Intravenous immunoglobulin for presumed viral myocarditis in children and adults (Review)

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TABLE OF CONTENTS

[Intervention Review]

Intravenous immunoglobulin for presumed viral myocarditis in children and adults

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ABSTRACT

Background

Case reports and case series have described dramatic responses to intravenous immunoglobulin (IVIG) in people with presumed viral myocarditis and its administration has become commonplace.

Objectives

To assess the effects IVIG in people with presumed myocarditis.

Search methods

We searched CENTRAL (2009, Issue 3), MEDLINE (1966-September 2009), EMBASE (1988-September 2009), CINAHL (1982-September 2009), Web of Science (1975-September 2009), LILACS (1982-September 2009), trials registries and conference proceedings. We contacted authors of trials and checked reference lists of relevant papers. No language restrictions were applied.

Selection criteria

Studies were included if: (1) patients had a clinical diagnosis of acute myocarditis with either a left ventricular ejection fraction (LVEF) <= 0.45, LVEDD of >2 SDs above the norm, or a shortening fraction (SF) >2 SDs below the mean and the duration of cardiac symptoms was less than 6 months; (2) patients had no evidence of non-infectious or bacterial cardiac disease; and, (3) patients were randomized to receive at least 1 gm/kg of IVIG versus no IVIG or placebo. Studies were excluded if: (1) patients had received immunosuppression prior to outcome assessment; or, (2) onset of myocarditis was less than 6 months postpartum.

Data collection and analysis

Searches were screened and data extracted independently by two reviewers. Quality was assessed by two reviewers using the Jadad scale and allocation concealment. Meta-analysis was not possible because only one relevant study was found.

Main results

The relevant study involved 62 adults with acute myocarditis randomized to receive IVIG or an equivalent volume of 0.1% albumin in a blinded fashion. The incidence of death or requirement for cardiac transplant or placement of a left ventricular assist device was low in both groups (OR for event-free survival was 0.52 ,95% CI 0.12 to 2.30). Follow-up at 6 and 12 months showed equivalent improvement in LVEF (mean difference 0.00, 95% CI -0.07 to 0.07 at 6 months, mean difference 0.01, 95% CI -0.06 to 0.08 at 12 months). Functional capacity as assessed by peak oxygen consumption was equivalent in the two groups at 12 months (mean difference -0.80, 95% CI -4.57 to 2.97). Infusion-related side effects were more common in the treated group, but all appeared to be mild (OR 30.16, 95% CI 1.69 to 539.42).

Authors' conclusions

Evidence from one trial does not support the use of IVIG for the management of adults with presumed viral myocarditis. There are no randomized paediatric trials. Further studies of the pathophysiology of this entity would lead to improved diagnostic criteria which would facilitate future research.

PLAIN LANGUAGE SUMMARY

Intravenous immunoglobulin for presumed viral myocarditis in children and adults

Acute myocarditis involves inflammatory cell infiltration of the myocardium, and is thought to most commonly begin as a viral infection. The disease affects all ages. Based on multiple case reports and case series, IVIG has become part of routine practice for treating patients with acute myocarditis in many centers. Only one randomized controlled trial (RCT) was identified: this trial evaluated 62 adults with acute myocarditis and found no treatment benefit among patients receiving IVIG.

BACKGROUND

Acute myocarditis is a disease that occurs in all age groups. It is presumed to usually start as a viral infection, although autoimmune and idiopathic forms also occur. It remains unclear if the primary problem is most commonly ongoing damage from a virus, a post-infectious inflammatory reaction, or a combination of both. If ongoing infection is the primary problem, intravenous immunoglobulin (IVIG) could be efficacious if it contains antibodies to the microbe. Intravenous immunoglobulin also seems to have anti-inflammatory properties, so could be efficacious even if the primary problem is a post-infectious inflammatory reaction, or a non-infectious process.

There are multiple case reports (Nigro 2001; Takeda 1998; Tedeschi 2002) and case series (Drucker 1994; McNamara 1997) of apparent dramatic responses to IVIG in adults and children with acute myocarditis. However, results from a randomised controlled trial showed no advantage in treated adults with acute idiopathic cardiomyopathy (or in the sub-group with histologic evidence of acute myocarditis) (McNamara 2001).

One problem in analysing the literature on treatment of acute myocarditis is that the enrolment criteria for the studies are far from uniform. The reasons for this are:

(1) It is not clear what the gold standard for the diagnosis of acute myocarditis should be, or how non-infectious etiologies can be differentiated. Isolation of organisms from cardiac tissue would be indisputable evidence of infectious myocarditis but almost never occurs - probably because the concentration of organisms is low by the time a biopsy is done. Molecular techniques for detection of viruses may prove to be more sensitive but the specificity is not yet clear. It has been suggested that one way to diagnose acute viral myocarditis is to do cardiac biopsies at a minimum of 5 sites to look for histology fulfilling the Dallas criteria. These criteria require evidence of lymphocytic infiltration and myocyte necrosis with or without degeneration (Towbin 2001). However, studies have shown that the biopsies on about half of adults with acute myocarditis at autopsy did not fulfil the Dallas criteria (Towbin 2001). The reason for this is that inflammation can be patchy or transient, and can progress to fibrosis (which would not be interpreted as acute myocarditis) (Levi 2001). Therefore, many studies include patients who do not fulfil the Dallas criteria for acute myocarditis. Another suggestion is that any diffuse, focal, or confluent infiltrate of >=14 leukocytes/mm2 should be labelled acute myocarditis (Maisch 2002; Meyer 1997).

(2) The nomenclature of myocarditis is not yet standardized. For example, the term "acute myocarditis" is used by some authors to refer to all cases of active myocarditis (Fuse 2000), whereas other authors use the term only for disease of indistinct onset, using the term "fulminant" for cases with a distinct onset and clear evidence of a recent viral illness (Hare 2001). Some authors use the term "acute myocarditis" for a presumed infectious process, but others included non-infectious entities. Some experts believe that infectious myocarditis progresses from a phase where viral infection dominates to a phase where auto immunity dominates (Liu 2001). If viral replication or cytokine production persists, the patient develops a dilated cardiomyopathy (Liu 2001). If viral replication and cytokine production ceases, the patient spontaneously recovers. An alternate viewpoint is that the disease begins as either rapidly progressive, acute, or chronic myocarditis and that these three presentations may not be part of a continuum (Fenoglio 1983). Because there is no agreement on the natural history of acute myocarditis and no uniform classification scheme, it is not possible for studies to consistently report results of treatment of different types of myocarditis.

(3) There is no consensus on what investigations must be done to exclude non-infectious causes of acute myocardial dysfunction. In previously well pediatric patients, clinical diagnosis of infectious myocarditis is quite accurate, as there are few other causes of the acute onset of poor myocardial function. However in adults, acute myocardial dysfunction is sometimes attributed to suspected viral myocarditis when it is actually on the basis of unrecognized ischemic heart disease. Other possibilities in the adult include drug-induced cardiac dysfunction (from alcohol, organic solvents, cocaine, chemotherapeutic or cardiac agents), collagen vascular disease, or post-partum cardiomyopathy.

It is not clear if acute myocarditis in children differs in any important way from acute myocarditis in adults. However one adult study showed that 17 of 18 patients with fulminant myocarditis survived (McCarthy 2000) whereas a pediatric study described survival in only 2 of 9 infants with fulminant myocarditis (Mounts 2001).

OBJECTIVES

The objective of this review was to compare the outcome of patients with presumed viral myocarditis treated with IVIG to the outcome of patients who did not receive IVIG, particularly with respect to transplant-free survival. A secondary objective was to determine if there is an identifiable group of patients with presumed viral myocarditis (based on age, duration of symptoms, acuity of onset of symptoms, cardiac function at presentation, virologic results, or the presence or absence of histologic evidence of acute myocarditis on cardiac biopsy in patients where a biopsy was performed) who would benefit from IVIG.

METHODS

Criteria for considering studies for this review

Types of studies

This review included randomized controlled trials (RCTs) that compared patients treated with IVIG to patients who did not receive IVIG. Because of the anticipated small number of trials, trials with quasi-randomisation were also considered for inclusion. Trials were considered for inclusion even if no placebo was given. We did not include trials that compared IVIG to immunosuppressive therapy as there is tremendous variability in the type and dose of immunosuppressive drugs used and in the timing of administration of these drugs. However if there were arms of a trial that included an IVIG group and a placebo or no-therapy group the patients from these arms were considered for inclusion in this review if possible.

Types of participants

This study included inpatients or outpatients of any age, sex or race. The inclusion criteria were:
(1) Patients had to have a clinical diagnosis of acute myocarditis and at least one of the following:
(a) a left ventricular ejection fraction (LVEF) of less than or equal to 0.45;
(b) a left ventricular end diastolic diameter (LVEDD) of more than 2 standard deviations above the norm as adjusted for body surface area;
(c) a left ventricular shortening fraction (LVSF) more than 2 standard deviations less than the mean as adjusted for age, or less than 29% in an adult.
(2) The duration of cardiac symptoms prior to randomisation had to be less than 6 months.
Because of the poor sensitivity of cardiac biopsy as a diagnostic tool for acute myocarditis, a histologic diagnosis was not required.
The exclusion criteria were:
(1) Patients could not have any evidence of non-infectious or bacterial cardiac disease. Any patient over 30 years of age must have had screening to exclude ischemic heart disease. Patients of all ages must have had an echocardiogram to exclude valvular or congenital heart disease;
(2) Studies that included patients who had received immunosuppression prior to the final assessment of outcome following IVIG/no IVIG were excluded as the benefit of immunosuppression remains controversial;
(3) Because the pathogenesis of postpartum cardiomyopathy is likely to differ from that of other cases of acute myocarditis patients were excluded if onset of myocarditis was less than 6 months postpartum.

Types of interventions

Standard therapy for myocarditis is supportive care. In addition to this, patients must have been randomised to receive at least 1 gm/kg of any standard formulation of IVIG versus either placebo or no additional therapy.

Types of outcome measures

The primary outcome was transplant-free survival. Other outcomes that were considered were improvement in LVEF, LVEDD, and LVSF. We planned to examine both change from baseline in each of these parameters and to look for the presence or absence of normalization of at least one of these parameters. We planned to also look at hospitalization status, and improvement in functional symptoms (as determined by increased exercise tolerance as measured by any objective test and New York Heart Association Functional Capacity). We planned to analyze outcome measures for 3 to 5 months, 6 to 11 months, and 12 months or greater after randomization. We planned to analyze all outcome measures separately in the sub-group of patients who had cardiac biopsies that fulfilled the Dallas criteria.

Search methods for identification of studies

Electronic searches

We systematically searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE) on *The Cochrane Library* (2009, Issue 3), MEDLINE on Ovid (1966 to September 2009), EMBASE (1988 to September 2009), CINAHL (1982 to September 2009), Web of Science (1975 September 2009), LILACS (1982 September 2009) and ACP Journal Club (searched to 2003). Details of the original, and current searches are available in Appendix 1 and Appendix 2. In addition to the Cochrane Heart Group's Trial Registry several other registries were searched to September 2009:

- http://www.nhlbi.nih.gov/index.htm;
- http://www.controlled-trials.com/, clinicaltrials.gov;
- the National Research Register Archive and NIHR Portfolio Database at https://portal.nihr.ac.uk/;
- http://www.centerwatch.com/search.asp;
- http://www.cardiosource.com;
- http://www.neri.org/html/research/clinical/pediatric.asp (to 2003).

Searching other resources

We contacted the primary author of the relevant study and reviewed the reference lists of all selected articles.

We hand searched proceedings from the following meetings: American Heart Association (1999-2002), American College of Cardiology (1998-2002), European Society of Cardiology (1998-2002), and International Heart and Lung Transplantation Society (1998-2003).

In 2003 (for the original review) we contacted the Pediatric Cardiomyopathy Registry to see if they were aware of any other trials. The search was not limited by language or publication status, and included all years available for each database.

Data collection and analysis

Selection of studies

Two reviewers (JR, LH) independently examined the title and abstract of trials generated by the search to identify those with potential relevance. Two reviewers (JR, LH) assessed the full text of each of these articles and used a standardized form to determine if they fulfilled the eligibility criteria. We planned to resolve discrepancies through discussion.

Data extraction and management

Data were extracted independently by two reviewers (JR, LH). A standard data form was used to capture the following information:

(1) characteristics of the study (e.g., design, quality, funding source);

(2) study participants (e.g., age, severity of illness, duration of symptoms);

(3) intervention (e.g., dose of IVIG);

(4) outcome measures (e.g., transplant-free survival, functional symptoms, and echo cardiographic measures of ventricular function);

(5) results.

There were no discrepancies in data extraction. Additional unpublished data were requested from the primary author of the included trial.

Assessment of risk of bias in included studies

All selected studies were assessed for quality independently by two researchers (LH, KR). First each study was evaluated using the previously validated Jadad 5-point scale (Jadad 1996) to assess randomization, double blinding, and losses to follow-up. Next concealment of allocation was assessed as adequate, inadequate, or unclear using the methodology described by Schulz (Schulz 1995). Disagreements were resolved by consensus.

Data synthesis

Since only one relevant study was found we were unable to prepare a meta-analysis. It was also not possible to examine publication bias using a funnel plot.

Dichotomous data (e.g. transplant-free survival, occurrence of side-effects) were expressed as odds ratios with 95% confidence intervals. The number needed to harm (NNH) was also derived to help clarify the degree of adverse effects. Continuous data (change in left ventricular ejection fraction and peak oxygen consumption) were converted to the mean difference with 95% confidence intervals.

For peak oxygen consumption, we assumed a correlation of 0.5 and used the methods of Follmann (Follmann 1992) to calculate the standard deviations of the change from baseline estimates. This variable was only calculated on a portion of the sample for which data were available. The study did not give the break down of sample size in each group, only a total sample size. An estimate of sample size in each group was calculated by pro-rating the original group sample sizes to the new total sample size.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

1682 unique references were identified. Twenty-three studies were identified as being potentially relevant. Only one study met the inclusion criteria. There was 100% agreement between the two reviewers with respect to study relevance. The excluded studies were either not randomized or did not evaluate IVIG. See Characteristics of excluded studies for further details.

The included study (McNamara 2001) was conducted in the United States and published in English. The placebo-controlled trial evaluated the efficacy of IVIG among 62 adults (mean age 43.0 years, SD 12.3 years) with idiopathic dilated cardiomyopathy or myocarditis for less than six months and LVEF<=0.40 (see Characteristics of included studies).

Risk of bias in included studies

The quality score of the included study was three out of five on the Jadad scale. The study was randomized and described an appropriate method of randomization. The study was described as double-blind but there was no description of methods used for double-blinding. The study did not adequately describe withdrawals and losses to follow-up. Allocation concealment was unclear. The study received funding from a pharmaceutical company in the form of an educational grant.

Effects of interventions

Only one randomized trial of IVIG for acute myocarditis has been reported to date (McNamara 2001). This study enrolled 62 adults, of which ten had cellular inflammation on endomyocardial biopsy (four fulfilled the Dallas criteria for myocarditis, three had borderline myocarditis and three had non-specific inflammation). Patients were randomized to receive either 2 g/kg IVIG or an equivalent volume of 0.1% albumin in a blinded fashion.

The incidence of death or requirement for cardiac transplant or placement of a left ventricular assist device was low in both groups: event-free survival was not significantly different but favoured the control group; the odds ratio was 0.52 (95% confidence interval 0.12 to 2.30; NNH=13). Follow-up at six and 12 months showed equivalent improvement in LVEF in cases and controls; the mean difference was 0.00 (95% confidence interval -0.07 to 0.07) at six months and the mean difference was 0.01 (95% confidence interval -0.06 to 0.08) at 12 months. Functional capacity as assessed by peak oxygen consumption was equivalent in the two groups at 12 months; the mean difference was -0.80 (95% confidence interval -4.57 to 2.97). Infusion-related side effects were more common in the treated group, but all appeared to be mild; the odds ratio was 30.16 (95% confidence interval 1.69 to 539.42; NNH=3).

The only ongoing trial that we could find on the use of IVIG in acute myocarditis is the European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID) (Hufnagel 2000). This trial involves different therapies depending upon the expected pathogenesis of the myocarditis, and at least one of the arms involves immunoglobulin therapy. Recent communications with one of the co-investigators did not uncover any reported data relevant to the review question.

DISCUSSION

The only RCT of IVIG for acute myocarditis was done in adults, and showed no apparent benefit. This is in contrast to multiple case reports and case series that suggested potential benefit (Drucker 1994; McNamara 1997; Nigro 2001; Takeda 1998; Tedeschi 2002). Spontaneous improvement is common with acute myocarditis and can be rapid or gradual, so it is possible that the improvement noted in these case series was part of the natural history of the disease. It is also possible that some of the patients in the McNamara trial had non-infectious etiologies for their myocarditis (McNamara 2001). Because acute myocarditis is a relatively non-specific entity, it is possible that there is a sub-set of patients who will respond to IVIG. This might include patients whose disease was precipitated by a specific virus, or patients who are treated with IVIG early in the course of their illness when they have ongoing viral replication in the myocardium. Perhaps pediatric patients are more likely to respond, as there is a greater chance

than in adults that an acute cardiomyopathy is due to viral myocarditis. One of the excluded studies warrants mention as it may be of interest to the reader (Maisch 2004). This was a controlled trial of cytomegalovirus hyperimmunoglobulin (CMVhlg), rather than IVIG, among 35 patients with CMV-positive myocarditis. The results showed a significant difference in favour of treatment in terms of elimination of CMV-DNA and infiltrate, and improvement of 1 NYHA-class.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence from one trial involving 62 adults does not support the use of IVIG for the management of presumed viral myocarditis, but it is not clear that all patients in this study had viral myocarditis. There is a paucity of data, and further randomised controlled trials are needed. Until there are studies demonstrating benefit in a particular group of patients, use of IVIG for presumed viral myocarditis should not be part of routine practice.

Implications for research

The greatest need is for further studies of the pathophysiology of acute myocarditis, which would allow for a better understanding of the aetiology and the natural history of the disease. This might allow for improved diagnostic criteria, which would make it much easier to design studies of treatment options. This might also lead to recognition of sub-groups of patients where IVIG has a greater potential to confer clinical benefit. It would be very useful to have a pediatric study of IVIG in acute myocarditis.

ACKNOWLEDGEMENTS

Ellen Crumley developed and ran the search strategy and identified sources of grey literature for the original review. We thank Natasha Wiebe for providing statistical input on the protocol. We thank Kelly Russell for assisting with quality assessment and Elizabeth Sumamo for assisting with screening for the 2007 update.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

McNamara 2001

Methods	Randomized, placebo-controlled, double-blind trial; block randomization stratified by clinical centre; intention-to-treat analysis not performed
Participants	62 adults (mean age 43.0, SD 12.3 years; 37 men; 4 patients met the Dallas criteria for acute myocarditis); patients had recent onset (<=6 months of symptoms) of dilated cardiomyopathy and LVEF <=0.40; exclusion criteria: coronary artery disease, significant valvular disease, significant diabetes mellitus, significant hypertension, uncorrected thyroid disease, giant cell myocarditis, sarcoid, haemochromatosis
Interventions	Treatment: 2 g/kg IVIG (Gamimune N, 10%, Bayer Corporation); administered at 1 g/kg IV each day on 2 consecutive days Control: 0.1% albumin in 10% maltose solution given in equivalent volume (10 ml/kg IV each day on 2 consecutive days)
Outcomes	Primary endpoint: change in LVEF from baseline to 6 and 12 months; secondary end-points: event-free survival (events defined as death, cardiac transplantation, or placement of an LVAD) and functional capacity as assessed by metabolic stress testing at 12 months
Notes	Jadad score: 3 Funding: educational grant from the Bayer Corporation Language of publication: English

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

IVIG = intravenous immunoglobulin
LVEF = left ventricular ejection fraction
LVEDD = left ventricular end diastolic diameter
SF = shortening fraction

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

Study	Reason for exclusion
Anon 1997	not RCT
Anon 2002	not RCT
Bauer 2002	not RCT
Bozkurt 1998	wrong population (post-partum cardiomyopathy)
Bozkurt 1999	not RCT
Drucker 1992	not RCT
Drucker 1994	not RCT
Felix 2000	different intervention (smaller doses)
Gullestad 2001	different population (included patients with symptoms >6 months)
Kishimoto 1999	not RCT
Levi 2002	not RCT
Maisch 1991	not RCT
Maisch 1995	no results
Maisch 2004	different intervention (CMV hyperimmunoglobulin)
Maisch 2007	not RCT
McNamara 1997	not RCT
Muller 1998	different intervention
Shioji 2000	different population (animals)
Staudt 2001	different population (included patients with symptoms >6 months)
Takada 1993	different population (animals)
Takada 1995	different population (animals)

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

Hufnagel 2000

Trial name or title	European Study of Epidemiology and Treatment of Cardiac Inflammatory Diseases (ESETCID)
Methods	
Participants	
Interventions	One of the arms involves immunoglobulin therapy
Outcomes	
Starting date	
Contact information	
Notes	Recent communication with a co-investigator did not uncover any reported data relevant to the review question

DATA AND ANALYSES

Comparison 1. IVIG vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Event-free survival	1	62	Odds Ratio (M-H, Fixed, 95% CI)	0.52 [0.12, 2.30]
2 Change in LVEF	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 6 months	1	62	Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 12 months	1	62	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.06, 0.08]
3 Peak oxygen consumption	1	48	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-4.57, 2.97]
4 Side effects	1	62	Odds Ratio (M-H, Fixed, 95% CI)	30.16 [1.69, 539.39]

Analysis 1.1. Comparison 1 IVIG vs placebo, Outcome 1 Event-free survival.

Review: Intravenous immunoglobulin for presumed viral myocarditis in children and adults

Comparison: 1 IVIG vs placebo

Outcome: 1 Event-free survival

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
McNamara 2001	27/33	26/29		100.0 %	0.52 [0.12, 2.30]
Total (95% CI)	**33**	**29**		**100.0 %**	**0.52 [0.12, 2.30]**
Total events: 27 (Treatment), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.86 (P = 0.39)					

Analysis 1.2. Comparison 1 IVIG vs placebo, Outcome 2 Change in LVEF.

Review: Intravenous immunoglobulin for presumed viral myocarditis in children and adults

Comparison: 1 IVIG vs placebo

Outcome: 2 Change in LVEF

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 6 months							
McNamara 2001	33	0.14 (0.12)	29	0.14 (0.14)		100.0 %	0.0 [-0.07, 0.07]
Subtotal (95% CI)	**33**		**29**			**100.0 %**	**0.0 [-0.07, 0.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
2 12 months							
McNamara 2001	33	0.16 (0.12)	29	0.15 (0.16)		100.0 %	0.01 [-0.06, 0.08]
Subtotal (95% CI)	**33**		**29**			**100.0 %**	**0.01 [-0.06, 0.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.28 (P = 0.78)							
Test for subgroup differences: Chi^2 = 0.04, df = 1 (P = 0.84), I^2 =0.0%							

Analysis 1.3. Comparison 1 IVIG vs placebo, Outcome 3 Peak oxygen consumption.

Review: Intravenous immunoglobulin for presumed viral myocarditis in children and adults

Comparison: 1 IVIG vs placebo

Outcome: 3 Peak oxygen consumption

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
McNamara 2001	26	2.5 (6.22)	22	3.3 (6.97)		100.0 %	-0.80 [-4.57, 2.97]
Total (95% CI)	**26**		**22**			**100.0 %**	**-0.80 [-4.57, 2.97]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.42 (P = 0.68)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 IVIG vs placebo, Outcome 4 Side effects.

Review: Intravenous immunoglobulin for presumed viral myocarditis in children and adults

Comparison: 1 IVIG vs placebo

Outcome: 4 Side effects

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
McNamara 2001	11/33	0/29		100.0 %	30.16 [1.69, 539.39]
Total (95% CI)	**33**	**29**		**100.0 %**	**30.16 [1.69, 539.39]**

Total events: 11 (Treatment), 0 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 2.31 (P = 0.021)

APPENDICES

Appendix 1. Search strategies

CENTRAL on The Cochrane Library

#1 MeSH descriptor Myocarditis explode all trees
#2 MYOCARDITIS
#3 CARDITIS
#4 CARDIOMYOPATH*
#5 (HEART near/3 INFLAMMATION)
#6 (MYOCARD* near/3 INFLAMMATION)
#7 MYOCARDIOPATH*
#8 (#1 or #2 or #3 or #4 or #5 or #6 or #7)
#9 MeSH descriptor Immunoglobulins, Intravenous explode all trees
#10 IMMUNOGLOBULIN*
#11 IMMUNE next GLOBULIN*
#12 GAMMAGLOBULIN*
#13 GAMMA-GLOBULIN*
#14 IMMUNE next SERUM next GLOBULIN*
#15 IVIG*
#16 IGG*
#17 (#9 or #10 or #11 or #12 or #13 or #14 or #15 or #16)
#18 (#8 and #17)

MEDLINE On Ovid

1 exp immunoglobulins/
2 (gammaglobulin$ or gamma-globulin$).tw.
3 ivig$.tw.
4 exp Immunoglobulin G/
5 igg$.tw.
6 exp Receptors, Antigen, B-Cell/
7 immunoglobulin$.tw.
8 ((immune$ or immuno$) adj5 (globulin$ or serum$)).tw.
9 or/1-8
10 Myocarditis/
11 exp Cardiomyopathy, Dilated/
12 myocarditis.tw.
13 carditis.tw. (1361)
14 myocardiopath$.tw.
15 cardiomyopath$.tw.
16 ((heart$ or myocard$) adj5 (inflammation$ or inflame$)).tw.
17 or/10-16
18 9 and 17
19 randomized controlled trial.pt.
20 controlled clinical trial.pt.
21 Randomized controlled trials/
22 random allocation/
23 double blind method/
24 single-blind method/
25 or/19-24

26 exp animal/ not humans/
27 25 not 26
28 clinical trial.pt.
29 exp Clinical Trials as Topic/
30 (clin$ adj25 trial$).ti,ab.
31 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
32 placebos/
33 placebo$.ti,ab.
34 random$.ti,ab.
35 research design/
36 or/28-35
37 36 not 26
38 27 or 37
39 18 and 38

EMBASE on Ovid

1 exp Immunoglobulin/
2 exp Myocarditis/
3 Congestive Cardiomyopathy/
4 exp immunoglobulins/
5 (gammaglobulin$ or gamma-globulin$).tw.
6 ivig$.tw.
7 igg$.tw.
8 immunoglobulin$.tw.
9 ((immune$ or immuno$) adj5 (globulin$ or serum$)).tw.
10 or/4-9
11 exp Myocarditis/
12 Congestive Cardiomyopathy/
13 myocarditis.tw.
14 carditis.tw.
15 myocardiopath$.tw.
16 cardiomyopath$.tw.
17 ((heart$ or myocard$) adj5 (inflammation$ or inflame$)).tw.
18 or/11-17
19 10 and 18
20 clinical trial/
21 random$.tw.
22 randomized controlled trial/
23 trial$.tw.
24 follow-up.tw.
25 double blind procedure/
26 placebo$.tw.
27 placebo/
28 factorial$.ti,ab.
29 (crossover$ or cross-over$).ti,ab.
30 (double$ adj blind$).ti,ab.
31 (singl$ adj blind$).ti,ab.
32 assign$.ti,ab.
33 allocat$.ti,ab.
34 volunteer$.ti,ab.
35 Crossover Procedure/
36 Single Blind Procedure/

37 or/20-36
38 (exp animal/ or nonhuman/) not exp human/
39 37 not 38
40 39 and 19

CINAHL on EBSCO

((MH "Myocardial Diseases+") or myocarditis or carditis or cardiomyopath*) and ((MH "Immunoglobulins+") or immunoglobulin* or gammaglobulin* or gamma-globulin* or ivig* or IGG) and (((MH "Clinical Trials+") or random$ or trial or clinical study or group$ or placebo$))

ISI Web of Science

TS=((myocarditis or carditis or cardiomyopath*) and (IMMUNOGLOBULIN* or GAMMAGLOBULIN* or GAMMA-GLOBULIN* or ivig* or IGG) and (random* or controlled or trial or RCT or clinical or placebo))

LILACs

myocarditis or carditis or cardiomyopath$ [Palavras] and IMMUNOGLOBULIN$ or GAMMAGLOBULIN$ or GAMMA-GLOBULIN$ or ivig$ or IGG$ [Palavras] and (random$ or clinical$ or trial$ or RCT) [Palavras]

Appendix 2. Previous search strategies

CINAHL 2007

1 exp immunoglobulins/
2 (gammaglobulin$ or gamma-globulin$).tw.
3 ivig$.tw.
4 igg$.tw.
5 immunoglobulin$.tw.
6 ((immune$ or immuno$) adj5 (globulin$ or serum$)).tw.
7 or/1-6
8 exp Myocardial Diseases/
9 myocarditis.tw.
10 carditis.tw.
11 myocardiopath$.tw.
12 cardiomyopath$.tw.
13 ((heart$ or myocard$) adj5 (inflammation$ or inflame$)).tw.
14 or/8-13
15 7 and 14
16 limit 15 to yr="2003 - 2007"
17 Randomized controlled trials/
18 clinical trial.pt.
19 exp Clinical trials/
20 (clin$ adj25 trial$).ti,ab.
21 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
22 placebos.sh.
23 placebo$.ti,ab.
24 random$.ti,ab.
25 exp evaluation studies/
26 prospective studies.sh.
27 (control$ or prospectiv$ or volunteer$).ti,ab.

28 or/17-27
29 16 and 28

All Evidence Based Medicine Reviews (Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, and CENTRAL [Issue 2, 2003].

1 myocarditis$.mp.
2 carditis$.mp.
3 cardiomyopath$.mp.
4 myocardiopath$.mp.
5 ((heart$ or myocard$) adj5 (inflammation$ or inflame$)).mp.
6 or/1-5
7 immunoglobulin$.mp.
8 (gammaglobulin$ or gamma-globulin$).mp.
9 ivig$.mp.
10 igg$.mp.
11 ((immune$ or immuno$) adj5 (globulin$ or serum$)).mp.
12 or/7-11
13 6 and 12

MEDLINE 2003

1 exp immunoglobulins/
2 (gammaglobulin$ or gamma-globulin$).mp.
3 ivig$.mp.
4 exp immunoglobulin g/
5 igg$.mp.
6 exp immunoglobulins, surface/
7 immunoglobulin$.mp.
8 ((immune$ or immuno$) adj5 (globulin$ or serum$)).mp.
9 or/1-8
10 myocarditis$.mp.
11 cardiomyopath$.mp.
12 myocardiopath$.mp.
13 carditis$.mp.
14 ((heart$ or myocard$) adj5 (inflammation$ or inflame$)).mp.
15 or/10-14
16 9 and 15

EMBASE 2003

1 immunoglobulin$.mp.
2 (gammaglobulin$ or gamma-globulin$).mp.
3 exp immunoglobulin g/
4 ivig$.mp.
5 igg$.mp.
6 exp cell surface immunoglobulin/
7 immunoglobulin/
8 exp human immunoglobulin/
9 exp hyperimmune globulin/
10 ((immune$ or immuno$) adj5 (globulin$ or serum$)).mp.
11 or/1-10
12 exp myocarditis/

13 myocarditis$.mp.
14 exp cardiomyopathy/
15 myocardiopath$.mp.
16 carditis$.mp.
17 ((heart$ or myocard$) adj5 (inflammation$ or inflame$)).mp.
18 cardiomyopath$.mp.
19 exp carditis/
20 or/12-19
21 11 and 20

CINAHL 2003

1 immunoglobulin$.mp.
2 (gammaglobulin$ or gamma-globulin$).mp.
3 ivig$.mp.
4 exp immunoglobulins/
5 igg$.mp.
6 ((immune$ or immuno$) adj5 (globulin$ or serum$)).mp.
7 or/1-6
8 myocarditis$.mp.
9 cardiomyopath$.mp.
10 myocardiopath$.mp.
11 carditis$.mp.
12 ((heart$ or myocard$) adj5 (inflammation$ or inflame$)).mp.
13 or/8-12
14 7 and 13

WHAT'S NEW

Last assessed as up-to-date: 27 September 2009.

Date	Event	Description
30 September 2009	New search has been performed	The search was updated to September 2009. No new studies were identified and the conclusions are unchanged

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 1, 2005

Date	Event	Description
18 June 2008	Amended	Converted to new review format.
18 June 2008	Amended	Amendment to authorship.
26 June 2007	New search has been performed	Searches were rerun to June 2007. Two new studies were identified as potentially relevant. Both studies were excluded. The conclusions of the review remain unchanged

CONTRIBUTIONS OF AUTHORS

Joan Robinson conceived the review, prepared the protocol, and provided the clinical perspective on the problem. JR screened searches, applied inclusion criteria, performed quality assessment and data extraction, participated in writing the review, and provided clinical expertise.

Lisa Hartling coordinated the review and helped prepare the protocol. LH organized the retrieval of papers, screened searches, applied inclusion criteria, performed quality assessment and data extraction, edited the review, and provided methodological expertise.

Ben Vandermeer conducted the analysis, assisted with interpretation of the data, and contributed to writing the review.

Terry Klassen helped prepare the protocol. TK provided clinical and methodological expertise, contributed to interpretation of results, and edited the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Alberta Research Centre for Child Health Evidence, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Immunoglobulins, Intravenous [*therapeutic use]; Myocarditis [*therapy; virology]; Randomized Controlled Trials as Topic; Virus Diseases [*therapy]

MeSH check words

Adult; Child; Humans