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[Intervention Review]

Intrathecal baclofen for treating spasticity in children with cerebral palsy

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ABSTRACT

Background

Cerebral palsy is a disorder of movement and posture arising from a non-progressive lesion in the developing brain. Spasticity, a disorder of increased muscle tone, is the most common motor difficulty and is associated with activity limitation to varying degrees in mobility and self care.

Oral baclofen, a gamma-aminobutyric acid (GABA) agonist, has been used in oral form to treat spasticity for some time, but it has a variable effect on spasticity and the dose is limited by the unwanted effect of excessive sedation. Intrathecal baclofen produces higher local concentrations in cerebrospinal fluid at a fraction of the equivalent oral dose and avoids this excessive sedation.

Objectives

To determine whether intrathecal baclofen is an effective treatment for spasticity in children with cerebral palsy.

Search methods

We searched the CENTRAL, MEDLINE, EMBASE and CINAHL databases, handsearched recent conference proceedings, and communicated with researchers in the field and pharmaceutical and drug delivery system companies.

Selection criteria

We included studies which compared the effect of intrathecal baclofen treatment on spasticity, gross motor function or other areas of function with controls.

Data collection and analysis

Two authors selected studies, two authors extracted data and two authors assessed the methodological quality of included studies.

Main results

Six studies met the inclusion criteria. The data obtained were unsuitable for the conduct of a meta-analysis; we have completed a qualitative summary.

All studies were found to have high or unclear risk of bias in some aspects of their methodology.

Five of the six studies reported data collected in the randomised controlled phase of the study. A sixth study did not report sufficient results to determine the effect of intrathecal baclofen versus placebo. Of these five studies, four were conducted using lumbar puncture or other

Intrathecal baclofen for treating spasticity in children with cerebral palsy (Review)

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short-term means of delivering intrathecal baclofen. One study assessed the effectiveness of implantable intrathecal baclofen pumps over six months.

The four short-term studies demonstrated that intrathecal baclofen therapy reduces spasticity in children with cerebral palsy. However, two of these studies utilised inappropriate techniques for statistical analysis of results. The single longer-term study demonstrated minimal reduction in spasticity with the use of intrathecal baclofen therapy.

One of the short-term studies and the longer term study showed improvement in comfort and ease of care. The longer term study found a small improvement in gross motor function and also in some domains of health-related quality of life.

Some caution is required in interpreting the findings of the all the studies in the review due to methodological issues. In particular, there was a high risk of bias in the methodology of the longer term study due to the lack of placebo use in the control group and the absence of blinding to the intervention after randomisation for both participants and investigators.

Authors' conclusions

There is some limited short-term evidence that intrathecal baclofen is an effective therapy for reducing spasticity in children with cerebral palsy. The effect of intrathecal baclofen on long-term spasticity outcomes is less certain.

The validity of the evidence for the effectiveness of intrathecal baclofen in treating spasticity in children with cerebral palsy from the studies in the review is constrained by the small sample sizes of the studies and methodological issues in some studies.

Spasticity is a impairment in the domain of body structure and function. Consideration must also be given to the broader context in determining whether intrathecal baclofen therapy is effective. The aim of therapy may be, for example, to improve gross motor function, to increase participation at a social role level, to improve comfort, to improve the ease of care by others or to improve the overall quality of life of the individual. Intrathecal baclofen may improve gross motor function in children with cerebral palsy, but more reliable evidence is needed to determine this. There is some evidence that intrathecal baclofen improves ease of care and the comfort and quality of life of the individuals receiving it, but again small sample sizes and methodological issues in the studies mean that these results should be interpreted with caution.

Further evidence of the effectiveness of intrathecal baclofen for treating spasticity, increasing gross motor function and improving comfort, ease of care and quality of life is needed from other investigators in order to validate these results.

The short duration of the controlled studies included in this review did not allow for the exploration of questions regarding whether the subsequent need for orthopaedic surgery in children receiving intrathecal baclofen therapy is altered, or the safety and the economic implications of intrathecal baclofen treatment when long-term therapy is administered via an implanted device. Controlled studies are not the most appropriate study design to address these questions, cohort studies may be more appropriate.

PLAIN LANGUAGE SUMMARY

Intrathecal baclofen for treating spasticity in children with cerebral palsy

Spasticity, which is an increase in muscle tone, is the most common difficulty with movement seen in children with cerebral palsy. Baclofen is a medication which acts on receptors in the brain and spinal cord to reduce abnormal muscle tone. It has been used as an oral medication for many years. The disadvantages of oral administration are that only a small amount of the medication crosses the blood-brain barrier before it can exert an effect, and that the dose is limited by the unwanted effect of excessive sedation. The administration of baclofen into the fluid surrounding the spinal cord overcomes these problems. This treatment is called intrathecal baclofen therapy and it is administered via a pump placed under the skin connected to a catheter which enters the membranes covering the spinal cord to deliver the baclofen directly into the fluid surrounding the spinal cord and brain.

This review concludes that there is a small amount of evidence from studies performed to date that intrathecal baclofen is an effective treatment for reducing spasticity in children with cerebral palsy in the short-term. The effect of intrathecal baclofen on spasticity in children with cerebral palsy over the long term is less clear.

Two short-term studies (by the same investigators) demonstrate a reduction in spasticity, but a single, longer term study shows minimal evidence for reduced spasticity with the use of intrathecal baclofen. Two further short-term studies showed reduction in spasticity with the use of intrathecal baclofen, but the authors used inappropriate methods of analysing the data, so it is uncertain whether these results are valid. All these studies had a small number of participants, making the findings less reliable.

The research also provides evidence from one short term study and one longer term study (again, by the same investigators), that intrathecal baclofen therapy improves the comfort, ease of care and some aspects of quality of life for children with cerebral palsy. However, the results of the longer term study may have been influenced by both the participants and the investigators being aware of whether they were receiving treatment or allocated to the control group. This same study found that intrathecal baclofen improves gross motor function a little in children with cerebral palsy, but again, these results may have been influenced by the way the study was conducted.

Further evidence of the effectiveness of intrathecal baclofen for treating spasticity is needed from other investigators in order to validate these results.

There is little evidence from the short-term randomised controlled trials about the safety and economic implications of this treatment when long-term therapy is administered through an implanted device. For the same reasons, we could not reach a conclusion on whether the subsequent need for orthopaedic surgery is altered in children receiving intrathecal baclofen therapy.

BACKGROUND

Cerebral palsy is a term which describes a group of permanent disorders of the development of movement and posture, causing activity limitation. They are attributed to non-progressive disturbances that occurred in the developing foetal or infant brain (Rosenbaum 2007). It has an incidence of approximately two per 1000 live births (Hagberg 1993; Himmelmann 2014; Oskoui 2013; Reid 2011b; Stanley 1984). Approximately 80-90% of individuals with cerebral palsy manifest spasticity as the predominant motor disorder (Hagberg 2001; Reid 2011a).

Spasticity is generally defined as a form of hypertonia (increased muscle tone) where there is velocity-dependent resistance of muscle to passive stretch due to a heightened stretch reflex (Lance 1980, as cited in Dietz 1999; Sheean 2002).

Spasticity is an impairment at the body structure and function level of the International Classification of Functioning, Disability and Health (WHO 2002). It can lead to activity limitation or participation restriction due to impairment of motor function and positioning to varying degrees, particularly in the functional domains of mobility and self-care. The comfort of the child and ease with which others are able to care for the child may also be negatively affected by spasticity. Spasticity also has role in producing the musculoskeletal problems seen in individuals with cerebral palsy, such as muscle/tendon contractures, bony torsions and hip dysplasia.

A range of methods are currently used to treat spasticity, including physiotherapy, casting and splinting, orthopaedic and neurosurgery, botulinum toxin injections and oral medications. Baclofen, a gamma-aminobutyric acid (GABA) agonist, acts selectively on GABA-B receptors in the brain and layers II and III of the dorsal grey matter of the spinal cord (Davidoff 1985) to produce an inhibitory effect on presynaptic transmitter release via the restriction of calcium influx into presynaptic terminals, as well as an effect at postsynaptic terminals to decrease neuronal activity by increasing potassium conductance (Zieglgansberger 1988). The oral form of this drug has been in clinical usage for the past four decades, and has a variable degree of effect in reducing spasticity, but often at the cost of producing untoward side effects such as sedation, related to its relative inability to cross the blood brain barrier and the need for high dose levels to achieve substantial clinical effect (Knuttsen 1974).

The use of intrathecal baclofen was first described in 1984 in the treatment of adults with spasticity from spinal cord injury (Penn 1984). Intrathecal baclofen is delivered via a drug delivery system consisting of a subcutaneously-placed pump containing a drug reservoir, connected to a catheter running posteriorly into the subarachnoid space, to produce much higher local concentrations in the cerebrospinal fluid at a fraction of the equivalent oral dose. Early studies highlighted the ability of intrathecal baclofen to reduce tone and other signs of spasticity in adult recipients (Hugenholtz 1992; Loubser 1991). Over the past 20 years there has been an increasing use of this therapy in children with spasticity. This review summarises the evidence for the effectiveness of intrathecal baclofen in children with spastic cerebral palsy.

OBJECTIVES

1. To determine the effectiveness of intrathecal baclofen in treating spasticity in children with cerebral palsy

2. To determine whether intrathecal baclofen reduces the need for subsequent orthopaedic surgery in children with spasticity.
3. To determine the safety of intrathecal baclofen therapy.
4. To consider the economic implications of the therapy.

METHODS

Criteria for considering studies for this review

Types of studies

This review focused on studies with the highest level of evidence (i.e. randomised controlled trials), but we also considered non-randomised controlled trials.

Types of participants

Eligible studies included children aged 0 to 18 years diagnosed with spastic-type cerebral palsy who had been treated with intrathecal baclofen. We considered studies where at least 90% of the population studied consisted of participants with this type of motor involvement and from this age group.

Types of interventions

Intrathecally-administered baclofen, delivered either by continuous infusion or intermittent bolus, via an implanted or externally-sited device.

Types of outcome measures

The primary outcome measures sought were measures of spasticity and gross motor function. The Ashworth scale and the modified Ashworth scale categorise the degree of increase in muscle tone during examination of the affected limb on a five-point scale. They are commonly-used measures of spasticity (Ashworth 1964; Bohannon 1987). Measures of gross motor function include, for example, the Gross Motor Function Measure (GMFM) (Russell 1989), a validated assessment tool administered by a physiotherapist.

We considered other measures of function, including the Pediatric Evaluation of Disability Inventory (PEDI), which measures functional capability and level of independence in the areas of self-care, mobility and social function (Haley 1992).

We also sought studies where other outcome measures were used, including measures of ease of care, comfort and quality of life.

We also collected data regarding the subsequent need for orthopaedic surgery, safety and the economic implications of this therapy where these outcomes were reported.

Search methods for identification of studies

See: [Cochrane Movement Disorders Group](#) methods used in reviews.

We identified studies for inclusion in the review using the following sources:

1. the Cochrane Central Register of Controlled Trials (CENTRAL);
2. MEDLINE;
3. EMBASE;
4. CINAHL;

5. the Cochrane Movement Disorders Review Group Specialised Trials Register;
6. handsearches of recent conference proceedings;
7. contact with principal researchers in the field; and
8. contact with pharmaceutical and drug delivery system companies.

The terms used to search MEDLINE (1948 to week 38 2013), EMBASE 1980 to Week 38 2013 and CINAHL 1982 to Week 38 2013 are listed in [Table 1](#), [Table 2](#) and [Table 3](#).

We placed no limitations on language of publication for this search. We searched the Cochrane Central Register of Controlled Trials using the same subject terms as above. The Cochrane Movement Disorders Review Group Specialised Trials Register was not available at the time of this review.

Conference proceedings handsearched included the American Academy for Cerebral Palsy and Developmental Medicine Annual Meeting Abstracts 1997-2013 and the European Academy Childhood Disability Annual Meeting Abstracts 1998-2013.

We contacted the authors of included studies and pharmaceutical and drug delivery system manufacturers by email, letter or both regarding whether they were aware of any studies, published or unpublished, which may be potentially eligible for inclusion in the review.

Data collection and analysis

Selection of studies

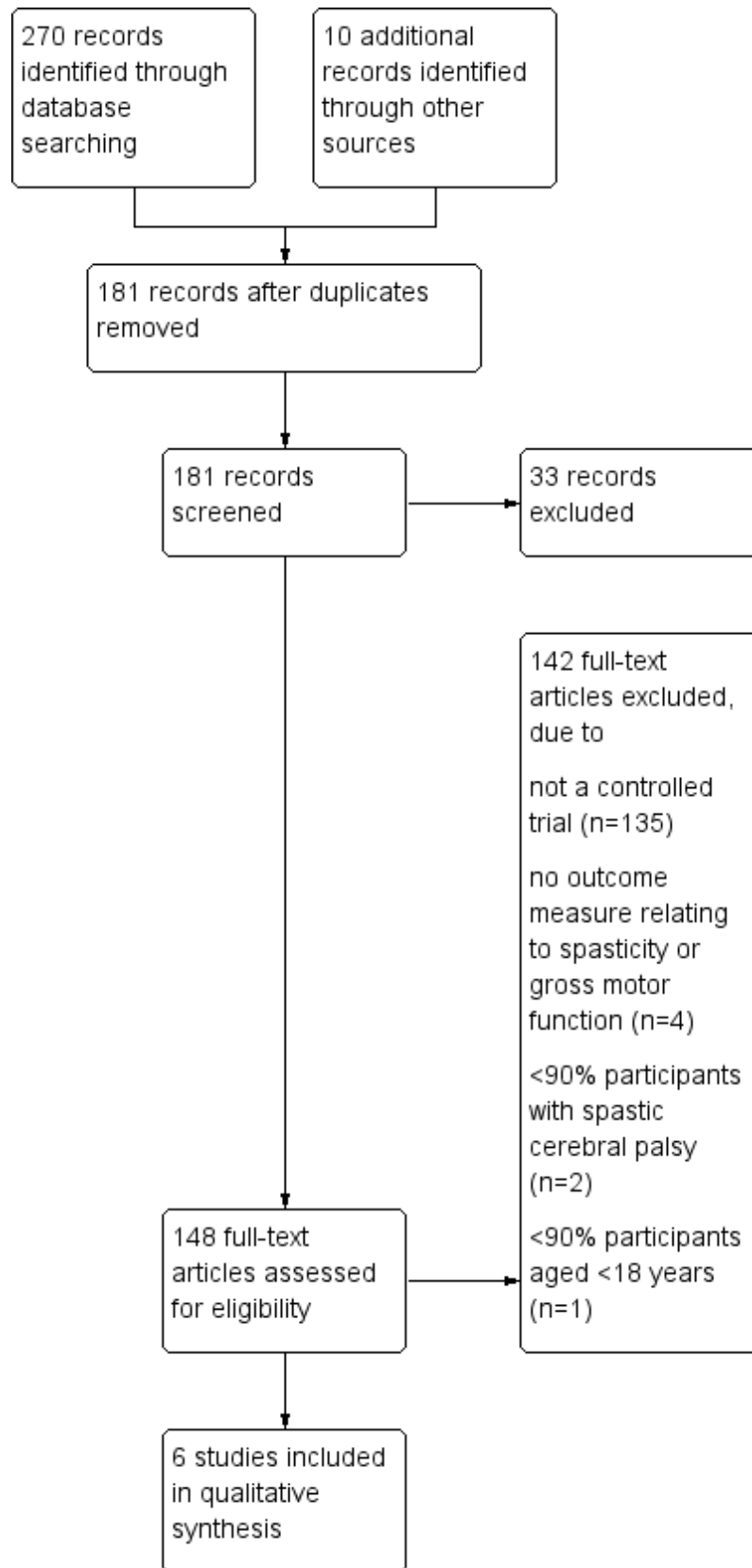
Two authors conducted an initial review of titles and abstracts of potentially eligible studies identified by the searches. Only those articles where there was sufficient information contained in the title and abstract to clearly determine that the study did not meet the selection criteria for the review were excluded at this stage.

Two authors then independently assessed the remaining trials in detail. We included studies if they were described as a randomised controlled trial or non-randomised controlled trial (i.e. another group received the same care but without intrathecal baclofen), at least 90% of the participants were diagnosed with spastic-type cerebral palsy, 90% of the participants were aged 0 to 18 years, the participants received intrathecal baclofen either by continuous infusion or intermittent bolus (either via an implanted or an externally-sited device) and if participants were assessed using at least one measure of spasticity (e.g. Ashworth scale) or gross motor function (e.g. GMFM). We also considered studies using other outcome measures for inclusion in the review.

We resolved disagreements by conducting a joint review of the relevant studies.

[Figure 1](#) summarises the process of selecting studies for inclusion in this review.

Figure 1. Study flow diagram.



Data extraction and management

Two authors extracted data from the published reports separately using a data collection form, resolving disagreements by joint review. We sought additional information, where required, through correspondence with the authors of the included studies.

Assessment of reporting biases

We assessed the included studies for methodological quality using the Cochrane Collaboration's tool for assessing bias, as described in Chapter 8 (section 8.5) of the *Cochrane Handbook for Systematic Reviews of Interventions*. We summarised the criteria for determining the risk of bias into an assessment form which contained the following domains:

- selection bias: including sequence generation and allocation concealment;
- performance bias: blinding of participants to assigned intervention;
- detection bias: blinding of those assessing outcome to allocation;
- attrition bias: incomplete outcome data
- reporting bias: selective outcome reporting
- other bias: potential for carry-over effect in cross over study design

Two authors independently reviewed studies for methodological quality using these criteria. We both allocated a score for study quality in each of the domains above, rating the risk of bias as either low, medium or high. Disagreements were resolved by conducting a joint assessment.

Exploration of publication bias through assessment of funnel plot asymmetry was not possible due to unsuitability of the data obtained from the included studies.

Data synthesis (meta-analysis)

Meta-analysis was not performed, as data obtained from the included studies were unsuitable for inclusion in a meta-analysis. This was for a number of reasons, including differing study designs, different outcome measures used and invalid statistical methods used in some included studies.

The studies were reasonably homogenous from a clinical and methodological viewpoint for the five studies utilising bolus administration of intrathecal baclofen. It is not possible to comment on statistical heterogeneity due to incomparable outcome data.

RESULTS

Description of studies

Design of studies

Six published papers referring to randomised controlled trials were found to meet the inclusion criteria for the review.

The five earlier studies ([Albright 1991](#), [Armstrong 1997](#), [Gilmartin 2000](#), [Hoving 2006](#), [Hoving 2007](#)) were trials with a cross over design, utilising the same repeated outcome measures with escalating doses of intrathecal baclofen versus placebo, given via lumbar puncture or spinal catheter, in a paired manner in random

order over a number of days. The [Hoving 2009a](#) study was a randomised trial of intrathecal baclofen therapy delivered via an implanted pump over 6 months versus a control group who did not receive an intrathecal baclofen pump.

The randomised controlled trial was only one component of the protocol in two studies ([Armstrong 1997](#); [Gilmartin 2000](#)). In both these studies the double-blind, randomised controlled trial was the first phase of the study. The code was broken at the end of this trial and the results used to determine which participants should receive implantable intrathecal baclofen pumps. The second phase of these studies involved an open-label, long-term intrathecal infusion of baclofen with no control group. The second phase of these studies is not considered in this review.

The references [Hoving 2006](#) and [Hoving 2007](#) refer to two studies performed on the same group of participants after the same intervention, using different outcome measures. It is the same group of participants which was then randomised to receive either an intrathecal baclofen pump immediately or remain as a control group for the subsequent study reported in [Hoving 2009a](#), where continuous intrathecal baclofen therapy via implanted pump was evaluated against a control group who did not receive this therapy.

The key features of these studies are described in the [Characteristics of included studies](#) table.

Participants

The characteristics of the participants in the included studies are described in the table [Characteristics of included studies](#) and [Table 4](#) ('Participant characteristics in included studies').

The participants in the included studies had spastic-type cerebral palsy, with a total of 76 children with quadriplegic distribution, 15 with diplegia and four described as paraplegic in distribution. The age range of the participants in the included studies ranged from 4 to 27 years. The method of classification of the severity of cerebral palsy varied between studies and included modes of classification based on degree of spasticity and gross motor function. [Albright 1991](#) reports that participants in that study had moderate severity cerebral palsy, defined as those "whose gait and other movements might improve if their spasticity was alleviated and their muscles strengthened by physical therapy." [Armstrong 1997](#) reports participants in that study had severe cerebral palsy defined as "interfering with daily care or function." [Gilmartin 2000](#) included children with severe cerebral palsy defined as "an average Ashworth scale score of three or more in the four lower extremity measurements." The Gross Motor Function Classification System (GMFCS), developed in 1997 ([Palisano 1997](#)) (subsequent to the publication of the two earlier studies, [Albright 1991](#) and [Armstrong 1997](#)), was used by [Hoving 2006](#) and [Hoving 2007](#) to classify the severity of cerebral palsy of participants, with the majority of participants in that study classified as GMFCS V (14 out of 17 participants), the most severe functional limitation category, where children have no means of independent mobility. One participant was classified as GMFCS III and two participants as GMFCS IV. 14 of 17 participants had quadriplegic distribution of spasticity and three had diplegic distribution. [Hoving 2009a](#) reports on the same group of 17 children enrolled in the earlier studies by the same author.

[Albright 1991](#) undertook the randomised controlled trial in two groups of participants. Group one were 17 children with spastic

cerebral palsy and group two were six participants with spasticity due to various disorders. The results obtained in these two groups were reported separately in the publication. Only data pertaining to group one are included in this review. In the [Armstrong 1997](#) study a total 19 participants were included, 10 with spastic cerebral palsy. The author was contacted to provide results for this group from the RCT phase, as this information was not available in the published report. This information was not available at the time of publication of this review.

Interventions

Five included studies involved paired baclofen and placebo bolus intrathecal injection in the same individuals. Escalating doses of baclofen were given versus placebo in four studies ([Albright 1991](#), [Armstrong 1997](#), [Hoving 2006](#), [Hoving 2007](#)). The dose range used was 10 to 100 µg. [Gilmartin 2000](#) trialled 50 µg intrathecal injections of baclofen against placebo in a double-blind fashion. The study blind was broken after the completion of this step. If no positive response had occurred, subsequent higher doses of baclofen (75 µg, 100 µg) were given as open-label injections.

The mode of intrathecal baclofen delivery was via lumbar puncture or temporary devices (percutaneous spinal catheter or implanted port with spinal catheter) in all five of these studies. The only exception to this is in [Armstrong 1997](#), where five children underwent a modified protocol to reduce the risk of infection by avoiding repeated injections through the access port. In these children infusion pumps were inserted and the double-blind trial was performed on an outpatient basis.

The duration of the shorter-term studies ([Albright 1991](#), [Armstrong 1997](#), [Gilmartin 2000](#), [Hoving 2006](#), [Hoving 2007](#)) ranged from 24 hours to eight days, however in the [Armstrong 1997](#) study the duration of the double-blind randomised controlled phase of the study is not clear from the published report. The children who underwent the regular protocol in this study had bolus injections on a daily basis, with a drug and placebo interval of four days and a washout period of at least two days. The five children who underwent the modified protocol in this study had a drug and placebo interval of 10 to 14 days with a washout period of four days, but the number of baclofen or placebo dosages trialled is not stated.

One study ([Hoving 2009a](#)) evaluated continuous intrathecal baclofen therapy via implanted pump (Synchromed, Medtronic Inc, Minneapolis) in comparison to a control group with no implanted pump. Standard treatment, including any physiotherapy, occupational therapy and speech therapy was continued in both groups. This study followed on from the previous studies ([Hoving 2006](#), [Hoving 2007](#)) by the same author. The participants were administered intrathecal baclofen and placebo injections via lumbar puncture in the earlier studies. Given that all participants had a positive response, they were then randomised to receive an implanted programmable infusion pump after either one month (intervention group) or six months (control group). There was no placebo used in the control group and, after randomisation, treatment was open-label with no blinding of participants or investigators. Participants were evaluated after six months treatment. In the intervention group, the mean daily dose of intrathecal baclofen was 67 µg immediately after pump implantation and 176 µg six months later.

Oral baclofen was used in three studies in some participants. There was no comment regarding its use in [Armstrong 1997](#) (see [Table 5](#) 'Use of oral baclofen').

Outcomes

Ashworth scale scores were used as a primary outcome measure for the majority of studies ([Albright 1991](#); [Armstrong 1997](#); [Gilmartin 2000](#); [Hoving 2007](#)) and a further study ([Hoving 2009a](#)) used the Ashworth scale score as a secondary outcome measure. [Hoving 2006](#) employed electrophysiological measures of spasticity the primary outcome measure. [Hoving 2009a](#) utilised the following primary outcome measures: Gross Motor Function Measure, 66 item (GMFM-66 - a measure of gross motor function, [Russell 1989](#)), the Pediatric Evaluation of Disability Inventory (PEDI - a measure of functional skills and need for caregiver assistance in daily life, [Haley 1992](#)) and the The Child Health Questionnaire Parent Form 50 (CHQ-PF50 - a quality of life measure, [Landgraf 1996](#)). [Hoving 2007](#) and [Hoving 2009a](#) also utilised the Visual Analogue Scale (VAS) as a primary outcome measure for individually formulated problems.

Spasticity

Clinical measures of spasticity

[Albright 1991](#) and [Gilmartin 2000](#) compared mean Ashworth scale scores pre and post intrathecal baclofen and placebo, calculated from examining a number of upper and lower limb muscle groups. [Hoving 2007](#) compared Ashworth scale scores pre and post intrathecal baclofen and placebo for individual muscle groups pre and post intrathecal baclofen and placebo administration. [Armstrong 1997](#) has not reported the results of the randomised controlled trial of baclofen versus placebo performed prior to implantation of intrathecal baclofen pumps in the publication and these data have not been available from the author to date. [Hoving 2009a](#) included Ashworth scale scores for individual muscle groups as one of the secondary outcome measures.

[Albright 1991](#) and [Gilmartin 2000](#) compared mean Ashworth scores at baseline and after treatment with intrathecal baclofen and placebo. However, the Ashworth scale is an ordinal scale. It is not appropriate to produce mean Ashworth scores, as it is not a continuous variable and, as such, values which fall between the defined scoring numbers have no meaning, as the difference between the consecutive score values on the scale are not necessarily proportionate. For example, the distance between one and two on the Ashworth scale is not necessarily equivalent to the distance between two and three. Therefore, it is not appropriate to combine the outcome measures from the included studies into a summary statistic. Results of the individual studies are thus reported below without the mean Ashworth scale scores and without their associated statistical results.

Electrophysiological measures of spasticity

[Hoving 2006](#) used electrophysiological measures of spasticity, the H-reflex and the flexor reflex, as outcome measures. The H-reflex can be used as a tool to measure the excitability of neural components of the stretch reflex arc. The ratio of the maximal H amplitude to maximal M amplitude (H/M ratio) is considered an index of spasticity ([Hoving 2006](#)). The flexor reflex is a polysynaptic and multisegmental spinal response which is influenced by spinal and supraspinal inputs. Lower limb flexor reflex excitability has been shown to be influenced by spasticity ([Sandrini 2005](#)).

Gross Motor Function

The GMFM-66 (Russell 1989) was used as a secondary outcome measure in the Hoving 2009a study. The GMFM is an activity-level measure, consisting of a standardised assessment of gross motor function in children with cerebral palsy, with items grouped into five dimensions; lying and rolling, sitting, crawling and kneeling, standing and walking.

Other Measures of Function

Subscales of the PEDI (Haley 1992) were used as outcome measures in Hoving 2009a. Specifically, the PEDI caregiver assistance scale of the self-care domain was used as a primary outcome measure and the PEDI functional skills scale as a secondary outcome measure. The PEDI is an assessment of key functional capabilities and performance in children which is norm-referenced from age six months to 7.5 years. It measures what children actually do in the daily life and, as such, is an ICF activity-domain measure (Hayley 2010). The PEDI consists of two sections; functional skills and caregiver assistance. The functional skills section assesses the child's current repertoire of daily life skills in each of 3 domains (self-care, mobility and social function), whereas the Caregiver Assistance section assesses the extent to which the child's overall performance of complex daily tasks such as dressing or moving around is supported by help from a caregiver (Hayley 2010).

Ease of Care, Comfort and Quality of Life

The Child Health Questionnaire, Parent Form 50 (CHQ-PF50) was another primary outcome measure employed in Hoving 2009a. The Child Health Questionnaire is a multidimensional quality of life instrument that focuses upon two components: physical and psychosocial functioning and well-being. It is designed and normed for children 5 to 18 years of age (Landgraf 1996).

The Visual Analogue Scale (VAS) was used as an outcome measure in Hoving 2007 and Hoving 2009a for individually formulated problems. The VAS is a widely used tool which allows the quantification of subjective experiences, such as pain. Popularised by Aitken (Aitken 1969) for the measurement of subjective physical symptoms (dyspnoea and fatigue), it has been found to be a valid and reliable measurement tool for pain in adults and children over six years of age (Tyler 1993), as well as variables such as satisfaction (Singer 1998) and quality of life (de Boer 2004; Jaeschke 1990; Parkin 2004;).

Need for Subsequent Orthopaedic Surgery

None of the included studies in this review reported outcomes relating to the subsequent need for orthopaedic surgery with intrathecal baclofen therapy.

Safety

All studies in the review recorded information about safety or adverse effects following administration of intrathecal baclofen or placebo, but in two cases (Hoving 2006 and Hoving 2009a) these were not included in the same publication.

Albright 1991 states that changes in medical or neurological condition and in vital signs was recorded hourly for eight hours.

Armstrong 1997 describes that participants vital signs were monitored during the trial.

Gilmartin 2000 describes that participants were monitored on an apnoea monitor or pulse oximeter and their vital signs recorded at the same interval as the Ashworth scale score.

Hoving 2006 does not include information regarding adverse effects, this is included in the Hoving 2007 publication, where it is stated that "side effects and complications were recorded on standardised forms," which were completed twice every test day (p655-6).

The Hoving 2009a report did not include information regarding the safety of the treatment and refers to a concurrent publication which contains this data (Hoving 2009b). However, the Hoving 2009b publication contains data regarding safety and complications for a mean duration of 18 months, a period beyond that of the initial randomised controlled trial. Adverse events were "recorded on standardised forms" and were defined as "any undesirable experience occurring to a participant during the study, whether or not considered to be related to continuous intrathecal baclofen therapy" (Hoving 2009b). "Serious adverse events" were defined as those that resulted in death, were life-threatening, resulted in hospitalisation, resulted in persistent or significant disability or incapacity (p248-9).

Economic Implications

None of the studies included studies in this review reported outcomes relating to the economic implications of intrathecal baclofen therapy.

Risk of bias in included studies

The Albright 1991, Armstrong 1997, Gilmartin 2000, Hoving 2006 and Hoving 2007 studies were all assessed as having unclear risk of bias in at least two of the domains evaluated.

Hoving 2009a was assessed as having high risk of performance and detection bias due to lack of blinding of participants and those assessing outcome to treatment allocation.

Results of the assessment of potential bias in the included studies are summarised in the Risk of bias in included studies table below.

Effects of interventions

It was not possible or appropriate to pool data from the included studies for a number of reasons.

Firstly, it is not appropriate to combine results where study methodology differs significantly. Hoving 2009a studied continuous ITB using implanted pumps and it would not be valid to compare this with the other included studies which utilised short duration bolus doses of intrathecal baclofen via lumbar puncture or spinal catheter.

For the remaining five studies where ITB boluses were administered via lumbar puncture or lumbar catheter, the Ashworth scale, was used as an outcome measure in four, with one study (Hoving 2006) using electrophysiological measures of spasticity. One of these four studies (Armstrong 1997) did not report results for the randomised controlled phase of the study and two studies (Albright 1991; Gilmartin 2000) utilised inappropriate statistical methods for handling the Ashworth scale data.

The Ashworth scale is an ordinal rather than a continuous scale and therefore it is not statistically valid to calculate mean values. Two of the six included studies utilised mean Ashworth scores (Albright 1991; Gilmartin 2000) as the outcome measure. The raw data were not available from the authors to permit another type of meta-analysis to be performed. A qualitative summary has been completed.

Spasticity

Clinical measures of spasticity

The reported results of all studies in this review suggest intrathecal baclofen is effective for reducing spasticity in children with cerebral palsy.

Albright 1991 reports that following intrathecal baclofen administration, "muscle tone in the lower extremities was significantly reduced but tone in upper extremities was not." There was no significant difference between the three doses (25 µg, 50 µg and 100 µg) in Ashworth score four hours after intrathecal baclofen bolus administration. Albright represented graphically the outcome of placebo and intrathecal baclofen injections. However, the placebo data are not published in the report. The report comments "there were significant differences ($p < 0.05$) in tone in the lower extremities between the placebo values and each of the baclofen dose values."

Armstrong 1997 did not report results of the randomised controlled phase of the study, but reports that following this phase, the code was broken and six out of 10 participants with cerebral palsy subsequently went on to intrathecal baclofen pump implantation.

Gilmartin 2000 reports statistically significant differences in mean Ashworth score in the lower limbs between treatment and control groups at four hours following injection of 50 µg baclofen or placebo. Statistically significant alteration of mean Ashworth score from baseline was observed at each time point (two, four, six and eight hours). A small (less than one point) but statistically significant alteration in Ashworth score was also observed in the upper limbs at each time point.

Hoving 2007 reports that "all children showed a positive clinical effect in response to intrathecal baclofen at some day during the test treatment and subsequently received a pump for continuous delivery of intrathecal baclofen." The effective intrathecal baclofen dose was defined as the dose at which a "satisfying improvement" in the individual treatment goals was achieved and a reduction of at least one point in the Ashworth score compared with baseline on that day in at least three of six selected muscle groups. The effective dose was found to be 12.5 µg in one child, 20 µg in another, 25 µg in 10 children and 50 µg in five children. Ashworth scores assessed at two, four and six hours after the effective intrathecal baclofen dose significantly decreased in comparison with baseline for all muscle groups except for the left hip flexors two hours after intrathecal baclofen administration.

Hoving 2009a determined a statistically significant reduction in spasticity in four of the 22 muscle groups assessed in the treatment group compared to the control group at six months from baseline.

Electrophysiological measures of spasticity

Hoving 2006 reported reduced motorneurone excitability in response to the intrathecal baclofen boluses. A statistically

significant difference was seen in response to injections of intrathecal baclofen compared to placebo in H-max and H/M ratio. No statistically significant difference was seen following intrathecal baclofen bolus versus placebo for the flexor reflex threshold values. Statistically significant differences were seen, however, in the flexor reflex area in those children who were not also taking oral baclofen at the time of the study.

Gross Motor Function

GMFM-66 showed a positive difference in favour of the treatment group (improvement of mean 1.2 points (SD 2.3) versus worsening of mean -1.3 points (SD 3.0) in the control group, $p = 0.028$) in the Hoving 2009a study after six months of treatment.

No statistically significant improvement at six months was seen in the Hoving 2009a study in the GMFM lying and rolling dimension, GMFM sitting dimension or GMFM goal dimensions.

Other Measures of Function

Hoving 2009a found no improvement in the PEDI functional skills scale or caregiver assistance scale in the treatment versus control group after six months ITB treatment.

Ease of Care, Comfort and Quality of Life

Two studies in the review found that intrathecal baclofen may be an effective treatment for improving comfort, ease of care and quality of life in children with cerebral palsy.

Hoving 2007 assessed Visual analogue scale (VAS) scores for individually formulated goals were assessed pre and post placebo and intrathecal baclofen injections. The VAS was completed by caregivers for 15 out of 17 participants due to inability of the participant to either understand the task or to draw a vertical line. Ease of care and pain were the two most common goals nominated, and these showed statistically significant improvement with intrathecal baclofen administration and not with placebo administration.

Hoving 2009a found statistically significant ($p = 0.001$) changes in VAS scores at six months from baseline in the treatment group (mean increase 4.0, SD 1.7) compared with the control group (mean -0.2 SD 1.3). The VAS scores were reported for individually formulated problems, with an average of three VAS scores per participant. In participants who nominated ease of care as a VAS goal ($n = 9$ treatment group, $n = 7$ control group), scores improved by a mean of 3.9 points (SD 2.2) in the treatment group and by a mean of 0.1 (SD 1.6) in the control group ($p = 0.008$). In those who nominated pain as a goal area on the VAS ($n = 6$ treatment group, $n = 6$ control group), scores improved by a mean of 4.2 (SD 2.9) in the treatment group and worsened by in the control group with a mean of -1.3 (SD 2.4) points ($p = 0.016$).

Hoving 2009a reported statistically significant improvement in the CHQ-PF50 psychosocial summary score (3.4 points, SD 7.9) versus control group (-5.7 points, SD 8.8, $p = 0.027$) at 6 months compared to baseline. Significant differences were also seen in the following sub-domains: bodily pain/discomfort, with an improvement of mean 24.4 points (SD 20.7) in the treatment group versus worsening of -10.6 points (SD 26.8) in the control group ($p = 0.014$); mental health, with an improvement of mean 9.1 points (SD 9.1) in the treatment group versus worsening in the control group of -3.5 points (SD 15.1) ($p = 0.045$); parental impact-time, with

improvement of 5.2 points (SD 18.1) in treatment group versus worsening in the control group of -19.8 points (SD 15.1) ($p=0.045$).

Safety

Sedation or lethargy is the commonest adverse effect noted in all included studies which reported on this outcome (Albright 1991, Armstrong 1997, Gilmartin 2000, Hoving 2007).

Complications reported in these studies (in the randomised controlled phase of the study, where relevant) are summarised in Table 6.

As previously discussed, Hoving 2009a does not report on adverse effects and refers to a concurrent publication, Hoving 2009b, which includes this data. The follow-up periods between the studies differ, however (mean six months in Hoving 2009a, and mean 18 months in Hoving 2009b) and adverse effects for the control group are not reported. For these reasons, the findings reported in the Hoving 2009b paper are not included in the table of results and are instead considered in the discussion below.

DISCUSSION

Main findings of the review

The randomised controlled trials in this review provide a little evidence that intrathecal baclofen is effective for reducing spasticity in children with cerebral palsy in the short-term. The effect of intrathecal baclofen on spasticity in children with cerebral palsy in the longer term is less clear.

The evidence for the effectiveness of intrathecal baclofen for treating spasticity in children with cerebral palsy is limited by small sample sizes and methodological issues, including high or unclear risk of bias, in the studies in this review.

Spasticity is an impairment at the body structure and function level. The aim of reducing spasticity by the use of intrathecal baclofen therapy is often to prevent or reduce the limitation at the activity and participation level or to address quality of life goals. For example, the ultimate goal may be to improve mobility and/or self-care or to increase participation at a social role level. The aim of reducing spasticity may also be directed at non-functional goals, such as to improve comfort, to increase the ease of care by others and to improve the overall quality of life of the individual.

Two studies demonstrate evidence that intrathecal baclofen reduces pain and improves ease of care (Hoving 2007, Hoving 2009a).

There is a small amount of evidence from one study (Hoving 2009a) that gross motor function and certain domains of health-related quality of life is improved with the use of intrathecal baclofen. Cautious interpretation of this result is required due to the small sample size and high risk of bias in the methodology in this study.

Many of the secondary questions of this review could not be addressed, as the short duration and temporary modes of intrathecal baclofen delivery utilised in the controlled trials included did not allow for the exploration of questions such as alteration in the subsequent need for orthopaedic surgery in children receiving intrathecal baclofen therapy, the rate of complications and the economic implications of this treatment when long-term therapy is administered via an implanted device.

Evidence relating to these questions is unlikely to be derived from randomised controlled trials due to the limited duration of this type of study. Data collection over a period of some years is required to assess these outcomes. Given this, a discussion of the evidence available from published studies regarding these outcomes is included below.

Outcome measures used to assess intrathecal baclofen therapy in children with cerebral palsy

Spasticity

The Ashworth scale (Ashworth 1964) and the modified Ashworth scale (Bohannon 1987) are commonly employed and accepted measures of spasticity in clinical practice and clinical research. The original Ashworth scale was the outcome measure used for all studies included in this review. The advantages of the Ashworth scales are that they can be performed rapidly (Scholtzes 2006) and are therefore useful when serial assessments over several hours are performed, as in the studies included in this review. The disadvantages of utilising the Ashworth scale as a measure of spasticity relate to questions about its validity and reliability.

Spasticity is generally defined as a form of hypertonia where there is velocity-dependent resistance of muscle to passive stretch due to a heightened stretch reflex (Lance 1980, as cited in Dietz 1999; Sheean 2002). The validity and reliability of the Ashworth score as a measure of spasticity has been questioned. The Ashworth scale was originally developed to measure the efficacy of an anti-spasticity drug in adults with multiple sclerosis (Ashworth 1964). This scale was modified to the form now commonly used in clinical practice by the addition of a further category, 1+, with the aim of increasing its sensitivity (Bohannon 1987). The Ashworth scale and the modified Ashworth scale describe the resistance perceived by the examiner when moving a joint through its range of movement (except for category four, where the limb is rigid) at a single, unspecified speed. It is therefore poorly able to assess any velocity-dependent alteration in muscle resistance to passive movement. Thus, the Ashworth and modified Ashworth scale are measures of passive resistance to movement, rather than of spasticity (Damiano 2002; Pandyan 1999). The contribution of spasticity versus other causes of increased muscle activity and tone (voluntary and reflex) and altered muscle, tendon and joint viscoelastic properties, to the passive resistance to movement cannot be differentiated from spasticity by the use of the Ashworth scales (Damiano 2002; Pandyan 1999).

The relevance of this theoretical limitation to the use of the Ashworth scale as a measure of spasticity for assessing the effectiveness of intrathecal baclofen therapy is not of great significance in practice, however. In the absence of other interventions that alter musculoskeletal viscoelastic properties, this component is likely to stay constant over the short term. Other causes of hypertonia, such as dystonia, may confound Ashworth scores in the context of assessing intrathecal baclofen therapy. In a clinical context, however, differentiating the relative contribution of spasticity and dystonia to the Ashworth score in a child with cerebral palsy is of uncertain importance as intrathecal baclofen addresses both these causes of hypertonicity. Intrathecal baclofen may be an effective treatment for the secondary dystonia seen in cerebral palsy, although high level evidence is not yet available (Albright 1998; Albright 2001; Dachy 2004; Motta 2004a; Woon 2007).

Studies investigating the reliability of the Ashworth scale have also shown mixed results. The interrater and intrarater (test-retest) reliability of the modified forms of the scale have been variable and frequently poor in studies performed in children with cerebral palsy (Clopton 2005; Fosang 2003; Yam 2006). There are few data available regarding the reliability of the original form of the scale in children with cerebral palsy, but in studies in other patient groups, the interrater reliability of the original form of the Ashworth scale (as used by all studies in this review) is somewhat better than the modified scale (Brashear 2002; Haas 1996). Protocols which use a single rater, as did the Gilmartin 2000, Hoving 2006, Hoving 2007 and Hoving 2009a studies, for assessing Ashworth scores remove the issue of interrater reliability.

The Tardieu scale, as originally described by Held in 1969 (Scholtes 2006), and the modified Tardieu scale (Boyd 1999) may be a more valid and reliable measure of spasticity in children with cerebral palsy. The original Tardieu scale assesses passive movement of the joints at three specified velocities, noting the duration of muscle reaction to stretch and the joint angle at which the muscle reaction is first felt. It is therefore very time-consuming (Scholtes 2006). The modified Tardieu scale defines only the joint angle at which muscle resistance is first encountered ('the catch') during rapid velocity movement (as fast as possible, faster than the natural drop of the limb segment under gravity (Boyd 1999). This examination is accompanied by measurement of joint range of motion using a slow speed of movement (Boyd 1999), thereby identifying the velocity-dependant component of resistance to passive movement. The construct validity of the Tardieu scales as a measure of spasticity is greater than that of the Ashworth scales and this has been supported by experimental studies of its validity (Boyd 1999; Patrick 2006). The reported interrater reliability of the modified Tardieu scale, however, has been found to be somewhat variable in studies involving children with cerebral palsy (Fosang 2003; Mackey 2004; Yam 2006).

A number of instrumented biomechanical and electrophysiological measures of spasticity have also been developed. These include the H-reflex and flexor reflex, as used by Hoving (Hoving 2006), instrumented torque and EMG measurements during passive motion at preset velocities, ramp and hold tests, pendulum tests and others (Damiano 2002). A complete review of these measures will not be discussed as part of this systematic review. None of these are in common use in the clinical setting.

As discussed previously, the issue of whether measures of spasticity are the most relevant outcome measure for assessing the efficacy of intrathecal baclofen therapy needs to be considered. The question of whether reduction of spasticity maximises function at the activity and participation levels, or improves the quality of life of the individual, must be addressed. For this reason, the use of outcome measures which evaluate function at the activity and participation level and those which address comfort and quality of life of the individual and ease of care by others are required to assess the effectiveness of intrathecal baclofen in addition to measures of spasticity.

Gross Motor Function and Other Measures of Function

Changes in the ICF dimensions of activity and participation with the use of intrathecal baclofen therapy were examined by one of the randomised controlled trials included in this review, Hoving 2009a. The GMFM-66 is a well-validated and is widely used as a measure

of gross motor function in clinical settings and in research (Wang 2006). The PEDI is similarly well-validated activity-level measure in wide use across clinical and research settings (Hayley 2010).

Ease of Care, Comfort and Quality of Life

Care and comfort outcome measures were used by two studies in this review (Hoving 2007, Hoving 2009a). It may be argued that these measures are of the greatest importance in assessing the effect of intrathecal baclofen in individuals with severe cerebral palsy (GMFCS IV and V). The visual analogue scale (VAS) for individually formulated problems was the outcome measure used in both these studies, with a majority of participants nominating pain and ease of care as problem areas.

Health-related quality of life is a construct which encompasses the impact of health status, including disease and treatment, on physical, psychological and social functioning (de Lissovoy 2007). The Child Health Questionnaire is a generic (rather than disease-specific) measure of health-related quality of life. The advantage of generic measures is that they are appropriate for use in all children and normative values have been generated which provide a baseline with which to make comparisons of children with disabilities, such as cerebral palsy (McCullough 2008). Evaluation of the CHQ in studies to date has demonstrated acceptable validity and reliability (Davis 2010; McCullough 2008). However, when assessing the effect of an intervention in children with cerebral palsy, a cerebral palsy-specific measure may have been a more appropriate tool (Davis 2010; McCullough 2008).

Effectiveness of intrathecal baclofen in treating children with cerebral palsy

Spasticity

The majority of the studies included in this systematic review indicate that intrathecal baclofen may be effective in reducing spasticity in children with cerebral palsy, but the evidence is limited by the small sample sizes used and inappropriate statistical methods used in two of the studies.

Six studies met the inclusion criteria for this review, five of which used spasticity as a primary outcome measure and a sixth used spasticity as a secondary outcome measure (Hoving 2009a). One of these studies had not reported the results of the randomised controlled phase of the study (Armstrong 1997) and therefore did not contribute any data to this review. The incorrect statistical handling of Ashworth scores by a further two studies (Albright 1991, Gilmartin 2000), introduces difficulty in determining the validity of the results of these studies.

Of the other studies included in the review, two were short-term (Hoving 2006, Hoving 2007) and one was conducted over 6 months (Hoving 2009a). The short term studies demonstrated reduction of spasticity with the use of intrathecal baclofen therapy. Hoving 2009a reported that reduction in spasticity with continuous intrathecal baclofen therapy was demonstrated in only a minority of muscle groups at 6 months compared to baseline.

In summary, therefore, reduction in spasticity was seen in four short-term randomised controlled trials with adequate methodology and of small size, but two of these studies have utilised questionable statistical analysis. A fifth randomised controlled study, which examined the use of intrathecal baclofen

via implanted pump over six months demonstrated minimal reduction of spasticity.

The magnitude of the treatment effect of intrathecal baclofen on spasticity cannot be determined by this review due to the inability to calculate a summary statistic from the outcome measures used in the studies. The Ashworth scale is an ordinal measure and therefore it is not statistically valid to average or summate scores. It was also not possible to discuss statistical heterogeneity in this instance.

In future, meta-analysis of Ashworth scale data may be possible if outcome data from future controlled studies can be dichotomised into two groups (following treatment with either intrathecal baclofen or placebo), as: 1. No improvement in Ashworth score 2. Improvement in Ashworth score by one or more points.

Gross Motor Function

[Hoving 2009a](#) utilised the GMFM to investigate the effect of intrathecal baclofen therapy on mobility and self-care. A positive impact was seen on gross motor function with the use of intrathecal baclofen reported in [Hoving 2009a](#). The treatment group demonstrated a small, statistically significant improvement in the 66 item GMFM score, with a mean improvement of 1.2 points (SD 2.3) in the treatment group and a mean worsening of -1.3 points (SD 2.4) in the control group. No statistically significant difference was seen in the individual dimensions of the 88 Item GMFM (lying and rolling; sitting; crawling and kneeling; standing; walking, running and jumping) between the treatment and control groups. Although the change seen in GMFM-66 is small, it is probably of clinical significance ([Oeffinger 2008](#); [Wang 2006](#)).

However, as mentioned previously, this result should be viewed with some caution due to the small sample size and risk of bias in the methodology, as there was no use of placebo in the control group and no blinding of either participants or investigators after randomisation. The deterioration in various outcome measures in the control group from baseline over the six months of the study may be explained by the participants and investigators knowing that the control had been selected to receive intrathecal baclofen treatment at a delayed time-point to the treatment group.

Other Measures of Function

No change in self-care or other functional abilities, as measured by the PEDI functional skills and caregiver assistance scales, was seen with intrathecal baclofen treatment in the [Hoving 2009b](#) study.

Ease of Care, Comfort and Quality of Life

Health-related quality of life, as measured by the CHQ-PF50, in the [Hoving 2009a](#) study was found to improve in children treated with intrathecal baclofen therapy in several domains of the measure: psychosocial summary, bodily pain/discomfort, parental impact-time and mental health. This is an important finding given that the ultimate goals of intrathecal baclofen treatment may often encompass improvement in health-related quality of life and the lack of evidence in the literature about the impact of this intervention upon this objective. Again, however, the lack of a placebo or blinding of either participants or investigators to allocation after randomisation introduces the risk of bias and these results should therefore be interpreted with caution.

Need for Subsequent Orthopaedic Surgery

It has been proposed that reducing spasticity by treating children with intrathecal baclofen leads to a reduced rate of muscle contracture and bony deformity and hence reduces the need for orthopaedic surgery ([Hagglund 2005](#)). There is also concern that intrathecal baclofen may increase the rate of spinal deformity. These questions cannot be addressed by the short-term, controlled trials included in this review, as data collection over a longer period would be required to ascertain this.

In relation to this question, [Gerszten 1998](#) completed retrospective analysis of 48 children who had received intrathecal baclofen pumps with a mean follow up period of 53 months found that orthopaedic surgery was planned at the time of pump insertion for 28 participants, but was subsequently required in only 10 children. In all participants who underwent surgery after intrathecal baclofen pump placement, this surgery had been planned prior to the pump insertion and the most commonly performed procedure was femoral osteotomy.

[Krach 2003](#) studied hip status in children with cerebral palsy one year after pump implantation (following on from the [Gilmartin 2000](#) study). The rate of change of migration percentage from baseline was 1.3%, a rate statistically significantly less than the 5% per year reported as the expected natural rate of progression in children with cerebral palsy.

Scoliosis is common in children with cerebral palsy, with a wide variation in reported incidence of 6.5-76% ([Loeters 2010](#); [Shilt 2008](#)), with the highest incidence occurring in non-ambulatory children ([Saito 1998](#); [Lonstein 1983](#)). Interpreting studies which seek to address the question of the influence of intrathecal baclofen upon spinal deformity is made more complex by issues relating to the high (but not precisely defined) background incidence of scoliosis in children with cerebral palsy and the large number of factors which can influence its development and progression. Also, the timing of intrathecal baclofen pump insertion in relation to skeletal maturity might also influence the rate of scoliotic curve progression, but again there is little evidence in the published literature to confirm this.

There are a number of published retrospective case series ([Burn 2010](#); [Ginsburg 2007](#); [Sansone 2006](#)) and case-control studies ([Krach 2005](#); [Motta 2002](#); [Seneran 2007](#)), with the majority of these suggesting an increased incidence or rate of progression of scoliosis with the use of intrathecal baclofen therapy. Evidence from [Shilt 2008](#) prospective cohort study determined that there was no statistically significant difference in the rate of progression of Cobb angles (6.6 degrees per year in the ITB group versus 5.0 degrees per year in the control group). The study compared individuals with cerebral palsy receiving ITB with a control group of children with cerebral palsy matched for age, sex, topographic motor involvement and initial Cobb angle (but not for GMFCS level). However, it should be noted that the method used to identify control participants may have been biased towards selection of patients with more significant scoliotic curves or curve progression, given that these participants were identified retrospectively from a clinic database, and only those individuals with at least two spinal radiographs on record were eligible for inclusion in the study.

Safety of Intrathecal Baclofen Therapy

The frequency and nature of complications is an important consideration in assessing the risk-benefit ratio of intrathecal baclofen therapy, particularly given that intrathecal baclofen therapy has the potential to cause adverse events of a life-threatening nature.

The studies included in this review are unable to answer this question as they were conducted over a short time period and most utilised temporary modes of intrathecal drug delivery, with one study (Hoving 2009a) utilising implantable pumps versus standard care for six months.

The Hoving 2009a article does not report on the safety of the continuous intrathecal baclofen therapy studied, but rather reports on this in a separate paper (Hoving 2009b). Hoving 2009b reports on adverse events recorded prospectively for a mean of 18.4 months from the insertion of an intrathecal baclofen pump (range 12-24 months). Eighty adverse events were recorded for the study population of 17 children, eight of which were serious, but not life-threatening in nature. Three of these serious adverse events were device-related complications requiring further surgery and four were drug-related (dysphagia, dysarthria, excessive hypotonia). One participant had new onset of seizures, although it is not clear that this was related to the use of intrathecal baclofen.

Elsewhere in the literature, exploration of the evidence available regarding the long-term safety of intrathecal baclofen in children with cerebral palsy reveals a large number of case series (Albright 1993; Albright 2003; Borowski 2010; Hoving 2009b; Krach 1999a; Motta 2007; Rippe 2005; Ward 2009). Several of these report on large number of paediatric participants (63-200 individuals) followed for significant periods of time (mean durations of 50-70 months) (Albright 2003; Borowski 2010; Motta 2007). Overall, these series reveal the rate of significant complications to be around 30% over the long term in those receiving intrathecal baclofen therapy. Motta 2007 calculated an incidence of one significant complication every 11.3 years of treatment

Of the serious complications of ITB therapy, common adverse events include device related complications, with catheter-related complications (disconnection, obstruction, migrations, tears and fractures) the most frequent complications seen in long-term intrathecal baclofen therapy, occurring in 10% to 30% of individuals (Albright 1993; Albright 2003; Borowski 2010; Krach 1999a; Motta 2007; Rippe 2005; Ward 2009;). Pump-related infections are also common, occurring in around 8% to 11% of individuals (Albright 1993; Albright 2003; Borowski 2010; Krach 1999a; Motta 2007; Rippe 2005; Ward 2009;). Cerebrospinal fluid leaks have been reported in 3% to 17% of individuals receiving intrathecal baclofen therapy (Albright 2003; Krach 1999a; Gilmartin 2000; Motta 2007; Ward 2009).

In relation to life expectancy, the best available published evidence does not show any increased mortality from the use of intrathecal baclofen therapy. Krach 2010 reports on a matched cohort study comparing survival in 359 individuals with cerebral palsy receiving intrathecal baclofen treatment with individuals without ITB pumps, matched for age, sex GMFCS level, the presence of epilepsy and feeding tube use. This study found no significant difference in survival curves between the two groups.

Economic implications

The cost-effectiveness of ITB was not addressed by the randomised controlled trials included in this review, but Dutch Study Group on Child Spasticity conducted a cost-effectiveness analysis alongside their randomised study (Hoving 2008). A number of other studies have examined the economic costs versus the benefits of intrathecal baclofen therapy via mathematical modelling (Bensmail 2009; de Lissovoy 2007; Sampson 2002).

Hoving 2008 determined in their cost-utility analysis that the cost per quality-adjusted life-year (QALY) for ITB was €32,737 (US \$36,665) in the year 2003. This was determined by prospective recording via a questionnaire and cost diary kept by the participants of the intervention and other health care costs in comparison with a retrospective questionnaire for the year preceding the ITB treatment. This cost per QALY is similar to US \$42,000 per QALY modelled by de Lissovoy 2007 in the context of the US health care system, but higher than the cost per QALY modelled by Sampson 2002 in the United Kingdom of US \$10,550-\$19,570. All these costs are well within the range that is widely accepted as offering good value for money (de Lissovoy 2007; Hoving 2008).

Potential limitations of the review

Risk of bias in review outcome

There is a clear risk of bias in the findings of this review.

A high risk of performance and detection bias due to lack of blinding of participants and those assessing outcome to treatment allocation in the Hoving 2009a study. These biases may have influenced the findings of worsening of the visual analogue scale scores, GMFM-66, and a number of the CHQ-PF50 domains in the control group from baseline to reassessment after six months. These are variables that would not be expected to alter over six months duration in the control group. This may have led to an incorrect finding of a statistically significant difference between the intrathecal baclofen treatment and control groups.

All studies in the review had small sample sizes, which can be more likely to be biased towards positive findings.

A particular limitation of this review is that three of the six included studies were from the same group of researchers and the studies performed on the same group of participants. Any biases inherent in these studies may therefore have been similar for all three studies, thus biasing the review outcome.

Potential bias in the conduct of the review

A thorough search of the published literature has been conducted in this review and it is likely that all published studies from journals indexed in the databases searched and trial registers have been identified.

Publication bias is difficult to overcome, although attempts were also made to identify unpublished studies via handsearching of conference proceedings and contact with researchers and with drug and device manufacturing companies. No unpublished studies were able to be identified.

AUTHORS' CONCLUSIONS

Implications for practice

Intrathecal baclofen may be an effective therapy for reducing spasticity in children with cerebral palsy, but the evidence for this is limited to date.

At present, there is a small amount of evidence from randomised controlled trials which suggest that intrathecal baclofen is effective for reducing spasticity in children with cerebral palsy in the short-term. The effect of intrathecal baclofen on spasticity outcomes in children with cerebral palsy in the long-term is less certain. The validity of the evidence is constrained by the small sample sizes of the studies and methodological issues in the studies.

Spasticity is a impairment in the domain of body structure and function and consideration must also be given to the broader context in determining whether intrathecal baclofen therapy is effective. The aim of therapy may be, for example, to improve motor function, to increase participation at a social role level, to improve comfort, to improve the ease of care by others or to improve the overall quality of life of the individual. There is some evidence that intrathecal baclofen improves ease of care and the comfort and quality of life of the individuals receiving it, but again small sample sizes and methodological issues in the studies mean that these results should be interpreted with caution. Intrathecal baclofen

therapy may improve gross motor function in children with cerebral palsy, but more reliable evidence is required.

The short duration of the studies included in this review did not allow for the exploration of questions regarding whether the subsequent need for orthopaedic surgery in children receiving intrathecal baclofen therapy is altered, or the safety and the economic implications of intrathecal baclofen treatment when long-term therapy is administered via an implanted device.

Implications for research

Further evidence of the effectiveness of intrathecal baclofen for treating spasticity, increasing gross motor function, improving comfort, ease of care and quality of life is required from other investigators in order to validate these results. In particular, evidence of the effectiveness of intrathecal baclofen for treating spasticity over longer durations of therapy is needed.

It is unlikely that randomised controlled trials will provide answers to the questions of whether the subsequent need for orthopaedic surgery in children receiving intrathecal baclofen therapy is altered, the long-term safety of the therapy and its economic implications. Cohort studies may be more an appropriate study design to answer these questions.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Albright 1991

Methods	Randomised, double-blind, paired placebo or intrathecal baclofen bolus treatment
Participants	Group 1: 17 patients with spastic cerebral palsy, 5 to 27 years Group 2: 6 patients with various disorders, 7 to 31 years
Interventions	Lumbar puncture; intrathecal baclofen bolus 25 mcg, 50 mcg or 100 mcg on different days or 0.9% saline
Outcomes	Ashworth score upper and lower limbs
Notes	Ashworth scores after placebo treatment not reported in published manuscript, but are represented graphically. Author unable to supply these data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	p1419 "The order of each pair of injections was randomised according to a coin toss by the pharmacist."
Allocation concealment (selection bias)	Unclear risk	No relevant detail recorded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	p1420 Table 2 records all results following ITB administration
Selective reporting (reporting bias)	Unclear risk	Placebo results not in report. Limited data in relation to upper limbs in report.
Blinding (performance bias and detection bias)	Low risk	Study described as "double blind."
Potential for carry-over effect in cross-over study design	Low risk	p1419 24 hours between injections

Armstrong 1997

Methods	<p>Phase 1: trial dose 25 mcg baclofen to determine whether beneficial and whether excessive sedation produced. A further trial with 10 mcg dose performed if the patient sedated with 25 mcg dose. If evidence of benefit without significant side effects, patients proceeded to next phase</p> <p>Phase 2: double-blind, placebo-controlled trial of baclofen or saline</p> <p>Phase 3: code broken, pump implantation in individuals who benefited, open-label, long-term infusion of intrathecal baclofen</p>
Participants	19 children with spasticity, of whom 10 had spastic cerebral palsy
Interventions	Subarachnoid catheter with subcutaneous access port; escalating dose of intrathecal baclofen (dose and bolus versus continuous infusion not specified), or intrathecal saline
Outcomes	Ashworth score upper and lower limbs
Notes	Ashworth score results of randomised phase not reported. Author unable to supply this data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation or methods relating to this not described.
Allocation concealment (selection bias)	Unclear risk	No relevant detail recorded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No relevant detail recorded.
Selective reporting (reporting bias)	Unclear risk	No relevant detail recorded.
Blinding (performance bias and detection bias)	Low risk	Study described as "double blind."
Potential for carry-over effect in cross-over study design	Low risk	Washout period of at least two to four days

Gilmartin 2000

Methods	<p>Phase 1: double-blind, placebo-controlled trial of intrathecal baclofen versus saline</p> <p>Phase 2: open-label, long-term intrathecal baclofen infusion</p>
Participants	51 patients with spastic cerebral palsy
Interventions	Lumbar puncture, percutaneous spinal catheter or spinal catheter with subcutaneous port; intrathecal baclofen bolus 50 mcg or 0.9% saline
Outcomes	Ashworth score lower limbs

Intrathecal baclofen for treating spasticity in children with cerebral palsy (Review)

Gilmartin 2000 (Continued)

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	p72 Study described as "randomised." No further details in relation to this
Allocation concealment (selection bias)	Unclear risk	No relevant details recorded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	p73 Table 2 records all results
Selective reporting (reporting bias)	Low risk	p73 Table 2 records all results
Blinding (performance bias and detection bias)	Low risk	p72 Study described as "randomised, double-blind."
Potential for carry-over effect in cross-over study design	Low risk	p72 "48-hour washout period between injections"

Hoving 2006

Methods	Randomised, double-blind, placebo-controlled dose escalation trial
Participants	16 patients with spastic cerebral palsy, 7 to 16 years
Interventions	External lumbar catheter; intrathecal baclofen bolus of 25 mcg, 50 mcg, 75 mcg or 100 mcg or placebo (not specified)
Outcomes	Electrophysiological changes - H-reflex, H/M ratio, flexor reflex threshold, flexor reflex threshold area
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	p1510 "Randomization lists were generated by an independent statistician"
Allocation concealment (selection bias)	Low risk	p1510 "the numbered study medication was delivered to the investigator....except for the pharmacist, all involved people were blinded to the contents of the study medication bolus"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	p1512 Table 3 and p1514 Table 4 records all results apart from two children who "received ITB at their first test day and showed a clear positive clinical response at once"

Hoving 2006 (Continued)

Selective reporting (reporting bias)	Unclear risk	p1512 Table 3 and p1514 Table 4 records all results apart from two children who "received ITB at their first test day and showed a clear positive clinical response at once"
Blinding (performance bias and detection bias)	Low risk	p1510 "except for the pharmacist, all involved people were blinded to the contents of the study medication bolus"
Potential for carry-over effect in cross-over study design	Low risk	p1510 24 hours between injections

Hoving 2007

Methods	Randomised, double-blind, placebo-controlled dose escalation trial
Participants	17 patients with spastic cerebral palsy, 7 to 16 years
Interventions	External lumbar catheter; intrathecal baclofen bolus of 25 mcg, 50 mcg, 75 mcg or 100 mcg or placebo (not specified)
Outcomes	Ashworth score in lower limbs and visual analogue scale for individually formulated problems
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	p655 "An independent statistician generated the randomisation lists"
Allocation concealment (selection bias)	Low risk	p655 "All other involved people were blinded to the contents of the study medication boluses"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	p656. Results of one child not included in statistical analysis as protocol and blinding were not adhered to due to adverse effects of the test treatment
Selective reporting (reporting bias)	Unclear risk	Not all results included in report
Blinding (performance bias and detection bias)	Low risk	p655 "All other involved people were blinded to the contents of the study medication boluses"
Potential for carry-over effect in cross-over study design	Low risk	p655 24 hours between injections

Hoving 2009a

Methods	Randomised controlled trial. Randomisation by random sequence generation, investigator blinded to next assignment in sequence. After randomisation, treatment was open-label and non-blinded
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Hoving 2009a (Continued)

Participants	17 patients with spastic cerebral palsy, 7 to 16 years
Interventions	Intrathecal baclofen via implanted pump
Outcomes	Evaluated after 6 months of treatment. Primary outcome measures: PEDI (Pediatric Evaluation of Disability Inventory) - caregiver assistance scale of the self-care domain and visual analogue scale for individually formulated problems. Other outcome measures Ashworth score, PEDI - functional skills scale and caregiver assistance scale within self-care domain, GMFM (Gross Motor Function Measure), CHQ-PF50 (Child Health Questionnaire -Parent Form 50)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	p241 "An independent statistician generated the allocation schedule with an unpredictable sequence of assignments."
Allocation concealment (selection bias)	Low risk	p241 "The investigator who enrolled the children has no entry to this list and was, at the time of each enrolment, not aware of the next assignment in the sequence."
Incomplete outcome data (attrition bias) All outcomes	Low risk	p242 Figure 1 documents no attrition.
Selective reporting (reporting bias)	Low risk	p243 Table 3 records all results
Blinding (performance bias and detection bias)	High risk	p241 "After randomisation, the treatment was open-label and non-blinded."
Potential for carry-over effect in cross-over study design	Low risk	Not relevant to this study as not cross-over design

H/M ratio: ratio of the maximal H amplitude to maximal M amplitude (an index of spasticity)

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Albright 1993	Not a controlled trial
Albright 1995	Not a controlled trial ; intrathecal baclofen versus selective dorsal rhizotomy
Albright 1998	Not a controlled trial ; patients with dystonia
Albright 2000	Not a controlled trial ; patients with dystonia
Albright 2001	Not a controlled trial ; patients with dystonia
Albright 2003	Not a controlled trial

Study	Reason for exclusion
Albright 2004	Not a controlled trial
Albright 2006	Not a controlled trial
Aldohondo 2013	Not a controlled trial
Aleton 2012	Not a controlled trial
Almeida 1997	Case report
Anonymous 1996	News item
Awaad 2000	Not a controlled trial
Awaad 2003	Not a controlled trial
Ayyangar 2002	Not a controlled trial
Ayyangar 2005	Not a controlled trial
Ayyangar 2007	Not a controlled trial.
Ayyangar 2011	Not a controlled trial.
Baker 2012	Not a controlled trial
Barry 2001	Not a controlled trial.
Bensmail 2006	Not a controlled trial.
Bensmail 2009	Cost-effectiveness modelling study.
Bjornson 2003	Not a controlled trial
Bleichman 2001	Not a controlled trial
Bleichman 2002	Not a controlled trial
Bleyenheuft 2007	Not a controlled trial
Bollo 2012	Not a controlled trial
Borowski 2008	Not a controlled trial.
Borowski 2010	Case series.
Bourg 2005	Not a controlled trial.
Bragg 2013	Not a controlled trial
Brochard 2009a	Case series.
Brochard 2009b	Case series.
Broseta 1990	Not a controlled trial.

Study	Reason for exclusion
Burn 2010	Case series
Cabrera 2004	Not a controlled trial
Caird 2008	Retrospective case-control study.
Campbell 1999	Case series.
Campbell 2002	Retrospective review.
Charles 2010	Not a controlled study.
Church 2008	Not a controlled study.
Concalves 1994	Not a controlled trial.
Creedon 1997	Meta-analysis.
Dachy 2004	Not a controlled trial ; patients with dystonia.
Damiano 2005	Not a controlled trial.
Dickey 2013	Not a controlled trial
Eldridge 2012	Not a controlled trial
Emery 2003	Review article.
Ethans 2005	Not a controlled trial.
Fares 1999	Case series.
Fares 2004	Case series.
Farfara 2007	Not a controlled trial
Filipetti 2006	Review.
Fitzgerald 2004	Not a controlled trial.
Gerszten 1997	Not a controlled trial.
Ginsburg 2002	Not a controlled trial.
Ginsburg 2007	Case series.
Giordano 2011	Not a controlled trial.
Gooch 2004	Case series
Gray 2007	Not a controlled trial.
Gutierrez-Solana 2003	Case series
Hagglund 2005	Not a controlled trial.

Study	Reason for exclusion
Haranhalli 2011	Case series.
Henry-Socha 2012	Not a controlled trial
Hester 2012	Not a controlled trial
Hoving 2008	Cost-effectiveness analysis.
Hoving 2009b	Not a controlled trial.
Kashii 2012	Not a controlled trial
Kolaski 2007	Review.
Krach 1997	Not a controlled trial.
Krach 1999	Case series.
Krach 1999a	Case series
Krach 2003	Case series
Krach 2005	Not a controlled trial
Krach 2005a	No outcome measure relating to spasticity or gross motor function
Krach 2005b	Not a controlled trial
Krach 2005c	Not a controlled trial
Krach 2006	No outcome measure relating to spasticity or gross motor function
Krach 2009	Review article.
Krach 2010	Not a randomised trial
Latash 1996	< 90% participants with spastic cerebral palsy
Lazorthes 1990	Not a controlled trial
Leslie 1999	Treatment guideline
Martinez Moreno 2013	Not a controlled trial
McCoy 2006a	Not a controlled trial
McCoy 2006b	Not a controlled trial
McMahon 2003	Case series
Meythaler 2001	Case series
Moosa 2008	Not a controlled trial.

Study	Reason for exclusion
Morton 2011	Controlled trial in subset of patients meeting study criteria, as participants were excluded if they did not respond to an initial test dose of ITB
Motta 2000	Not a controlled trial
Motta 2001	Not a controlled trial
Motta 2002	Not a controlled trial
Motta 2004	Not a controlled trial
Motta 2004a	Not a controlled trial
Motta 2007	Case series
Motta 2008	Case series
Motta 2009	Not a controlled trial.
Motta 2011	Not a controlled trial.
Mukherjee 2002	Not a controlled trial
Muquit 2012	Not a controlled trial
Murphy 2002	Case series
Najarian 2012	Not a controlled trial
Ochs 1996	Not a controlled trial
Penn 1995	Not a controlled trial
Piccinini 1999	Case series
Piccinini 2001	No outcome measurement relating to spasticity or gross motor function
Pin 2011	Not a controlled trial
Pritula 2012	Not a controlled trial
Ramstad 2010	No a controlled trial
Rawicki 1999	Not a controlled trial
Revivo 2001	Not a controlled trial
Revivo 2002	Not a controlled trial
Rippe 2005	Not a controlled trial
Rippe 2005a	Not a controlled trial
Saltuari 1992	Not a controlled trial

Study	Reason for exclusion
Sansone 2006	Retrospective review.
Saval 2008	Case series
Scheinberg 2001	Not a controlled trial
Seneran 2007	Retrospective case-control study
Sgouros 2002	Not a controlled trial
Shilt 2008	No measure of spasticity or gross motor function utilised
Silva 2012	Not a controlled trial
Simpson 1999	Review article
Sivakumar 2010	Not a controlled trial
Staal 2003	Retrospective review
Steinbok 1995	Not a controlled trial
Taira 2006	Not a controlled trial
Tasseel Ponche 2010	Not a controlled trial
Turner 2012	Not a controlled trial
Ughratadar 2012	Not a controlled trial
Ushewokunze 2012	Not a controlled trial
van Hulst 2009	Not a controlled trial
van Schaeybroeck 2000	< 90% patients aged 18 years or less
van Schie 2001	Patients with dystonia
Vitztum 2000	Treatment guideline
Vloeberghs 2005	Study yet to be completed ; protocol and pre-intervention baseline comparisons published only
von Koch 2001	Review article
Ward 2009	Not a controlled trial
Wunderlich 2006	Not a controlled trial
Zdolsek 2011	Not a controlled trial
Zierski 1988	Not a controlled trial

ADDITIONAL TABLES

Table 1. Search strategy - MEDLINE

Search terms
1. intrathecal.af.
2. infusion pump\$.af.
3. infusion pumps/
4. infusion pumps, implantable/
5. infusion system\$.af.
6. injections, spinal/
7. injection\$.af.
8. infusion.af.
9. infusions, parenteral/
10. continuous infusion.af.
11. drug infusion.af.
12. drug infusion/
13. chronic drug administration.af.
14. bolus.af.
15. or/1-14
16. baclofen.af.
17. Baclofen/
18. aminobutyric acid\$.af.
19. 4 Aminobutyric Acid/
20. GABA.af.
21. muscle relaxant\$.af.
22. muscle relaxants, central/
23. or/16-22
24. spastic\$.af.
25. exp Muscle Hypertonia/
26. hypertoni\$.af.
27. MUSCLE RIGIDITY/
28. exp Muscle Spasm/
29. exp muscle contraction/
30. exp muscle tonus/
31. muscle spasm\$.af.
32. muscle stiff\$.af.
33. muscle spasm\$.af.
34. muscle contraction\$.af.
35. muscle ton\$.af.
36. muscle rigidity.af.
37. ashworth score.af.
38. PEDI.af.
39. GMFM\$.af.
40. exp motor skills/
41. functional assessment.af.
42. exp treatment outcome/
43. exp "Activities of Daily Living"/
44. exp ambulation/
45. exp locomotion/
46. or/24-45
47. cerebral palsy.af.
48. Cerebral Palsy/
49. 47 or 48
50. 15 and 23 and 46 and 49
51. ("randomi#ed controlled trial\$" or "randomi#ed controled trial\$").af.
52. Randomized Controlled Trial/
53. randomization/
54. (randomi#ation or "random allocation\$").af.
55. exp controlled study/

Table 1. Search strategy - MEDLINE *(Continued)*

56. ("controlled stud\$" or "controled stud\$").af.
57. ("controlled clinical trial\$" or "controled clinical trial\$").af.
58. exp evidence based medicine/
59. exp clinical trial/
60. (clin\$ adj5 trial\$).af.
61. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).af.
62. Double Blind Procedure/
63. Single Blind Procedure/
64. Placebo/
65. placebo\$.af.
66. random\$.af.
67. exp methodology/
68. "research design\$".af.
69. follow up/
70. evaluation/
71. exp comparative study/
72. prospective study/
73. retrospective study/
74. exp prevalence/
75. "cross sectional stud\$".af.
76. (control\$ or prospectiv\$ or volunteer\$).af.
77. or/51-76
78. 50 and 77
79. limit 78 to (humans and ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)"))
80. limit 79 to (case reports or comment or "review")
81. 79 not 80

Table 2. Search strategy - EMBASE
Search Terms

1. intrathecal.af.
2. exp intrathecal drug administration/
3. infusion pump\$.af.
4. exp infusion pump/
5. infusion system\$.af.
6. exp infusion system/
7. exp injection/
8. injection\$.af.
9. infusion.af.
10. exp infusion/
11. exp infusion system/
12. continuous infusion.af.
13. exp continuous infusion/
14. drug infusion.af.
15. drug infusion/
16. chronic drug administration.af.
17. chronic drug administration/
18. bolus.af.
19. exp bolus injection/
20. or/1-19
21. baclofen.af.
22. Baclofen/
23. aminobutyric acid\$.af.
24. 4 Aminobutyric Acid/
25. 4 aminobutyric acid derivative/
26. GABA.af.

Table 2. Search strategy - EMBASE (Continued)

27. muscle relaxant\$.af.
28. exp Muscle Relaxant Agent/
29. spasmolytic agent/
30. or/21-29
31. exp spasticity/
32. spastic\$.af.
33. exp Muscle Hypertonia/
34. hypertoni\$.af.
35. MUSCLE RIGIDITY/
36. muscle stiffness/
37. exp Muscle Spasm/
38. exp muscle contraction/
39. exp muscle tone/
40. muscle spasm\$.af.
41. muscle stiff\$.af.
42. muscle spasm\$.af.
43. muscle contraction\$.af.
44. muscle ton\$.af.
45. muscle rigidity.af.
46. exp muscle function/
47. exp motor performance/
48. exp motor control/
49. exp motor dysfunction/
50. exp treatment outcome/
51. exp activities of daily living/
52. exp ambulation/
53. ashworth score.af.
54. PEDI.af.
55. GMFM\$.af.
56. or/31-55
57. cerebral palsy.af.
58. Cerebral Palsy/
59. spastic paresis/
60. 57 or 58 or 59
61. 20 and 30 and 56 and 60
62. ("randomi#ed controlled trial\$" or "randomi#ed controled trial\$").af.
63. Randomized Controlled Trial/
64. randomization/
65. (randomi#ation or "random allocation\$").af.
66. exp controlled study/
67. ("controlled stud\$" or "controled stud\$").af.
68. ("controlled clinical trial\$" or "controled clinical trial\$").af.
69. exp evidence based medicine/
70. exp clinical trial/
71. (clin\$ adj5 trial\$).af.
72. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).af.
73. Double Blind Procedure/
74. Single Blind Procedure/
75. Placebo/
76. placebo\$.af.
77. random\$.af.
78. exp methodology/
79. "research design\$".af.
80. follow up/
81. evaluation/
82. exp comparative study/
83. prospective study/
84. retrospective study/
85. exp prevalence/
86. "cross sectional stud\$".af.
87. (control\$ or prospectiv\$ or volunteer\$).af.

Table 2. Search strategy - EMBASE (Continued)

88. or/62-87
89. 61 and 88
90. limit 89 to (human and (infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>))
91. limit 90 to (letter or "review")
92. 90 not 91

Table 3. Search strategy - CINAHL
Search terms

1. intrathecal.af.
2. Infusions, Intraspinal/
3. Infusion Pumps, Implantable/
4. infusion pump\$.af.
5. injection\$.af.
6. infusion\$.af.
7. Infusion Devices, Intermittent/
8. continuous infusion\$.af.
9. Infusions, Parenteral/
10. infusion rates/
11. Injections, Intraspinal/
12. Neurosurgery/
13. bolus.af.
14. or/1-13
15. baclofen.af.
16. baclofen/
17. muscle relaxants, central/
18. aminobutyric acid\$.af.
19. Aminobutyric Acids/
20. GABA.af.
21. GABA/
22. or/15-21
23. spastic\$.af.
24. Muscle Spasticity/
25. exp Muscle Hypertonia/
26. hypertoni\$.af.
27. "Range of Motion"/
28. muscle contraction/
29. Muscle Tonus/
30. muscle spasm\$.af.
31. Spasm/
32. ashworth score.af.
33. PEDI.af.
34. Physical Therapy Assessment/
35. Occupational Therapy Assessment/
36. GMFM\$.af.
37. Functional Assessment/
38. Motor Skills/
39. Treatment Outcomes/
40. exp locomotion/
41. exp "Activities of Daily Living"/
42. or/23-41
43. cerebral palsy.af.
44. Cerebral Palsy/
45. 43 or 44
46. 14 and 22 and 42 and 45
47. randomized controlled trial\$.mp.

Table 3. Search strategy - CINAHL (Continued)

48. exp randomized controlled trials/
49. random allocation\$.mp.
50. controlled clinical trials.mp.
51. clinical trial.pt.
52. exp clinical trials/
53. (clin\$ adj5 trial\$).tw.
54. double blind method\$.mp.
55. single blind method\$.mp.
56. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj5 (blind\$ or mask\$)).tw.
57. placebos/
58. placebo\$.tw.
59. random.tw.
60. exp research design/
61. exp follow up studies/
62. exp evaluation studies/
63. exp prospective studies/
64. retrospective design/
65. retrospective panel studies/
66. exp case control studies/
67. comparative study/
68. cross-sectional studies/
69. (control\$ or prospectiv\$ or volunteer\$).tw.
70. or/47-69
71. 46 and 70
72. limit 71 to (infant <1 to 23 months> or preschool child <2 to 5 years> or child <6 to 12 years> or adolescence <13 to 18 years>)
73. limit 72 to "review"
74. 72 not 73

Table 4. Participant characteristics in included studies

Study ID	Age range (mean)	Distribution of spasticity	Severity	M:F	Co-morbidities
Albright 1991	5 to 27 years (12.2 years)	17/17 quadriplegia	'moderate'	11:6	ND
Armstrong 1997	4 to 16 years (8.9 years)	10/10 quadriplegia	'severe'	ND	ND
Gilmartin 2000	4 to 31 years (10.3 years)	35/51 quadriplegia, 12/51 diplegia; 4/51 paraplegia	severe - Ashworth score \geq 3	29:22	ND
Hoving 2006/Hoving 2007	7 to 16 years (13 years)	14/17 quadriplegia; 3/17 diplegia	GMFCS 3 - 1; GMFCS 4 - 2; GMFCS 5 - 13	8:8	ND
Hoving 2009a	as above	as above	as above	as above	ND

F: female

GMFCS: Gross Motor Function Classification System

M: male

Table 5. Use of oral baclofen during studies

Study ID	Oral baclofen use	Comments
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Table 5. Use of oral baclofen during studies (Continued)

Albright 1991	No	
Armstrong 1997	ND	
Gilmartin 2000	Yes	2/51 participants (in whom withdrawal was considered hazardous); withdrawn from other subjects
Hoving 2006/Hoving 2007	Yes	7/17 participants
Hoving 2009a	Yes	3/9 participants in intervention group and 4/8 participants in control group. Withdrawn over period of 10 days from commencement continuous intrathecal baclofen therapy in intervention group

Table 6. Complications of intrathecal baclofen

Study	CNS	Cardiovascular	Respiratory	Nausea/vomiting	Other
Albright 1991 (n = 23) NB children with cerebral palsy not differentiated from other participants	Sedation: 1 treatment Disorientation/agitation/lethargy: 1 treatment Control results not reported	NR	NR	NR	
Armstrong 1997 (n = 19) NB patients with cerebral palsy not differentiated from other participants	Sedation: 5 treatment Control results not reported	Bradycardia: 2 treatment Hypotension: 2 treatment Control results not reported	Respiratory depression: 1 treatment Apnoea: 1 treatment Control results not reported	NR	1 death due to respiratory arrest. Melatonin had been commenced concurrent with the appearance of apnoea
Gilmartin 2000 (n = 51)	Sedation: 5 treatment, 0 placebo Hypotonia: 1 treatment, 0 placebo Headache: 2 treatment, 3 placebo Dizziness: 1 treatment, 0 placebo	NR	NR	8 treatment, 2 placebo	
Hoving 2006 (n=16)	NR	NR	NR	NR	
Hoving 2007 (n = 17)	Symptoms reduced CSF pressure: 14 Lethargy: 7 treatment Hypotonia: 1 treatment Excessive perspiration: 1 treatment Radiculopathy: 1 participant	NR	NR	gastroenteritis: 1 participant	

Table 6. Complications of intrathecal baclofen (Continued)

Hoving 2009a	Complications not discussed in this paper. See Hoving 2009b for discussion of complications of intrathecal baclofen (no data on complications experienced by control group).
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CNS: central nervous system

CSF: cerebrospinal fluid

HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 11, 2015

Date	Event	Description
14 November 2008	Amended	Converted to new format.

CONTRIBUTIONS OF AUTHORS

Protocol written by Dr James Rice and Dr Maureen O'Donnell.

Review conducted by Dr Monika Hasnat and Dr James Rice.

Paper written by Dr Monika Hasnat.

DECLARATIONS OF INTEREST

Nil known.

INDEX TERMS

Medical Subject Headings (MeSH)

Baclofen [*administration & dosage]; Cerebral Palsy [*complications]; Injections, Spinal [methods]; Muscle Relaxants, Central [*administration & dosage]; Muscle Spasticity [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Young Adult