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Calcium channel blockers for acute traumatic brain injury (Review)

Langham J, Goldfrad C, Teasdale G, Shaw D, Rowan K

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TABLE OF CONTENTS

[Intervention Review]

Calcium channel blockers for acute traumatic brain injury

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ABSTRACT

Background

Acute traumatic brain injury is a major cause of death and disability. Calcium channel blockers (calcium antagonists) have been used in an attempt to prevent cerebral vasospasm after injury, maintain blood flow to the brain, and so prevent further damage.

Objectives

To estimate the effects of calcium channel blockers in patients with acute traumatic brain injury, and in a subgroup of brain injury patients with traumatic subarachnoid haemorrhage.

Search methods

We searched the Cochrane Injuries Group's Specialised Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and the reference lists of relevant articles. We also contacted experts in the field. The searches were updated in November 2005.

Selection criteria

Randomised controlled trials (RCTs) in patients with all levels of severity of clinically diagnosed acute traumatic brain injury.

Data collection and analysis

Two authors independently assessed the identified studies for eligibility and extracted data from each study. Summary odds ratios were calculated using the Mantel-Haenszel method.

Main results

Six RCTs involving 1862 participants were included. The effect of calcium channel blockers on the risk of death was reported in five of the RCTs. The pooled odds ratio (OR) for the five studies was 0.91 (95% confidence interval [95% CI] 0.70 to 1.16). For the five RCTs that reported death and severe disability (unfavourable outcome), the pooled OR 0.97 (95%CI 0.81 to 1.18). In the two RCTs which reported the risk of death in a subgroup of traumatic subarachnoid haemorrhage patients, the pooled OR 0.59 (95% CI 0.37 to 0.94). Three RCTs reported death and severe disability as an outcome in this subgroup, and the pooled OR 0.67 (95% CI 0.46 to 0.98).

Authors' conclusions

This systematic review of randomised controlled trials of calcium channel blockers in acute traumatic head injury patients shows that considerable uncertainty remains over their effects. The effect of nimodipine in a subgroup of brain injury patients with subarachnoid haemorrhage shows a beneficial effect, though the increase in adverse reactions suffered by the intervention group may mean that the drug is harmful for some patients.

PLAIN LANGUAGE SUMMARY

Does a group of drugs known as calcium channel blockers reduce mortality and unfavourable complications in patients with traumatic brain injury?

Acute traumatic brain injury is a major cause of death and disability. Not all damage to the brain occurs at the moment of injury; reduction of blood flow and oxygen supply to the brain can occur afterwards and cause further brain damage, which is an important cause of avoidable death and disability. In the early stages after injury it is therefore important that efforts are made to minimise secondary brain damage and to provide the best chances of recovery from established brain damage.

The use of calcium channel blockers has been proposed for the prevention or treatment of cerebral vasospasm (that is, sudden narrowing of blood vessels in the brain), which can occur after brain injury and cause secondary brain damage due to a reduction in blood flow.

It is important to determine whether or not calcium channel blockers might be effective in reducing mortality and unfavourable outcomes in head-injured patients.

This review looked at all high quality trials comparing the use of calcium channel blockers with a control, in head-injured patients of any age. The authors also looked at trials involving patients suffering from subarachnoid haemorrhage (that is, bleeding into the space between the brain and the skull) caused by an injury, as a subgroup.

The authors found six eligible trials involving 1862 patients. The results indicate that there is insufficient evidence to support the use of calcium channel blockers. The authors conclude that there is some evidence that a calcium channel blocker called nimodipine may be beneficial for some patients with subarachnoid haemorrhage. However, there is also an indication of certain adverse reactions amongst patients treated with nimodipine which may mean that the drug is harmful for some individuals.

The authors recommend that the promising results in patients with subarachnoid haemorrhage are replicated in a larger well designed trial, before any firm conclusions about the effectiveness of the drug can be drawn. In future trials, data on outcomes other than death and severe disability, such as quality of life of the survivors and the economic utility of the drug, should be measured; such outcomes have not been considered in existing research.

BACKGROUND

Acute traumatic brain injury is a major cause of death and disability (Jennett 1977) and has been defined as "an acquired injury to the brain caused by an external physical force, resulting in total or partial disability or impairment" (Moscato 1994). Not all damage to the brain occurs at the moment of impact. Reduction of blood flow and oxygen supply to the brain can occur and cause secondary brain damage, which is an important cause of avoidable death and disability (Gentleman 1990). For most secondary events after head injury, the final common path is a critical reduction in cerebral blood flow, leading to loss of cellular integrity and ischaemic neuronal damage (Matthews 1995).

The management of acute traumatic brain injury is thought to be of critical importance in determining the eventual outcome. The aim in the early stages is to minimise the secondary brain damage and to provide the best chances of recovery from established brain damage. In the later stages, the aim is to improve the functional health of the patient (Sharples 1995).

Calcium channel blockers (also known as calcium antagonists) reduce the influx of calcium into the cell by blocking the calcium channels. Their use has been suggested for prevention or treatment

of cerebral vasospasm after acute traumatic brain injury, based on the hypothesis that these drugs can counteract the influx of extracellular calcium in the vascular smooth-muscle cells and prevent the blood vessels constricting (Graham 1989). It is important to determine whether or not calcium channel blockers might reduce the incidence of ischaemia in head-injured patients.

Why it is important to do this review

The evidence for the use of calcium channel blockers is unconvincing, and the known side-effects of the drugs (induced hypotension, cerebral vasodilatation, and impaired cerebrovascular reactivity) may outweigh the benefits. Hence, the primary motivation and rationale for this review is to assess the available evidence from randomised controlled trials, to estimate better the effects of calcium channel blockers in patients with acute traumatic brain injury and in a subgroup of traumatic subarachnoid haemorrhage patients (tSAH).

OBJECTIVES

Objective 1

To estimate the effect of calcium channel blockers in head-injured patients. The primary outcome measures are, first, total mortality and, second, an unfavourable outcome — defined as death, severe disability or persistent vegetative state as described by the Glasgow Outcome Scale (Jennett 1975). Secondary outcome measures are listed under "Types of outcome measure".

Objective 2

To estimate the effects of calcium channel blockers as a function of the following variables:

- time between injury and admission to hospital and the administration of treatment;
- method of administration;
- dosage;
- age of the patient;
- type of calcium channel blocker;
- severity of the brain damage;
- duration of treatment;
- adverse side-effects of the treatment (for example, hypotension).

Objective 3

To estimate the effects of calcium channel blockers in a subgroup of brain injury patients with tSAH.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Patients with clinically diagnosed acute traumatic brain injury, of any age and in any healthcare setting.
Patients with traumatic subarachnoid haemorrhage were included, but patients with spontaneous subarachnoid haemorrhage were excluded.

Types of interventions

Any calcium channel blocker (calcium antagonist), namely: verapamil, nifedipine, nicardipine, amlodipine, felodipine, isradipine, lacidipine, nimodipine and diltiazem, administered in any dose, by any route, for any duration, and at any time of onset.

Types of outcome measures

Primary outcomes

The primary outcome measures are:

- total mortality;
- an unfavourable outcome - defined as death, severe disability or persistent vegetative state as described by the Glasgow Outcome Scale (Jennett 1975). A favourable outcome is usually defined as good recovery (for example, return to work) or moderate disability.

Secondary outcomes

Other outcomes for which data were also sought were:

- quality of life;
- personality changes in adults;
- disruption to family;
- delayed development in children (for example, speech development);
- physiological/biological measures (computerized axial tomography (CAT) scans, cerebral blood flow);
- economic factors.

In addition, adverse side-effects of the treatment (for example, hypotension) were studied.

Search methods for identification of studies

The aim was to undertake a comprehensive search for all relevant RCTs, in order to avoid bias resulting from the exclusion of any studies.
The search was not restricted by language, publication status or publication date.

Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Group's Specialised Register (up to November 2005);
- Cochrane Central Register of Controlled Trials (The Cochrane Library, issue 4, 2005);
- MEDLINE (1966 to November 2005);
- EMBASE (1988 to November 2005);
- Intensive Care National Audit & Research Centre's (ICNARC) database of RCTs (contains the results of the hand searching of 33 selected journals relevant to intensive care and emergency medicine);
- Ottawa Stroke Trials Registry.

The searches were based on the search strategy shown in Appendix 1, modified as appropriate to the specifications of each database.

Searching other resources

We searched reference lists of pertinent articles for eligible RCTs. In addition, we asked experts active in the field and drug companies who manufacture calcium channel blockers if there were other studies, published or otherwise, that might be eligible for inclusion.

Data collection and analysis

The authors were supported by a steering group. In advance of collating and reviewing the relevant literature, a meeting was held between the authors of the review and members of the steering group to decide on the inclusion criteria for the studies and the methods of identifying these studies. A further meeting was held once the studies had been identified and quality assessed to discuss the results of the literature search and propose a plan for analysis. Finally, once the analysis was completed, a meeting was held to discuss the results and possible implications.

Selection of studies

One author scanned all abstracts of all studies identified through electronic searching and retrieved the full text of relevant articles. Two authors (JL and CG) independently assessed the identified studies for eligibility. Any disagreements were discussed with a third review author (KR) until agreement was reached.

Data extraction and management

We extracted the following data from each study:

- the number of participants randomised to each group;
- inclusion and exclusion criteria;
- interventions;
- outcomes measured;
- number of participants lost to follow-up;
- summary of the results.

Assessment of risk of bias in included studies

An assessment of the methodological quality of each trial report was carried out using two validated scales (Downs 1996; Jadad 1996). Two authors (JL and CG) independently carried out this assessment. Any disagreements were discussed with a third author (KR) until consensus was reached.
The first scale (Jadad 1996) is designed to measure the likelihood of bias in RCTs, based on three items: randomisation, double-blinding, and withdrawals or drop outs after randomisation. This scale assesses validity with three questions with a highest score attainable of five. A second quality assessment scale was used to assess the trials, with a highest score obtainable of 32 (Downs 1996), in order to find a greater differentiation of quality between the four trials, not provided with Jadad 1996.

Data synthesis

Summary odds ratios were calculated in RevMan software, using the Mantel-Haenszel method.

RESULTS

Description of studies

See: Characteristics of included studies.
After a full text review seven trials (Compton 1990; HIT I 1990; HIT II 1994; HIT III 1996; HIT IV; Sahuquillo 2000; Sinha 2002) were judged to meet the inclusion criteria. Two of these were unpublished reports (HIT IV; Sinha 2002). We wrote to the principal investigators of these two studies for information. Data for HIT IV were not made available by the principal investigators of this trial but were, nevertheless, accessible to us, as they had been presented publicly at a conference. The author of Sinha 2002 has not responded, despite repeat letters, and we have found no other way of accessing the data for the 50 participants in this nimodipine study.
Contact with experts in the area and pharmaceutical companies did not identify any additional trials, although out of the six letters sent out to experts, and four to pharmaceutical companies only

two replies were received (one expert, Professor Braakman and one drug company, Roche Pharmaceuticals) Bayer and Baker Norton did not respond.
This review is therefore based on six RCTS comprising a total of 1862 participants.
The combined search strategies identified nine reports of studies that satisfied the inclusion criteria, relating to four eligible RCTs that comprised 1315 randomised participants.
Details for each study are presented in the table 'Characteristics of included studies'.

Risk of bias in included studies

We assessed the quality of RCTs using the Jadad scale, the scores were:
Compton 1990 (5/5);
HIT I 1990 (5/5);
HIT II 1994 (2/5);
HIT III 1996 (3/5);
HIT IV (unable to assess as results not published);
Sahuquillo 2000 (3/5).
The scores on the Downs scale were:
Compton 1990 (27/32);
HIT I 1990 (22/32);
HIT II 1994 (15/32);
HIT III 1996 (18/32);
HIT IV (unable to assess as results not published);
Sahuquillo 2000 (23/32).

There was good agreement between the two scales, Compton 1990 scored highest on both scales, followed by HIT I 1990. The reports of HIT II 1994 and HIT III 1996, however, were of lower quality. Both scored poorly on reporting of sample size calculations, masking and presentation of statistics.

Effects of interventions

Objective 1

Five RCTs provided data for the primary objective to estimate the effects of calcium channel blockers on the risk of death (total mortality): Compton 1990; HIT I 1990; HIT II 1994; HIT III 1996; Sahuquillo 2000. There were slightly fewer deaths in the treatment group 23.2% versus 25.0%, but the difference was not statistically significant: summary odds ratio 0.91 (95% CI 0.70 to 1.16). Exclusion of the nicardipine trials (Compton 1990 and Sahuquillo 2000) made no difference to the result.
The four nimodipine trials (HIT I 1990; HIT II 1994; HIT III 1996; HIT IV) and Sahuquillo 2000 (nicardipine trial) also provide data to assess the effect of calcium channel blockers on an unfavourable outcome (mortality, severe disability and persistent vegetative state). Again, the occurrence of an unfavourable outcome is only marginally less in the treatment group, 38.9% versus 39.1%, and this did not reach statistical significance: summary odds ratio 0.97 (95% CI 0.81 to 1.18). Again, excluding the nicardipine trial made no difference.
No information was available to consider any of the other outcomes.

Objective 2

Data on adverse events or side-effects (e.g. hypotension, increase in pancreatic and liver enzymes) occurring during the trial were available in three of the trials (HIT I 1990; HIT II 1994; HIT III 1996). The occurrence of an adverse event is greater in the treatment (nimodipine) group, 21.1% versus 19.1%, though this difference is not statistically significant: summary odds ratio 1.15 (95% CI 0.87 to 1.52).
However, the number of participants suffering from hypotension in the treatment group (nimodipine) was significantly greater than the controls, 12.0% versus 7.4%: summary odds ratio 1.74 (95% CI 1.20 to 2.52). No information was available to estimate the effects of calcium channel blockers in subgroups defined by dose, age, severity etc.

Objective 3

Information was available in two of the trials (HIT II 1994; HIT III 1996) for estimating the effects of calcium channel blockers in a subgroup of tSAH patients on total mortality. Fewer deaths occur in the treatment group, 26.9% versus 38.9%. This difference does reach statistical significance: summary odds ratio 0.59 (95% CI 0.37 to 0.94).
Information was available in three of the trials (HIT I 1990; HIT II 1994; HIT III 1996) for estimating the effects of calcium channel blockers in a subgroup tSAH patients on total mortality and severe disability. Fewer unfavourable outcomes occur in the treatment (nimodipine) group, 48.2% versus 57.9%. Again, this does reach statistical significance: summary odds ratio 0.67 (95% CI 0.46 to 0.98).

DISCUSSION

Objective 1

This systematic review of randomised controlled trials of calcium channel blockers in head injury patients shows that considerable uncertainty remains over their clinical effects. Current data make it improbable that nimodipine has a marked beneficial or harmful effect in unselected head injury patients.

Objective 2

There is a significant increase in hypotension in the nimodipine group, which may mean that the drug negates its potential beneficial effects in some patients. In addition, since the trials studied were small, there could be other adverse reactions that were not experienced by any of the patients studied.

Objective 3

The effect of nimodipine in a subgroup of brain injury patients with subarachnoid haemorrhage shows a clearer beneficial effect. There is a significant increase in favourable outcome in the treatment group in this subgroup of patients. However caution should be taken over inferring too much from this result, as the quality assessment of the reporting of showed, the quality of this study is unclear and it contributes a large proportion of the sample size (121 out of a sample of 460).

Not surprisingly, when the data were analysed again for the total population excluding those with tSAH the moderate beneficial effect seen in the analysis of all patients disappears. For the outcome total mortality the summary odds ratio was 0.91 (95% CI 0.71 to 1.17) for all patients together compared to 1.17 (95% CI 0.86 to 1.60) after exclusion of the tSAH patients. For the outcome mortality and severe disability the summary odds ratio was 0.85 (95% CI 0.68 to 1.07) for all patients together, compared to 1.02 (95% CI 0.77 to 1.36) excluding tSAH patients.

Quality assessment of RCTs

As is often the case, we found that the quality of reporting of some of the RCTs was below the standard needed in order to make a true assessment of the validity of the trial (Altman 1990). Poor reporting does not, of course, constitute a poor trial, though there is evidence to suggest that this might be the case (Schulz 1995). Since the quality of these trials was assessed only from the written papers, if the quality of reporting was poor, then the score for quality assessment will be poor.

A number of points should be stressed here. First, no attempt was made to discuss the quality of each trial with the principal investigators. Second, the purpose of assessing the quality of RCTs before inclusion into a review is to exclude those trials whose quality is found to be below a certain standard and therefore to reduce the potential for bias in the results; no trials were excluded on this basis. Third, the quality assessment score was not used to weight RCTs used in the meta-analysis. In view of this, it may be important to communicate with all investigators regarding the actual procedure of the trial in order better to assess its quality. For example in trials where there is not adequate allocation concealment, trials are more likely to over estimate the effect size. This is a common fault and may not be easily assessed from the written report (Schulz 1995). It may also be important to discuss what definitions in each trial were used, for example, the definitions of adverse events and severity of pathology differ from trial to trial. Therefore, it may be useful to obtain the original protocols for each trial to determine how data were collected and variables defined. Preliminary enquiries have been made to principal investigators of each trial and to Bayer Pharmaceuticals (who funded HIT I, II, III and IV) regarding the possibility of obtaining the original data, in order to conduct an individual patient data pooled analysis. Professor Teasdale (HIT I 1990) and Professor Braakman (HIT II 1994) have provided informal verbal permission for use of the data, and further efforts are underway to contact Harders (HIT III 1996) and Compton (Compton 1990). Permission is still being sought from Bayer, who have so far not responded, despite two letters.

The risk of bias figures are presented in Figure 1 and Figure 2.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

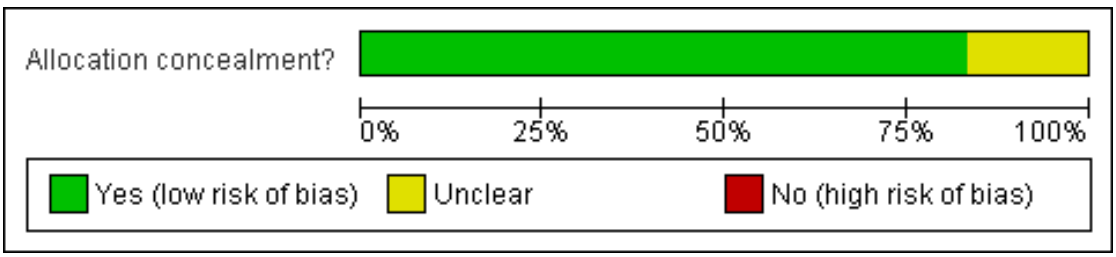
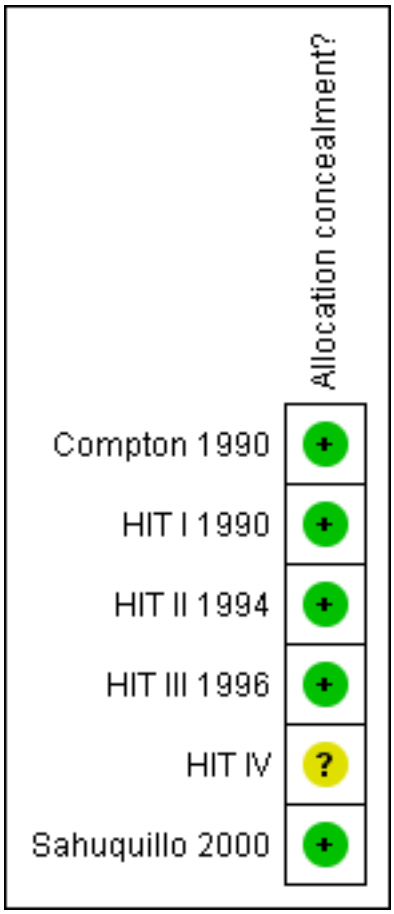


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of calcium channel blockers in an unselected group of patients with traumatic head injury, although a clinically significant benefit cannot be ruled out with the data available.

There is some evidence to suggest that nimodipine may be of benefit to a subgroup of patients with tSAH.

Implications for research

The promising results in tSAH patients need to be replicated in a larger RCT, before any firm conclusions about the effectiveness of the drug can be drawn.

The outcomes to consider should include not only outcomes of death and severe disability, but also the quality of life of the survivors and the economic utility of the drug. These are issues that have not been addressed in the trials to date.

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- Phil Alderson – Deputy Director, UK Cochrane Centre, Oxford, UK;
- Ian Basnett – Consultant in Public Health Medicine, Camden and Islington Health Authority, London, UK;

- Nick Black — Professor of Health Services Research, London School of Hygiene & Tropical Medicine, London, UK.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Compton 1990

Methods	Patients n=31 Treatment n=20 Placebo n=11
Participants	Inclusion • Severe head Injury <8 Glasgow coma score, or making a flexor response, or response to pain following initial resuscitation) • DFV>100cm/s on 2 consecutive readings • after 6 hours • >10 years old • >40kg body weight Exclusions • pregnant • suffering from heart, renal or liver failure
Interventions	• Nicardipine vs placebo • 1mg/ml, in isotonic buffer, Syntex Research • Placebo (sorbitol and vehicle) • initially at 2.5ml/h increase to 7.5ml/h after 4 h if no response • IV infusion • continued for 24 hours
Outcomes	• Glasgow outcome scale at discharge • GOS at 3 months • Doppler flow velocity
Notes	• Increased favourable outcome in Nicardipine group (on DFV) • RR = 2.67 95% CI 1.08 to 6.60 Losses to follow-up • 1 no data, and • 6 lost to follow-up

Risk of bias

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

HIT I 1990

Methods	Patients n=351 Treatment n=176 Placebo n=175
Participants	Inclusion • Severe head injury patients, not obeying simple commands • <24 hours of injury • Adults (16-70 years) • 6 European Neurosurgical units Exclusions • haemodynamic instability • clinically brain dead • pregnant • renal • hepatic pulmonary or cardiac decompensation
Interventions	• Nimodipine vs placebo • dosage: 1mg initially to 2mg per hour if blood pressure did not decline • IV • <24 hours of injury • up to 7 days
Outcomes	• Glasgow outcome scale • follow-up 6 months
Notes	• Increased favourable outcome in Nimodipine group • RR= 1.075; 95% CI 0.88 to 1.32 • 2 excluded from analysis • 14 withdrawn from treatment

Risk of bias

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

HIT II 1994

Methods	Patients n=852 Treatment n=423 Placebo n=429
Participants	Inclusion • head injured, of obeying commands at time of entry (within 12 hours of patient not obeying commands) undergone CT • <24 hours since head injury. • 16-70 years • 21 Neurosurgical centres in 13 European countries Exclusions

	responses could not be assessed due to previous treatment, gunshot wounds, haemodynamic instability, pregnant, wide non reacting pupils and motor response absent for >2 hours, likely to die within 24 hours, unlikely to be available for follow up at 6 months
Interventions	• Nimodipine vs placebo • initially 1mg/hour, increased to 2mg/hour after 2 hours • IV • for 7 days or death of patient.
Outcomes	• Glasgow outcome scale • 6 months
Notes	• increased favourable outcome in Nimodipine group • RR = 1.02; 95% CI 0.91 to 1.14 • 33 lost to follow up

Risk of bias

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

HIT III 1996

Methods	Patients n=123 Treatment n=63 Placebo n=60
Participants	Inclusion • tSAH on an initial CT scan • within 12 hours after head injury • 16-70 years • 21 German Centres Exclusions gunshot wounds
Interventions	• Nimodipine vs Placebo • within 12 hours injury • 2mg/hour intravenously, for 7- 10 days then • orally 360mg/day to day 21.
Outcomes	• Disability rating scale Barthel Index • Glasgow outcome scale • Presence of post- traumatic epilepsy • 6 months follow up

HIT III 1996 (*Continued*)

Notes	• Reduced unfavourable outcome in Nimodipine group • OR=0.34; 95% CI 0.15 to 0.76 • 2 lost to follow up	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

HIT IV

Methods	Patients n= 592 (525 ITT with definite diagnosis of tSAH) treatment n= 290 Placebo n= 287 13 countries participating, international.
Participants	Inclusion - tSAH on an initial CT scan - within 12 hours after head injury - 16-70 years - start of treatment within 12 hours - written consent - at randomisation the patient had to have a GCS <15, unless patient was intubated Exclusion: - gunshot injury and penetrating head injury - patients with non reacting pupils and no motor response for more than 1hr at time of entry to trial - patients with low blood pressure <61/91 - co-existing pathology, e.g. cancer. - patients who were likely to die within next 24 hours - pregnancy - known treatment by another investigational drug since injury - previous enrolment to study - impaired liver function.
Interventions	Nimodipine first dosage within 12 hours
Outcomes	GOS at six months Mortality see HIT III
Notes	

Risk of bias		
Item	**Authors' judgement**	**Description**

Allocation concealment?	Unclear	B - Unclear

Sahuquillo 2000

Methods	Patients n=22 Treatment n=11 Placebo n=11
Participants	Moderate and severe traumatic brain injury, GCS <12 with mean Doppler flow velocity of >=100cm/second within the first week. At least one hemisphere with suggested vasospasm age 18-65 inclusive. Neuro ICU Spain less than 7 days after trauma. Exclusions: Brain death or predictable death within 72 hours of admission Weight > 40 kg Severe concomitant injury or disease CPP < 60 mm Hg at randomization No informed consent Known medical history of intolerance to calcium channel blockers
Interventions	Nicardipine 5 mg/hour for 7 days Intravenous As soon as possible after mean DFV > 100 cm/second placebo: Same as treatment
Outcomes	Death, morbidity, GOS. Main variable assessed was the temporal evolution of the middle cerebral artery Doppler flow velocity (DFV) at baseline and days 1, 3, 5 and 7. At least one hemisphere with suggested vasospasm was an indication for inclusion
Notes	Mean DFV dropped below 100 cm/second within 24 hours of treatment initiation in the treatment group and within 72 hours in the control group Mean time for recovery of elevated mean DFV was 3.33 days in the placebo group and 1.22 in the nicardipine group (P=0.0039) Nicardipine is effective in the reversal and prevention of increased mean DFV in patients with moderate or severe head injury

Risk of bias

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

DATA AND ANALYSES

Comparison 1. Calcium channel blockers versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all-cause mortality)	5	1337	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.70, 1.16]
1.1 Nicardipine	2	46	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.0 [0.20, 4.90]
1.2 Nimodipine	3	1291	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.70, 1.17]
2 Death and severe disability	5	1838	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.81, 1.18]
2.1 Nicardipine	1	22	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.25 [0.05, 1.27]
2.2 Nimodipine	4	1816	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.99 [0.82, 1.20]
3 Adverse events	3	1324	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.87, 1.52]
3.1 Nicardipine	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
3.2 Nimodipine	3	1324	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.87, 1.52]
4 Hypotension	3	1324	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.74 [1.20, 2.52]
4.1 Nicardipine	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
4.2 Nimodipine	3	1324	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.74 [1.20, 2.52]
5 Mortality (by participant subgroups)	4		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
5.1 tSAH	2	331	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.37, 0.94]
5.2 no tSAH	3	984	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.83, 1.54]
6 Death and severe disability (by participant subgroups)	3		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
6.1 tSAH	3	460	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.46, 0.98]
6.2 no tSAH	2	831	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.77, 1.36]

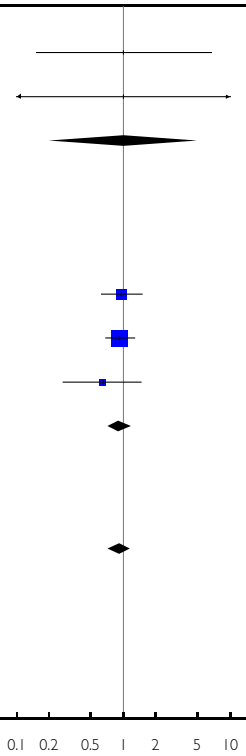
Analysis 1.1. Comparison 1 Calcium channel blockers versus control, Outcome 1 Death (all-cause mortality).

Review: Calcium channel blockers for acute traumatic brain injury

Comparison: 1 Calcium channel blockers versus control

Outcome: 1 Death (all-cause mortality)

Study or subgroup	n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Nicardipine					
Compton 1990	4/16	2/8		1.7 %	1.00 [0.15, 6.81]
Sahuquillo 2000	1/11	1/11		0.8 %	1.00 [0.06, 17.12]
Subtotal (95% CI)	**27**	**19**		**2.5 %**	**1.00 [0.20, 4.90]**
Total events: 5 (), 3 (Placebo)					
Heterogeneity: Chi^2 = 0.0, df = 1 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 Nimodipine					
HIT I 1990	49/176	50/175		29.3 %	0.96 [0.61, 1.53]
HIT II 1994	90/405	98/414		59.5 %	0.92 [0.67, 1.28]
HIT III 1996	11/60	16/61		8.7 %	0.64 [0.27, 1.49]
Subtotal (95% CI)	**641**	**650**		**97.5 %**	**0.90 [0.70, 1.17]**
Total events: 150 (), 164 (Placebo)					
Heterogeneity: Chi^2 = 0.74, df = 2 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 0.78 (P = 0.44)					
Total (95% CI)	**668**	**669**		**100.0 %**	**0.91 [0.70, 1.16]**
Total events: 155 (), 167 (Placebo)					
Heterogeneity: Chi^2 = 0.75, df = 4 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 0.77 (P = 0.44)					
Test for subgroup differences: Chi^2 = 0.02, df = 1 (P = 0.90), I^2 =0.0%					



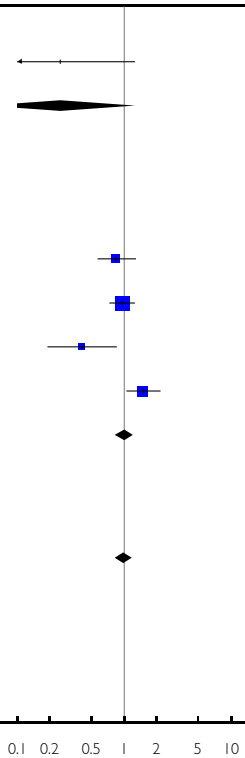
Analysis 1.2. Comparison 1 Calcium channel blockers versus control, Outcome 2 Death and severe disability.

Review: Calcium channel blockers for acute traumatic brain injury

Comparison: 1 Calcium channel blockers versus control

Outcome: 2 Death and severe disability

Study or subgroup	n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Nicardipine					
Sahuquillo 2000	3/11	7/11		1.3 %	0.25 [0.05, 1.27]
Subtotal (95% CI)	**11**	**11**		**1.3 %**	**0.25 [0.05, 1.27]**
Total events: 3 (), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.67 (P = 0.094)					
2 Nimodipine					
HIT I 1990	82/176	89/175		20.4 %	0.84 [0.56, 1.28]
HIT II 1994	160/405	168/414		45.8 %	0.96 [0.72, 1.26]
HIT III 1996	15/60	28/61		6.5 %	0.40 [0.19, 0.85]
HIT IV	93/266	68/259		26.0 %	1.50 [1.04, 2.18]
Subtotal (95% CI)	**907**	**909**		**98.7 %**	**0.99 [0.82, 1.20]**
Total events: 350 (), 353 (Placebo)					
Heterogeneity: Chi^2 = 11.12, df = 3 (P = 0.01); I^2 =73%					
Test for overall effect: Z = 0.08 (P = 0.94)					
Total (95% CI)	**918**	**920**		**100.0 %**	**0.97 [0.81, 1.18]**
Total events: 353 (), 360 (Placebo)					
Heterogeneity: Chi^2 = 13.85, df = 4 (P = 0.01); I^2 =71%					
Test for overall effect: Z = 0.27 (P = 0.78)					
Test for subgroup differences: Chi^2 = 2.73, df = 1 (P = 0.10), I^2 =63%					



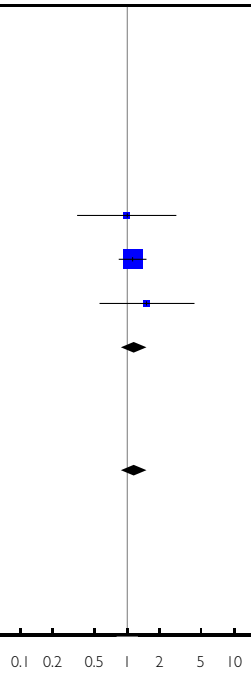
Analysis 1.3. Comparison 1 Calcium channel blockers versus control, Outcome 3 Adverse events.

Review: Calcium channel blockers for acute traumatic brain injury

Comparison: 1 Calcium channel blockers versus control

Outcome: 3 Adverse events

Study or subgroup	n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Nicardipine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Nimodipine					
HIT I 1990	7/176	7/175		6.8 %	0.99 [0.34, 2.89]
HIT II 1994	122/423	113/429		85.8 %	1.13 [0.84, 1.53]
HIT III 1996	10/60	7/61		7.4 %	1.53 [0.55, 4.25]
Subtotal (95% CI)	**659**	**665**		**100.0 %**	**1.15 [0.87, 1.52]**
Total events: 139 (), 127 (Placebo)					
Heterogeneity: Chi^2 = 0.38, df = 2 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 0.98 (P = 0.33)					
Total (95% CI)	**659**	**665**		**100.0 %**	**1.15 [0.87, 1.52]**
Total events: 139 (), 127 (Placebo)					
Heterogeneity: Chi^2 = 0.38, df = 2 (P = 0.83); I^2 =0.0%					
Test for overall effect: Z = 0.98 (P = 0.33)					
Test for subgroup differences: Not applicable					



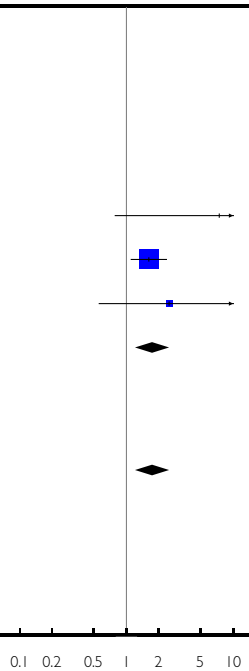
Analysis 1.4. Comparison 1 Calcium channel blockers versus control, Outcome 4 Hypotension.

Review: Calcium channel blockers for acute traumatic brain injury

Comparison: 1 Calcium channel blockers versus control

Outcome: 4 Hypotension

Study or subgroup	n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Nicardipine					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
2 Nimodipine					
HIT I 1990	3/176	0/175		2.7 %	7.43 [0.77, 71.91]
HIT II 1994	71/423	47/429		91.4 %	1.63 [1.10, 2.40]
HIT III 1996	5/60	2/61		6.0 %	2.51 [0.55, 11.47]
Subtotal (95% CI)	**659**	**665**		**100.0 %**	**1.74 [1.20, 2.52]**
Total events: 79 (), 49 (Placebo)					
Heterogeneity: Chi^2 = 1.90, df = 2 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 2.93 (P = 0.0034)					
Total (95% CI)	**659**	**665**		**100.0 %**	**1.74 [1.20, 2.52]**
Total events: 79 (), 49 (Placebo)					
Heterogeneity: Chi^2 = 1.90, df = 2 (P = 0.39); I^2 =0.0%					
Test for overall effect: Z = 2.93 (P = 0.0034)					
Test for subgroup differences: Not applicable					



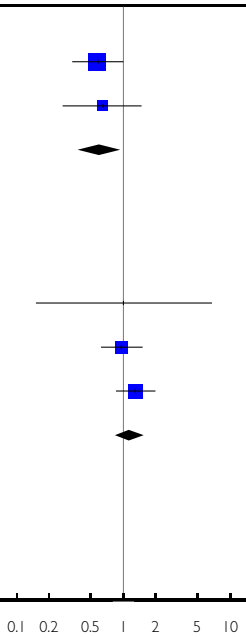
Analysis 1.5. Comparison 1 Calcium channel blockers versus control, Outcome 5 Mortality (by participant subgroups).

Review: Calcium channel blockers for acute traumatic brain injury

Comparison: 1 Calcium channel blockers versus control

Outcome: 5 Mortality (by participant subgroups)

Study or subgroup	n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 tSAH					
HIT II 1994	31/96	52/114		70.3 %	0.57 [0.33, 1.00]
HIT III 1996	11/60	16/61		29.7 %	0.64 [0.27, 1.49]
Subtotal (95% CI)	**156**	**175**		**100.0 %**	**0.59 [0.37, 0.94]**
Total events: 42 (), 68 (Placebo)					
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 2.21 (P = 0.027)					
2 no tSAH					
Compton 1990	4/16	2/8		2.6 %	1.00 [0.15, 6.81]
HIT I 1990	49/176	50/175		43.9 %	0.96 [0.61, 1.53]
HIT II 1994	59/309	46/300		53.6 %	1.30 [0.85, 1.98]
Subtotal (95% CI)	**501**	**483**		**100.0 %**	**1.13 [0.83, 1.54]**
Total events: 112 (), 98 (Placebo)					
Heterogeneity: Chi^2 = 0.89, df = 2 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 0.80 (P = 0.43)					
Test for subgroup differences: Chi^2 = 5.22, df = 1 (P = 0.02), I^2 =81%					



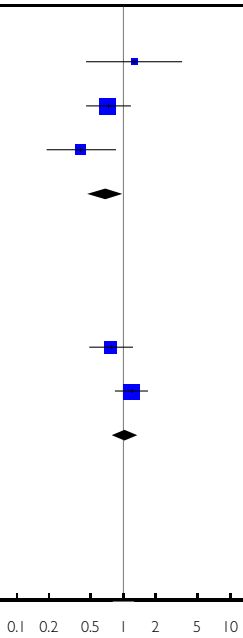
Analysis 1.6. Comparison 1 Calcium channel blockers versus control, Outcome 6 Death and severe disability (by participant subgroups).

Review: Calcium channel blockers for acute traumatic brain injury

Comparison: 1 Calcium channel blockers versus control

Outcome: 6 Death and severe disability (by participant subgroups)

Study or subgroup	n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 tSAH					
HIT I 1990	26/35	25/36		13.5 %	1.27 [0.45, 3.54]
HIT II 1994	64/123	87/145		60.7 %	0.72 [0.45, 1.17]
HIT III 1996	15/60	28/61		25.8 %	0.40 [0.19, 0.85]
Subtotal (95% CI)	**218**	**242**		**100.0 %**	**0.67 [0.46, 0.98]**
Total events: 105 (), 140 (Placebo)					
Heterogeneity: Chi^2 = 3.35, df = 2 (P = 0.19); I^2 =40%					
Test for overall effect: Z = 2.07 (P = 0.038)					
2 no tSAH					
HIT I 1990	56/141	64/139		36.4 %	0.77 [0.48, 1.24]
HIT II 1994	96/282	81/269		63.6 %	1.20 [0.84, 1.71]
Subtotal (95% CI)	**423**	**408**		**100.0 %**	**1.02 [0.77, 1.36]**
Total events: 152 (), 145 (Placebo)					
Heterogeneity: Chi^2 = 2.09, df = 1 (P = 0.15); I^2 =52%					
Test for overall effect: Z = 0.14 (P = 0.89)					
Test for subgroup differences: Chi^2 = 3.02, df = 1 (P = 0.08), I^2 =67%					



APPENDICES

Appendix 1. Search strategy

#1 explode “Calcium-Channel-Blockers” / all SUBHEADINGS
#2 (((calcium) near ((channel*) next (block* or inhibit* or antagonist*))) in TI) or (((calcium) near ((channel*) next (block* or inhibit* or antagonist*))) in AB)
#3 ((verapimil* or nifedipine* or nicardipine* or amlodipine* or felodipine* or isradipine* or iacidipine* or nimodipine* or diltiazem*) in TI)or((verapimil* or nifedipine* or nicardipine* or amlodipine* or felodipine* or isradipine* or iacidipine* or nimodipine* or diltiazem*) in AB)
#4 #1 or #2 or #3
#5 explode “Brain-Injuries” / all SUBHEADINGS in MIME,MJME
#6 explode “Craniocerebral-Trauma” / all SUBHEADINGS in MIME,MJME
#7 explode “Subarachnoid-Hemorrhage” / all SUBHEADINGS in MIME,MJME
#8 (((head or crani* or capitis or brain* or forebrain* or skull* or hemisphere* or intracran* or orbit*) next (injur* or trauma* or lesion* or damag* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)) in TI) or (((head or crani* or capitis or brain* or forebrain* or skull* or hemisphere* or intracran* or orbit*) next (injur* or trauma* or lesion* or damag* or wound* or destruction* or oedema* or edema* or fracture* or contusion* or commotion* or pressur*)) in AB)
#9 (Subarachnoid near (hemorrhage or haemorrhage)) in TI) or ((Subarachnoid near (hemorrhage or haemorrhage)) in AB)
#10 #5 or #6 or #7 or #8 or #9
#11 #4 and #10
#12 #11 and Cochrane HSSS phases 1-2

WHAT’S NEW

Last assessed as up-to-date: 31 October 2005.

Date	Event	Description
7 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 1998

Review first published: Issue 3, 1998

Date	Event	Description
2 November 2005	New search has been performed	The search was updated in November 2005, no new studies were identified for inclusion
5 January 2002	New search has been performed	New studies found and included or excluded.

CONTRIBUTIONS OF AUTHORS

JL contributed to the design of the protocol, searched for trials, extracted and entered data, contacted authors and wrote the paper. CG contributed to protocol design, extracted data, gave statistical advice and helped to write the paper. GT contributed to the design of the protocol, contacted authors of included trials and gave clinical input. KR contributed to the design of the protocol, attended steering group meetings and helped to write the paper. DS attended steering group meetings, commented on the design of the protocol and the paper.

DECLARATIONS OF INTEREST

The individual views of members of the Steering Group regarding the clinical effectiveness and safety of calcium channel blockers, together with any possible conflicts of interest, were recorded at the first Steering Group meeting before the start of the review.

Professor Teasdale, the principal investigator of study and a participant in study, believed that calcium channel blockers were clinically effective in patients with tSAH but was not sure how clinically effective and felt that they were less useful, if at all useful, in patients with acute traumatic brain injury.

Mr Shaw believed that calcium channel blockers were clinically effective in patients with spontaneous subarachnoid haemorrhage and that there would probably be no effect in head-injured patients. However, there was a possibility that they might be of some benefit in the subgroup of patients with tSAH.

Both Professor Teasdale and Mr Shaw have received funding from Bayer Pharmaceutical company, one of the producers of calcium channel blockers. Both stated that there was no conflict of interest regarding the outcome of the review.

Dr Alderson, Dr Basnett, Professor Black, Miss Goldfrad, Ms Langham and Dr Rowan had no prior knowledge of the use of calcium channel blockers and therefore had no prior views that might bias the review.

SOURCES OF SUPPORT

Internal sources

- Intensive Care National Audit & Research Centre, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Brain Injuries [complications; *drug therapy]; Calcium Channel Blockers [*therapeutic use]; Randomized Controlled Trials as Topic; Subarachnoid Hemorrhage [complications; *drug therapy]; Vasospasm, Intracranial [etiology; *prevention & control]

MeSH check words

Humans