study. *Spine* 2001;**26**(24S):S87-98.

Geisler FH, Coleman WP, Grieco G, et al. Measurement and recovery patterns in a multicenter study of acute spinal cord injury. *Spine* 2001;**26**(Suppl 1):S68-86.

Geisler FH, Coleman WP, Grieco G, et al. Recruitment and early treatment in a multicenter study of acute spinal cord injury. *Spine* 2001;**26**(Suppl 1):S58-67.

References to studies excluded from this review

Walker 1993 *{published data only}*

Walker JB, Harris M. GM-1 ganglioside administration combined with physical therapy restores ambulation in humans with chronic spinal cord injury. *Neuroscience Letters* 1993;**161**(2):174-8.

References to studies awaiting assessment

Liu 2002 *{published data only}*

Liu X G, Liu ZJ, Dang G. The role of GM-1 ganglioside in acute spinal cord injury: a clinical controlled investigation. *Chinese Journal of Spine and Spinal Cord* 2002;**12**(5):344-7.

Additional references

Blight 2002

Blight A. Miracles and molecules - progress in spinal cord repair. *Nature Neuroscience Supplement* 2002;**5**:1051-4.

Candelise 2003

Candelise L, Ciccone A. Gangliosides for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2003, Issue 1. [DOI: 10.1002/14651858.CD000094]

Geisler 2001

Geisler FH, Coleman WP, Grieco G, Poonian D. (Collective Name - the Sygen Study Group). The Sygen multicenter acute spinal cord injury study. *Spine* 2001;**26**(24 Suppl): S87-98.

Karamehmetoglu 1997

Karamehmetoglu SS, Nas K, Karacan I, Sarac AJ, Koyuncu H, Ataoglu S, Erdogan F. Traumatic spinal cord injuries in southeast Turkey: an epidemiological study. *Spinal Cord* 1997;**35**(8):531-5.

Kirshblum 2002

Kirshblum SC, Groah SL, McKinley WO, Gittler MS, Stiens SA. Spinal cord injury medicine. 1. Etiology,

- classification, and acute medical management. *Archives of Physical Medicine & Rehabilitation* 2002;**83**(3 Suppl 1):S50-7, S90-8.
- Lasfargues 1995**
Lasfargues JE, Custis D, Morrone F, Carswell J, Nguyen T. A model for estimating spinal cord injury prevalence in the United States. *Paraplegia* 1995;**33**(2):62-8.
- Ledeen 1984**
Ledeen RW. Biology of gangliosides: neuritogenic and neurotrophic properties. *Journal of Neuroscience Research* 1984;**12**(2-3):147-59.
- Roisen 1981**
Roisen F, Bartfield H, Nagele R, Yorke G. Ganglioside stimulation of axonal sprouting in vitro. *Science* 1981;**214**(4520):577-8.
- Schneider 1998**
Schneider JS. GM1 ganglioside in the treatment of Parkinson's disease. *Annals of the New York Academy of Science* 1998;**845**(Jun):363-73.
- Schulz 1995**
Schulz KF, Chalmers I, Hayes RJ, Altman DG. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Journal of the American Medical Association* 1995;**273**(5):408-12.
- Sekhon 2001**
Sekhon LH, Fehlings MG. Epidemiology, demographics, and pathophysiology of acute spinal cord injury. *Spine* 2001;**26**(24):Suppl S2-12.
- Shingu 1994**
Shingu H, Ikata T, Katoh S, Akatsu. Spinal cord injuries in Japan: a nationwide epidemiological survey in 1990. *Paraplegia* 1994;**32**(1):3-8.
- Torg 1995**
Torg JS, Currier B, Douglas R, Hershman E, O'Leary PF. Symposium: spinal cord resuscitation. *Contemporary Orthopaedics* 1995;**30**(6):495-504, 507-9.
- * Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Geisler 1991

Methods	Randomised, placebo, double-blind trial.
Participants	37 patients with spinal cord injury, either cervical or thoracic. Entry criteria excluded patients with no or minor neurological deficit and various other criteria; thus 314 other patients seen during the trial were not included
Interventions	GM1 ganglioside, 100mg daily i.v., starting within 72 hours of injury. Number of doses varied between 18 and 32. Exact mode of administration varied slightly
Outcomes	The following at one year: 1) Frankel grades (patients who improved two or three grades, but six excluded as their grade at entry was such that they did not have 'room to improve' by 2+ grades. 2) ASIA motor scores 3) all adverse effects.
Notes	1) Allocation: each patient assigned the next sequential pre-randomised drug-study number. 2) Three patients (one treatment, two placebo) did not receive all the study doses for 'technical reasons'

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Geisler 2001

Methods	'Prospective, double-blind, randomised, stratified, multicenter trial' . Stratification according to severity of injury and whether thoracic or cervical
Participants	SCI patients: 3165 screened according to several eligibility criteria and 760 randomised. (A further 37 were randomised in error but no data is available on these patients)
Interventions	1) 300mg loading dose of GM1 ganglioside ('Sygen') followed by 100mg/day for 56 days, plus MPSS [n=331]. 2) 600mg loading dose of GM-1 ganglioside followed by 200mg/day for 56 days, plus MPSS [n=99]. 3) Placebo plus MPSS [n=330].
Outcomes	The following at six months and one year: 1) mortality 2) patients considered to have made 'marked recovery' 3) motor and sensory scores 4) bowel and bladder function 5) safety.

Geisler 2001 (Continued)

Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

MPSS - methylprednisolone, given at standard dose rate of the US National Acute Spinal Cord Injury Studies (see - Bracken MB. Steroids for acute spinal cord injury. The Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD001046. DOI: 10.1002/14651858.CD001046).

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Walker 1993	All patients had chronic (not acute) SCI.

Characteristics of studies awaiting assessment [ordered by study ID]**Liu 2002**

Methods	Multi-centre, double-blinded, parallel, randomised study.
Participants	144 (72 in each group) patients with acute spinal cord injury aged between 12 and 70
Interventions	100mg of drug A (GM-1) for 14 days followed by 40mg of drug B (placebo) for 7 days [n=72]
Outcomes	After 3 weeks and 3 months; 1) Ability to urinate and defecate, 2) Modified Benzel classification, 3) Changes in sensational responses (skin touch, skin prick, anus sensation)
Notes	

DATA AND ANALYSES

Comparison 1. Mortality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality at 365 days	2	797	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.61, 2.07]

Comparison 2. Adverse events

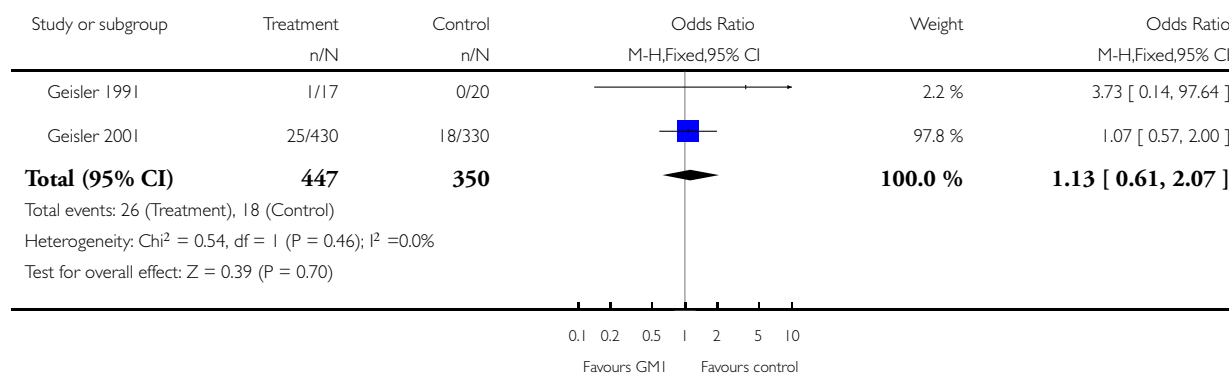
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Numbers of patients experiencing any kind of adverse effect(s)	1	37	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.05, 14.57]

Analysis 1.1. Comparison 1 Mortality, Outcome 1 All-cause mortality at 365 days.

Review: Gangliosides for acute spinal cord injury

Comparison: 1 Mortality

Outcome: 1 All-cause mortality at 365 days

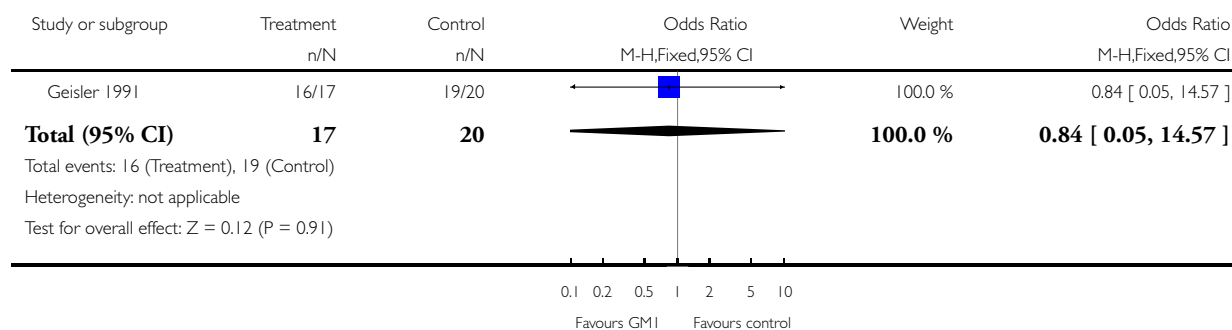


Analysis 2.1. Comparison 2 Adverse events, Outcome 1 Numbers of patients experiencing any kind of adverse effect(s).

Review: Gangliosides for acute spinal cord injury

Comparison: 2 Adverse events

Outcome: 1 Numbers of patients experiencing any kind of adverse effect(s)



APPENDICES

Appendix I. Detailed search strategies

Cochrane Injuries Group's Specialised Register (searched 04-06-08)

((spine or spinal) and (fracture* or wound* or trauma* or injur* or damag*)) or (("spinal cord" and (contusion or laceration or transaction or trauma or injur* or ischemia)) or (SCI or paraplegi* or paraparesis or qadriplegi* or quadriparesi* or tetraplegi* or tetraplagi* or tetraparesis)) and (ganglioside* or gm1 or gm-1 or gm2 or gm-2 or gm3 or gm-3 or sygen* or sialoglycosphingolipid*)

CENTRAL (*The Cochrane Library issue 2, 2008*)

- #1 exp Spinal Cord Injuries/
- #2 ((spine or spinal) near (fracture* or wound* or trauma* or injur* or damag*))
- #3 (spinal cord) near (contusion or laceration or transaction or trauma or injur* or ischemia)
- #4 SCI
- #5 exp Paraplegia/
- #6 paraplegi* or paraparesis
- #7 exp Quadriplegia/
- #8 qadriplegi* or quadriparesi*
- #9 tetraplegi* or tetraplagi* or tetraparesis
- #10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
- #11 exp Gangliosides/
- #12 anglioside* or gm1 or gm-1 or gm2 or gm-2 or gm3 or gm-3 or sygen* or sialoglycosphingolipid*
- #13 11 or 12
- 14. 10 and 13

MEDLINE to May (week 3) 2008

1. exp Spinal Cord Injuries/
2. ((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).ab,ti.
3. (spinal cord adj3 (contusion or laceration or transaction or trauma or injur* or ischemia)).ab,ti.
4. SCI.ti,ab.
5. exp Paraplegia/
6. (paraplegi* or paraparesis).ti,ab.
7. exp Quadriplegia/
8. (quadriplegi* or quadriparesi*).ti,ab.
9. (tetraplegi* or tetraplagi* or tetraparesis).ti,ab.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp Gangliosides/
12. (ganglioside* or gm1 or gm-1 or gm2 or gm-2 or gm3 or gm-3 or sygen* or sialoglycosphingolipid*).ti,ab.
13. 11 or 12
14. 10 and 13
15. (randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial*).tw,hw.
16. clinical trial.pt.
17. randomized controlled trial.pt.
18. 15 or 16 or 17
19. exp models, animal/
20. exp Animals/
21. exp Animal Experimentation/
22. exp Disease Models, Animal/
23. exp Animals, Laboratory/
24. or/19-23
25. Humans/
26. 24 not 25
27. 18 not 26
28. 14 and 27

PUBMED searched June 5 2008 (Limit: added to database in last 90 days)

- #1 ("Gangliosides"[Mesh] OR ganglioside* or gm1 or gm-1 or gm2 or gm-2 or gm3 or gm-3 or sygen* or sialoglycosphingolipid*)
- #2 (SCI OR paraplegi* OR paraparesis OR quadriplegi* OR quadriparesi* OR tetraplegi* OR tetraplagi* OR tetraparesis OR "Spinal Cord Injuries"[Mesh] OR "Paraplegia"[Mesh] OR "Quadriplegia"[Mesh])
- #3 ((spine or spinal) AND (fracture* or wound* or trauma* or injur* or damag*)) OR ((spinal cord) AND (contusion or laceration or transaction or trauma or injur* or ischemia))
- #4 #2 OR #3
- #5 #1 AND #4

EMBASE to June 2008

1. exp Spinal Cord Injury/
2. ((spine or spinal) adj3 (fracture* or wound* or trauma* or injur* or damag*)).ab,ti.
3. (spinal cord adj3 (contusion or laceration or transaction or trauma or injur* or ischemia)).ab,ti.
4. SCI.ti,ab.
5. exp Paraplegia/
6. (paraplegi* or paraparesis).ti,ab.
7. exp Quadriplegia/
8. (quadriplegi* or quadriparesi*).ti,ab.
9. (tetraplegi* or tetraplagi* or tetraparesis).ti,ab.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. exp Ganglioside/
12. (ganglioside* or gm1 or gm-1 or gm2 or gm-2 or gm3 or gm-3 or sygen* or sialoglycosphingolipid*).ti,ab.
13. 11 or 12
14. 10 and 13

15. exp animal model/
16. Animal Experiment/
17. exp ANIMAL/
18. exp Experimental Animal/
19. 15 or 16 or 17 or 18
20. Human/
21. 19 not 20
22. (randomised or randomized or randomly or random order or random sequence or random allocation or randomly allocated or at random or controlled clinical trial*).tw,hw.
23. exp clinical trial/
24. 22 or 23
25. 24 not 21
26. 14 and 25

Current Controlled Trials metaRegister (searched 5 June 2008)

((spine or spinal) and (cord or fracture* or wound* or trauma* or injur* or damag*)) and ganglioside*

WOK Science Citation Index (searched 5 June 2008)

- 1.Topic=(SCI or paraplegi* or paraparesis or qadriplegi* or quadriparesi* or tetraplegi* or tetraplagi* or tetraparesis)
- 2.Topic=(spine or spinal) AND Topic=(fracture* or wound* or trauma* or injur* or damag*) OR Topic=(spinal cord) AND Topic=(contusion or laceration or transaction or trauma or injur* or ischemia)
- 3.1 or 2
- 4.Topic=(ganglioside* or gm1 or gm-1 or gm2 or gm-2 or gm3 or gm-3 or sygen* or sialoglycosphingolipid*)
- 5.3 and 4

WHAT'S NEW

Last assessed as up-to-date: 3 June 2008.

Date	Event	Description
18 September 2008	New search has been performed	The search was updated to 4 June 2008. None of the newly identified studies were eligible for inclusion

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 2, 2005

Date	Event	Description
23 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

PC wrote the protocol with input from IR. PC and IR screened the studies found in the search. PC obtained the papers required and entered data from the included studies; checked by IR. PC contacted study authors for additional information. PC wrote the review with input from IR. KB ran the searches, scanned search results for selection of studies and obtained translations for the update in 2008.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Health Service, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; G(M1) Ganglioside [therapeutic use]; Gangliosides [*therapeutic use]; Randomized Controlled Trials as Topic; Spinal Cord Injuries [*drug therapy; mortality]

MeSH check words

Humans