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Granulocyte colony stimulating factor therapy for acute myocardial infarction (Review)

Moazzami K, Roohi A, Moazzami B

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TABLE OF CONTENTS

[Intervention Review]

Granulocyte colony stimulating factor therapy for acute myocardial infarction

Kasra Moazzami[1], Aria Roohi[2], Bobak Moazzami[2]

[1]Cardiovascular Research Center (CVRC), Massachusetts General Hospital, Harvard Medical School, Charlestown, MA, USA. [2]Student Research Committee, Babol University of Medical Sciences, Babol, Iran

Contact: Kasra Moazzami, kasra.moazzami@gmail.com.

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ABSTRACT

Background

Acute myocardial infarction (AMI) is the leading cause of death in developed countries, and current treatment modalities have failed to regenerate the dead myocardium resulting from the ischemic damage. Stem cells have the potential to regenerate the damaged myocardium. These cells can be mobilized from the bone marrow by factors such as granulocyte colony stimulating factor (G-CSF).

Objectives

To assess the effects of stem cell mobilization following granulocyte colony stimulating factor therapy in patients with acute myocardial infarction.

Search methods

We searched CENTRAL (*The Cochrane Library* Issue 4, 2010), MEDLINE (1950 to November week 3, 2010), EMBASE (1980 to 2010 week 48), BIOSIS Previews (1969 to 30 November 2010), ISI Science Citation Index Expanded (1970 to 4 December 2010) and ISI Conference Proceedings Citation Index - Science (1990 to 4 December 2010). We also checked reference lists of articles.

Selection criteria

We included randomized controlled trials including participants with a clinical diagnosis of AMI who were randomly allocated to the subcutaneous administration of G-CSF through a daily dose of 2.5, 5 or 10 microgram/kg for four to six days or placebo. No age or other restrictions were applied for the selection of patients.

Data collection and analysis

Two authors independently selected trials, assessed trials for eligibility and methodological quality, and extracted data regarding the clinical efficacy and adverse outcomes. Disagreements were resolved by the third author.

Main results

We included seven trials reported in 30 references in the review (354 participants). In all trials, G-CSF was compared with placebo preparations. Dosage of G-CSF varied among studies, ranging from 2.5 to 10 microgram/kg/day. Regarding overall risk of bias, data regarding the generation of randomization sequence and incomplete outcome data were at a low risk of bias; however, data regarding binding of personnel were not conclusive. The rate of mortality was not different between the two groups (RR 0.64, 95% CI 0.15 to 2.80, P = 0.55). Regarding safety, the limited amount of evidence is inadequate to reach any conclusions regarding the safety of G-CSF therapy. Moreover, the results did not show any beneficial effects of G-CSF in patients with AMI regarding left ventricular function parameters, including left ventricular ejection fraction (RR 3.41, 95% CI -0.61 to 7.44, P = 0.1), end systolic volume (RR -1.35, 95% CI -4.68 to 1.99, P =

0.43) and end diastolic volume (RR -4.08, 95% CI -8.28 to 0.12, P = 0.06). It should also be noted that the study was limited since the trials included lacked long enough follow up durations.

Authors' conclusions

Limited evidence from small trials suggested a lack of benefit of G-CSF therapy in patients with AMI. Since data of the risk of bias regarding blinding of personnel were not conclusive, larger RCTs with appropriate power calculations and longer follow up durations are required in order to address current uncertainties regarding the clinical efficacy and therapy-related adverse events of G-CSF treatment.

PLAIN LANGUAGE SUMMARY

Granulocyte colony stimulating factor treatment following a heart attack

People who suffer a heart attack (due to a blockage in the artery supplying blood to the heart) are usually affected by the damage to a portion of their heart muscle. Current treatment options are unable to restore the damaged section of the heart. Recently, stem cells have been shown to be able to restore and replace the damaged tissue in patients with heart attack. These cells could be mobilized to the heart with agents such as granulocyte colony stimulating factor (G-CSF).

In this review, analysis of seven included studies with low risk of bias using G-CSF to improve the function of damaged heart of patient with heart attack failed to show any beneficial effects of this treatment. The rate of mortality was not different between the two groups (RR 0.64, 95% CI 0.15 to 2.80, P = 0.55). Also, left ventricular parameters including left ventricular ejection fraction (RR 3.41, 95% CI -0.61 to 7.44, P = 0.1), end systolic volume (RR -1.35, 95% CI -4.68 to 1.99, P = 0.43) and end diastolic volume (RR -4.08, 95% CI -8.28 to 0.12, P = 0.06) did not show significant changes between the treatment and the control groups. There was no evidence that the study was associated with serious adverse effects, however it should be noted that the study was limited since the trials included lacked long enough follow up durations. Additionally four studies had either high or unclear risk of bias for blinding. Therefore, based on the results of the current study, G-CSF treatment should not be administered for patients with heart attack.

BACKGROUND

Description of the condition

Acute myocardial infarction (AMI) is the most common cause of morbidity from ischemic heart disease and is the leading cause of death in developed countries (BHF 2004). Worldwide more than seven million people suffer from AMI each year (White 2008). Following occlusion of a coronary artery, the inadequate supply of blood to the myocardium causes necrosis of the affected area. This in turn can lead to complications such as cardiogenic shock, cardiac perforations, embolism, heart failure, papillary muscle rupture, rhythm disturbances or autoimmune pericarditis, all of which can result in the death of affected individuals (Burton 1996).

Current pharmacologic and interventional strategies have been shown to be effective in terms of improved survival in patients with AMI (Lindquist 2003; Stone 2003). However, such treatment options can only limit the ongoing process and have failed to regenerate the dead myocardium resulting from the ischemic damage (Hartwell 2005). While these revascularization therapies such as catheterization and balloon angioplasty or stenting can reestablish the epicardial blood flow, the damage to the myocardium is usually unavoidable and may result in heart failure caused by adverse left ventricular remodeling (Hartwell 2005). Therefore, given the current advances, new therapeutic approaches are needed in order to target the lost cells during the ischemic damage and to restore the normal myocardial function.

While measurement of ejection fraction has been considered as a measure for cardiac function, echocardiographic assessment of function may have inherent limitations because of two-dimensional imaging as compared to both radionuclide blood pool imaging (with a three-dimensional component) and volumetric magnetic resonance imaging (Martin-Rendon 2008). However, since this method has been applied by most studies, it was considered in the present review as the main assessment tool for cardiac function evaluation.

A similar systematic review was published in 2008 assessing the role of stem cells in the treatment of AMI (Martin-Rendon 2008). The authors of the review found beneficial effects of stem cell therapy by direct implantation of cells into the ischaemic regions for patients suffering from AMI. Our review was developed to address the question of whether mobilization of stem cells from the bone marrow by granulocyte colony stimulating factor (G-CSF), which is a growth factor, could show similar beneficial effects without direct implantation.

Description of the intervention

In recent years, both animal and human studies have suggested that stem cells derived from the bone marrow have the potential to differentiate into specialized cells such as cardiomyocytes, endothelial cells, and smooth muscle cells (Asahara 1999; Kawamoto 2001). Based on this finding, a novel approach to treat AMI has developed from the observation in animal models that bone marrow-derived stem cells may regenerate myocardium by inducing neovascularization and myogenesis in the ischemic myocardium, and improve cardiac function after AMI (Kocher 2001; Martin-Rendon 2008; Orlic 2001). Later, preliminary human studies demonstrated that cardiac function was improved following infusion of bone marrow stem cells into the infracted myocardium (Assmus 2002; Fernandez-Aviles 2004; Meyer 2006). However, since this approach requires a sizable bone marrow aspiration in a potentially hemodynamically unstable patient, less invasive methods to repopulate the damaged myocardium with stem cells would be required.

Alternatively, stem cell mobilization with cytokines such as G-CSF may be a viable option, since it obviates the need for bone marrow aspiration and repeated cardiac catheterization (Abdel-Latif 2008). Several studies being conducted in different regions of the world have demonstrated the recruitment of mobilized stem cells to the ischemic myocardium and their differentiation into myoblasts and endothelial cells following G-CSF administration (Ellis 2006; Engelmann 2006; Ince 2005b; Leone 2007; Ripa 2006). The dosage of G-CSF administration in these studies have been between 2.5 and 10 microgram/kg for four to six days. However, most of these studies have been performed on a low number of patients, and have therefore yielded disparate results. While some of these studies have demonstrated beneficial effects of G-CSF treatment (Ince 2005b; Leone 2007), others have not yielded such results (Ellis 2006; Engelmann 2006; Ripa 2006). Therefore this novel approach may constitute a potential, new clinical treatment strategy for patients suffering from AMI.

Early clinical studies have raised some safety issues associated with G-CSF administration (Hill 2005; Kang 2004). These include initiation or exaggeration of plaque instability, myocardial infarction and rupture and increased risk of neointima formation and restenosis (Hill 2005; Kang 2004). However, further clinical trials have failed to address these side effects in patients treated with G-CSF (Ince 2005b; Kuethe 2005; Ripa 2006).

How the intervention might work

The exact mechanism of action of G-CSF administration has not been fully elucidated. Providing stem cells through mobilization of these cells from the bone marrow and homing of them into the damaged myocardium is the most clearly known mechanism of G-CSF administration (Kawada 2004). It has also been proposed that G-CSF accelerates the healing process by inducing growth factors and attenuates early ventricular expansion after AMI through collagen deposition in the infracted area (Minatoguchi 2004; Sugano 2005). Also through activation of specific receptors in the heart, G-CSF may enhance the survival of cardiomyocytes and reduce the rate of apoptosis (Hasegawa 2006). Thus, it seems that by supplying endothelial progenitor cells and providing multiple angiogenic factors or cytokines, G-CSF may improve the cardiac function and reverse the ischemic status of the affected myocardium (Ince 2005a).

Why it is important to do this review

Since administration of G-CSF in combination with already established therapeutic weapons for patients suffering from AMI has emerged as a novel intervention in clinical practice, it is important that a systematic review is undertaken in order to assess the safety and efficacy of this intervention. Therefore, we performed the current systematic review in order to investigate the potential therapeutic benefits of G-CSF therapy for AMI.

OBJECTIVES

To determine the safety, feasibility, tolerability and efficacy of stem cell mobilization following granulocyte colony stimulating factor as a treatment for acute myocardial infarction.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials of patients suffering from AMI who received G-CSF treatment in comparison to placebo or no intervention in addition to routine treatment. Studies published in all languages were eligible.

Types of participants

Any participants (of any age) with a clinical diagnosis of AMI.

Types of interventions

Studies involving the subcutaneous administration of G-CSF through a daily dose of 2.5, 5 or 10 microgram/kg for four to six days as treatment for AMI.

Participants in the control treatment arm would have had either no intervention or placebo such as isotonic saline infusion. Trials in which surgery (e.g. coronary artery bypass graft (CABG)) or percutaneous coronary intervention (PCI) were administered were eligible for inclusion.

Types of outcome measures

Primary outcomes

1. All-cause mortality.
2. Left ventricular ejection fraction (LVEF).

Secondary outcomes

1. Cardiovascular morbidity (a composite outcome) including reinfarction, incidence of arrhythmias, incidence of restenosis, hospital readmission, congestive heart failure (CHF) requiring rehospitalization, tamponade, cardiac perforation, cardiogenic shock and target vessel revascularisation.
2. Left ventricular end-systolic volume (LVESV).
3. Left ventricular end-diastolic volume (LVEDV).
4. Economic costs.
5. Patient-reported outcomes including pain-free walking distance (PFWD) and the total amount of pain measured by visual analogue scale (VAS).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 4, 2010), MEDLINE (1950 to November week 3, 2010), EMBASE (1980 to 2010, week 48), BIOSIS Previews (1969 to 30 November 2010), ISI Science Citation Index Expanded (1970 to 4 December 2010) and ISI Conference Proceedings Citation Index - Science (1990 to 4 December 2010). See Appendix 1 for the search strategies for all databases.

We used the Cochrane sensitive-maximizing search strategy for identifying randomized trials in searching MEDLINE and EMBASE (Lefebvre 2009).

Searching other resources

We checked the bibliographic references of relevant studies and reviews. We contacted the authors of the studies and experts in the field for information about other possible trials.

We also looked for unpublished and ongoing studies by searching the metaRegister of controlled trials (including International Standard Randomised Controlled Trial Number Register (ISRCTN) and National Institutes of Health (NIH) - randomized trial records) at www.controlled-trials.com/. Finally we also attempted to obtain individual patient level data.

No language restrictions were applied.

Data collection and analysis

Selection of studies

The titles and abstracts of references identified by the search were screened by KM and their eligibility for inclusion in the review was assessed independently by two review authors (KM and AR). Any disagreements were resolved by a third author (BM). We obtained full versions of articles that potentially met the inclusion criteria based on the title or abstract, and assessed them independently against the inclusion criteria. We recorded the reasons for exclusion of any study previously considered for inclusion in the Characteristics of excluded studies table.

Data extraction and management

KM and AR independently extracted both dichotomous and continuous data concerning outcome measures. Disagreements were resolved by a third author (BM). Once disagreements were resolved, we recorded the consensus data extracted on a third data extraction form. We sought any additional information necessary from trial authors.

Assessment of risk of bias in included studies

We assessed the risk of bias in included studies according to the Cochrane Collaboration's tool for assessing risk of bias (Higgins 2011):

1. Sequence generation
2. Allocation concealment
3. Blinding of participants, personnel and outcome assessors
4. Incomplete outcome data
5. Selective outcome reporting
6. Other sources of bias

Accordingly, each specified risk of bias item was assigned as low, unclear or high risk.

Measures of treatment effect

We used relative risk as the measure of effect for each dichotomous outcome. Where continuous scales of measurement were used to assess the effects of treatment, we analyzed these data using mean difference (MD). If different scales were used in the different studies,

the results were standardized, where possible, and then combined (i.e. standardized mean difference).

Assessment of heterogeneity

We explored and assessed clinical heterogeneity using the I^2 and Q statistics, and by subjective judgment of comparability of patients, interventions, and outcomes. An I^2 greater than 30% or Q statistic with a P value less than 0.1 was considered indicative of heterogeneity. Where there was significant heterogeneity among the studies, we explored the reasons for such heterogeneity and discussed in the review possible explanations for the observed heterogeneity.

Assessment of reporting biases

We used funnel plots to assess publication bias.

Data synthesis

We used both random-effects and fixed-effect models for robustness of results. If heterogeneity did not exist, we reported a fixed-effect model. If statistical, but not clinical, heterogeneity existed, we reported a random-effects model.

Subgroup analysis and investigation of heterogeneity

If sufficient trials were available, we would have performed subgroup analyses using age, sex, the mean LVEF at baseline, the dose of G-CSF, and the peak white blood cell (WBC) and CD34+ cell counts as indicators of bone marrow cell mobilization efficacy with G-CSF therapy.

Sensitivity analysis

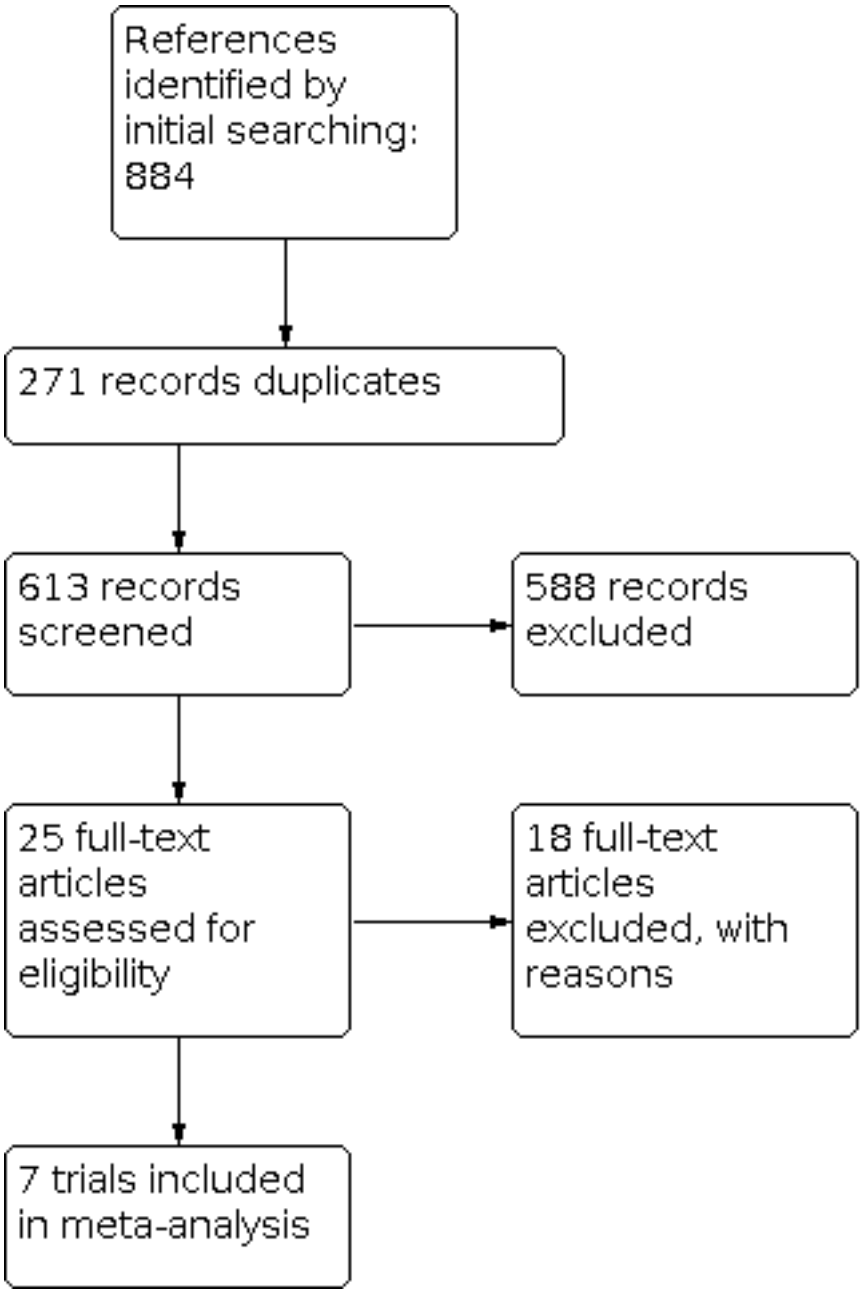
Had sufficient studies been identified, we would have conducted sensitivity analyses to examine the robustness of the observed findings in relation to a number of factors including study quality and patient type.

RESULTS

Description of studies

See Figure 1.

Figure 1. Study flow diagram.



We identified 884 references from the searches (442 from ISI Science Citation Index Expanded, 154 from ISI BIOSIS Previews, 143 from EMBASE, 102 from MEDLINE and 43 from CENTRAL). Following de-duplication, 613 records were left. Initial screening of the citations excluded 548 references. All remaining references were assessed on the basis of their full text for inclusion or exclusion against the Criteria for considering studies for this review.

Included studies

See table of Characteristics of included studies.

Seven trials were included in the review (354 participants) (Ellis 2006; Ince 2005a; Leone 2007; Ripa 2006; Takano 2007; Valgimigli 2005; Zohlnhöfer 2006). The number of participants included ranged from six to 58. We provide data regarding the proportion of each sex and the range of age for each trial in the table Characteristics of included studies.

All trials use percutaneous coronary intervention as primary treatment for AMI. Follow up was variable, from one month to one year.

Dosage of G-CSF varied among studies, ranging from 2.5 to 10 microgram/kg/day. In two trials, dosages of 2.5 (Takano 2007) and 5 (Zohlnhöfer 2006) microgram/kg/day were administered, respectively. All other trials administered the dosage of 10 microgram/kg/day for study subjects. Duration of G-CSF treatment ranged from four to six days.

The trials included in the review were conducted in five countries: USA, Germany, Denmark, Japan and Italy. The trials were published between 2005 and 2007. All trials were presented as full journal articles and all of them were published in English. All trials were parallel RCTs. None of studies were funded by industry.

All trials administrated a standard set of drugs including aspirin, clopidogrel, heparin, B-blockers, statins, angiotensin converting enzyme (ACE) inhibitors, nitrates and/or diuretics. However, different trials used different sets of drugs for their patients. ACE-I were administered in six trials (Ellis 2006; Ince 2005a; Ripa 2006; Takano 2007; Valgimigli 2005; Zohlnhöfer 2006), aspirin in five trials (Ince 2005a; Leone 2007; Takano 2007; Valgimigli 2005; Zohlnhöfer 2006), B- blockers and statins in five trials (Ellis 2006; Ripa 2006; Takano 2007; Valgimigli 2005; Zohlnhöfer 2006), clopidogrel in three trials (Ince 2005a; Leone 2007; Ripa 2006), and nitrates in one trial (Zohlnhöfer 2006).

Excluded studies

See the table Characteristics of excluded studies.

We excluded 18 studies for the following reasons:

1. In 11 trials, the diagnoses of patients were other than AMI (Engelmann 2006; Gloekler 2009; Huttmann 2006; Hyun-Jae 2003; Li 2004; Meier 2009; Subramaniyam 2009; Suzuki 2006; Wnag 2005; Wolfram 2007; Zbinden 2005);
2. In three trials, the study had more than one active arm of investigation which was out of the scope of the current review (De Lezo 2007; Kang 2006; Suarez 2004);
3. In three trials, the study was not randomized (Joseph 2008; Kuethe 2004; Kuo 2009);
4. One study included patients with AMI and leukopenia (Guo 2008).

Risk of bias in included studies

In summary, the overall risk of bias was considered low among the studied trials. Since only seven trials were included in the review, no funnel plots were generated (see Table 1, Figure 2 and Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

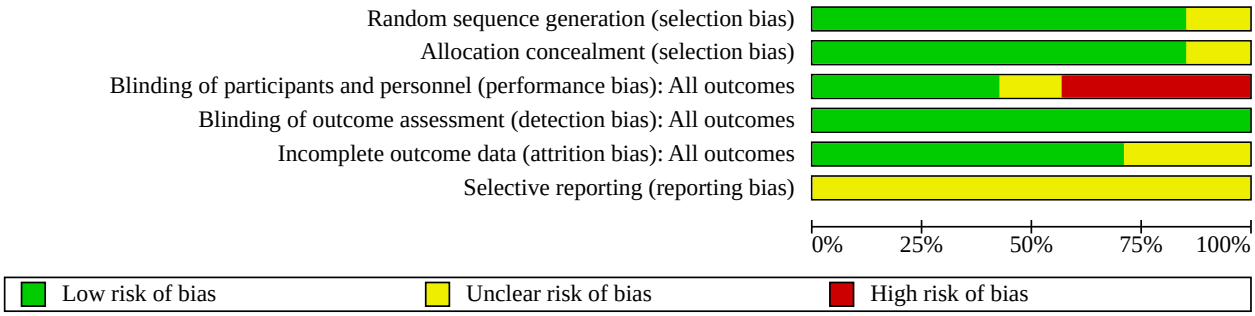
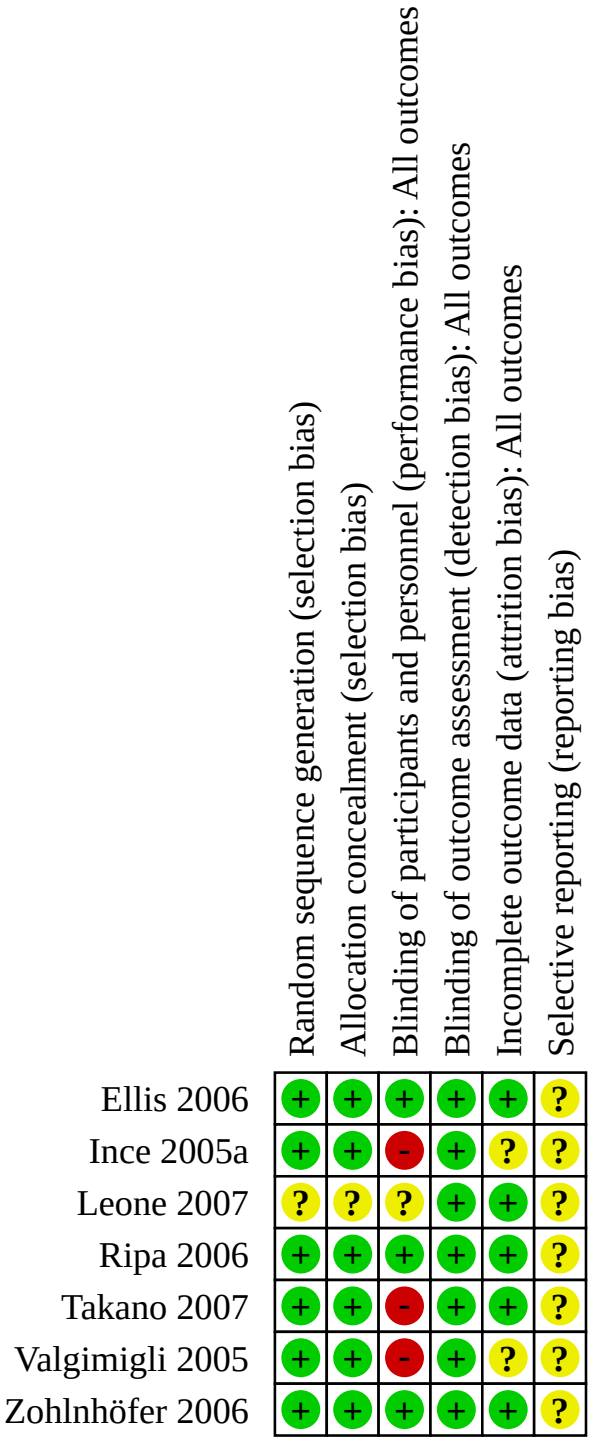


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Six trials provided details as to the generation of the randomization sequence (Ellis 2006; Ince 2005a; Ripa 2006; Takano 2007; Valgimigli 2005; Zohlnhöfer 2006). The methods included permutated block design in densely opaque envelopes in one trial (Ellis 2006), closed envelope In one trial (Ince 2005a), sealed envelope in two trials (Ripa 2006; Zohlnhöfer 2006); minimization method in one trial (Takano 2007); and computer-based randomization in one trial (Valgimigli 2005).

The generation of the randomization sequence was defined as unclear in one trial (Leone 2007) . No description was given in this publication as to which methods were used to generate the random sequence.

Blinding

In three trials, the blinding of all trial personnel (participants, clinicians and outcome assessors) was adequate (Ellis 2006; Ripa 2006; Zohlnhöfer 2006). In one trial, the blinding of participants and outcome assessors was adequate, but the blinding of clinicians was unclear (Ince 2005a). In three trials, the blinding of outcome assessors was adequate, but the blinding of participants and clinicians was unclear (Leone 2007; Takano 2007; Valgimigli 2005).

Incomplete outcome data

In one trial, all participants randomized to the trial were included in the final analysis of outcome data and the studies did not lose any participants during follow-up (Ellis 2006). In four trials, not all participants were included in the outcome data analysis (Leone 2007; Ripa 2006; Takano 2007; Zohlnhöfer 2006). In these studies between 2% and 15% of participants initially screened for the study were lost during follow up. In Leone 2007, one patient in the treatment group was lost during the follow up. In Ripa 2006, 6 and 2 patients in the control and comparator group were lost during the follow up, respectively. In another study, three and two patients in the control and treatment group were lost during the follow up, respectively (Takano 2007). Finally, one study lost 11 and 7 participants in the control and treatment group, respectively (Zohlnhöfer 2006).

In the remaining two studies, description of follow-up and withdrawals was incomplete (Ince 2005a; Valgimigli 2005).

Selective reporting

No reporting bias was identified in the current study. However, selective reporting is difficult to rule out in most of the cases.

Other potential sources of bias

Equal use of co-interventions in each trial arm

None of the trials reported the use of any other co-intervention in their trial.

Power calculation

Four trials reported power calculations (Ellis 2006; Leone 2007; Ripa 2006; Zohlnhöfer 2006). In Leone 2007, while 60 participants were included in order to detect a possible significant difference of 5% in LV ejection fraction, the study enrolled 41 patients and acknowledged the limited power of the study to discriminate a potential significant difference between patients in each treatment arm. In Ellis 2006 **,** a statistical power of 59% was calculated in order to see a trend in LVEF improvement. In another trial (Ripa 2006), a sample size of 50 was estimated in order to yield an expected power of 90% to detect a difference of 15% between the treated and the placebo groups, with a 2-sided significance level of 0.05. Finally, Zohlnhöfer 2006 calculated a total sample size of 90 patients to detect a difference of 6% or higher with a power of 80% and a 2-sided error of 0.05.

Effects of interventions

Mortality

Six trials (341 participants) reported the incidence of mortality (Ellis 2006; Ince 2005a; Leone 2007; Ripa 2006; Takano 2007; Zohlnhöfer 2006). In three studies, no deaths were reported (Ince 2005a; Leone 2007; Zohlnhöfer 2006). In the four remaining studies, one death was reported per study; in two of these trials, the patient belonged to the control group and in the other two trials (Ellis 2006; Ripa 2006), the patient from the experimental group died during the follow up period (Takano 2007; Zohlnhöfer 2006).

Overall, the rate of mortality was not statistically significant (RR 0.64, 95% CI 0.15 to 2.80, P = 0.55, Analysis 1.1). No heterogeneity was identified.

Left ventricular ejection fraction (LVEF)

All seven trials (354 participants) measured left ventricular ejection fraction (LVEF) (Ellis 2006; Ince 2005a; Leone 2007; Ripa 2006; Takano 2007; Valgimigli 2005; Zohlnhöfer 2006). Different methods were applied in order to measure the LVEF. In four studies, echocardiography was applied in isolation (Ellis 2006; Leone 2007; Ripa 2006) or in combination with angiography (Ince 2005a). Two trials used SPECT in order to study the left ventricular parameters (Takano 2007; Valgimigli 2005). Finally, in one trial, both MRI and angiography was used as the method of choice for measuring LVEF (Zohlnhöfer 2006).

All studies reported the timing of LVEF measurement outcomes of LV differences at short (less than 6 months) follow up durations.

Overall, no significant difference was observed between the two groups regarding LVEF (RR 3.41, 95% CI -0.61 to 7.44, P = 0.1, Analysis 1.2). Substantial statistical heterogeneity was observed (I^2 = 84%) among the two groups. The reasons for the observed heterogeneity could be attributed to the different modalities of measurement used and also different timing of outcome measurements (from one to six months).

Cardiovascular morbidity outcomes

Six trials measured cardiovascular outcomes as a treatment outcome (343 participants). Five trials measured only the observed side effects in short term follow up (Ince 2005a; Leone 2007; Ripa 2006; Takano 2007; Valgimigli 2005; Zohlnhöfer 2006). In only one study, the outcomes were reported at one year following AMI (Ellis 2006).

Incidence of reinfarction

Incidence of reinfarction was reported in four trials (244 participants) (Ellis 2006; Ripa 2006; Takano 2007; Zohlnhöfer 2006). In two trials, none of the patients developed reinfarction during the follow up period (Ripa 2006; Takano 2007). In the other two trials, one patient developed reinfarction in each study (Ellis 2006;

Zohlnhöfer 2006). In the Ellis 2006 study, the patient who developed reinfarction was reported to be in the study group at three weeks after G-CSF therapy, while in the other study (Zohlnhöfer 2006), one patient in the comparator arm developed reinfarction following MI.

Overall, there was no significant difference regarding the incidence of reinfarction in these trials (RR 1.02, 95% CI 0.15 to 6.86, P = 0.99, Analysis 1.3). No heterogeneity was observed among studies.

Incidence of arrhythmia

Three trials reported the incidence of arrhythmia among participants (232 participants) (Ripa 2006; Takano 2007; Zohlnhöfer 2006). In only one trial arrhythmia was observed in one patient in the study group (Zohlnhöfer 2006). This patient died of ventricular fibrillation 12 days after enrolment.

Incidence of restenosis

Six trials reported the incidence of restenosis (343 participants) (Ince 2005a; Leone 2007; Ripa 2006; Takano 2007; Valgimigli 2005; Zohlnhöfer 2006). In all of these trials, restenosis was observed among participants. In one trial, only one patient in the comparator arm developed restenosis following MI treatment (Valgimigli 2005). In the other studies, restenosis was observed among both the study and comparator arms.

Overall, meta-analysis of data revealed no significant difference in restenosis between participants in the treatment and control arms (RR 0.97, 95% CI 0.65 to 1.46, P = 0.89, Analysis 1.4). There was no statistical heterogeneity.

Hospital readmission

Two studies reported the incidence of hospital readmission (118 participants) (Ripa 2006; Takano 2007). In one study, (Takano 2007), there were no cases of hospital readmission during the follow up period. In the other study (Ripa 2006), two patients in the control group were readmitted to the hospital following MI treatment.

Congestive heart failure (CHF) requiring rehospitalization

Two studies reported data regarding the number of CHF cases requiring rehospitalization after MI (58 participants) (Ellis 2006; Takano 2007). In one study, none of the patients developed CHF following treatment (Takano 2007). In another study two patients, one in each arm developed CHF after MI treatment (Ellis 2006). There were no data regarding the timing of CHF development. However, the screening was performed 12 months after MI.

Tamponade

Only one study reported the incidence of tamponade in participants following treatment (18 participants) (Ellis 2006). None of the patients in this trial developed tamponade following treatment.

Cardiac perforation

None of the studies reported data regarding the occurrence of cardiac perforation.

Cardiogenic shock

The incidence of cardiogenic shock was assessed in one trial (78 participants) (Ripa 2006). In this trial, only one patient in the control group developed cardiogenic shock after the primary PCI and died 2.5 days later, despite aggressive treatment (intra-aortic balloon pump, dialysis, and ventilator therapy).

Target vessel revascularization

The rate of target vessel revascularization was assessed in two trials (192 participants) (Ripa 2006; Zohlnhöfer 2006). The trials reported the incidence of target vessel revascularization by six months in Ripa 2006, and four to six months in Zohlnhöfer 2006. The incidence was not shown to be significantly different between the treatment and comparator group (RR 0.94, 95% CI 0.56 to 1.57, P = 0.8, Analysis 1.5). No heterogeneity was reported between the trials.

Left ventricular end-systolic volume (LVESV)

Left ventricular end-systolic volume (LVESV) was measured in five trials (285 participants) (Ellis 2006; Leone 2007; Ripa 2006; Takano 2007; Zohlnhöfer 2006). All studies reported the timing of LVESV measurement at short (less than six months) follow up durations.

Overall, no significant difference was observed between the two groups regarding LVESV (RR -1.35, 95% CI -4.68 to 1.99, P = 0.43, Analysis 1.6). Statistical heterogeneity was observed (I^2 = 34%) among the two groups. This heterogeneity could be attributed to different modalities for measurement of systolic volume.

Left ventricular end-diastolic volume (LVEDV)

Six trials reported changes in LVEDV between the study and control groups (343 participants) (Ince 2005a; Leone 2007; Ripa 2006; Takano 2007; Valgimigli 2005; Zohlnhöfer 2006). The reported measurements were performed at short follow up durations.

Meta-analysis revealed no significant difference between the two groups (RR -4.08, 95% CI -8.28 to 0.12, P = 0.06, Analysis 1.7). Significant heterogeneity was present between the groups (I^2 = 55%). As for LVEF and LVESV, different measurement procedures could contribute to the observed heterogeneity between the studies.

DISCUSSION

Summary of main results

Despite the fact that several clinical trials have investigated the effects of G-CSF therapy on cardiac repair, the role of this cytokine remains controversial. In the present systematic review, seven trials were eligible to be considered in the final analysis (354 participants). In summary, our results indicate that regarding efficacy, G-CSF therapy did not show any evidence of beneficial effects in patients with MI following reperfusion. The parameters of LV function including LVEF, LVESV, and LVEDV did not show any further improvement in patients receiving G-CSF compared to the control group.

Regarding safety, the limited amount of evidence is inadequate to reach any conclusions regarding the safety of G-CSF therapy.

Overall completeness and applicability of evidence

While the total number of participants may be adequate to reach final conclusions, the sample sizes of each individual study included in the present review were small. Four trials used power calculations to estimate the minimum number of participants to be randomized in the trial (Ellis 2006; Leone 2007; Ripa 2006;

Zohlnhöfer 2006). The follow up duration varied in different studies, and none of the studies had long follow up duration (more than 18 months). Therefore, data regarding safety should be interpreted with caution, as longer follow up data should be assessed to fully determine any adverse effects of therapy.

Quality of the evidence

In the current review, six out of seven trials reported details of their method of randomization and were considered to be at low risk for this parameter. In only three trials were all trial personnel adequately blinded. Finally, while two trials did not report details regarding the number of patients lost to follow up, in the other five trials, less than 20% of participants were lost to follow up.

In conclusion, while the overall data regarding the generation of randomization sequence and incomplete outcome data were at low risk of bias, data regarding binding of personnel are not conclusive. Therefore, the results of the current review should be interpreted with caution.

Potential biases in the review process

While we conducted a comprehensive search, the possibility of publication bias cannot be ruled out completely. Selection of studies and extraction of data were performed independently by two authors in order to minimize the risk of introducing bias. Finally, individual patient level data could not be retrieved and the results were based solely on summary reports.

Agreements and disagreements with other studies or reviews

A number of meta-analyses have investigated the role of G-CSF treatment in patients with AMI (Abdel-Latif 2008; Fan 2008; Ince 2008; Kang 2007; Zohlnhöfer 2008). Regarding safety outcomes, all these reviews have documented G-CSF to be a safe modality and associated with minor side effects which are similar to the results of our findings. Moreover, in a meta-analysis performed to investigate the incidence of coronary restenosis or progression of coronary lesions in patients with AMI following G-CSF therapy, the results were in line with our findings, indicating that G-CSF does not elevate the risk for coronary restenosis (Ince 2008).

All of these meta-analyses except one have found similar results to those of our review regarding clinical efficacy (Abdel-Latif 2008; Fan 2008; Ince 2008; Zohlnhöfer 2008). In these studies, G-CSF did not enhance the improvement of LV function parameters at follow-up in comparison with the control group. In one systematic review, however, the mean LVEF was significantly increased in the G-CSF group in comparison to the control group (3.46%; 95% CI 0.60 to 6.32; P = 0.018) (Kang 2007). The observed discrepancy may be attributed to the fact that Kang 2007 included two studies which were not included in our study. We excluded one study (Kang 2006) because it investigated more than one active arm. The other study used granulocyte-macrophage colony stimulating factor, which was out of the scope of our study (Deng 2006).

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from the included studies indicating that G-CSF treatment in dosage from 2.5 to 10 microgram/kg for four to six days is not safe or associated with major side effects. However, the limited amount of evidence is inadequate to reach any conclusions regarding the safety of G-CSF therapy. Regarding clinical efficacy, the results do not show this modality to be beneficial in patients with AMI in terms of both mortality and left ventricular functional parameters. However, the results of the current study should be interpreted with caution given the low number of studies and participants, and potential risk of bias.

Implications for research

Larger RCTs with appropriate power calculations are needed in order to address current uncertainties regarding the clinical efficacy of G-CSF treatment. In order to clearly define therapy-related adverse events, studies with longer follow up durations are needed. Moreover, future studies should also evaluate economic costs and patient-reported outcomes.

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CHARACTERISTICS OF STUDIES

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

Ellis 2006

Study characteristics	
Methods	Study design: stated as randomized Method of randomization: permutated block design in densely opaque envelopes Losses to follow up: No
Participants	Country: USA Participants: 18 randomized Mean age: 62 and 60 years for control and treatment groups respectively Sex (M/F): 6/0 and 11/1 for control and treatment groups respectively Inclusion criteria: Patients 21 to 79 years of age with acute ST-segment elevation MI re perfused (TIMI 3 flow) more than 4 hours after symptom onset with baseline left ventricular ejection fraction 20% to 39% eligible to receive study drug in less than 48 hours from symptom onset. Exclusion criteria: Patients with a mechanical complication of MI such as ventricular septal defect, severe mitral insufficiency or contained rupture, anatomy likely to require bypass surgery within 30 days, clinical features suggestive of extremely limited likelihood of survival to 30 days (eg, severe oliguria), known malignancy, sepsis, vasculitis, gout, sickle cell trait or disease, lithium use, or possible pregnancy.
Interventions	Treatment group: G-CSF injected subcutaneously (one injection for the 5 microgram/kg dose, 2 injections for the 10 microgram/kg dose) once daily for 5 days. Control group: identical-appearing normal saline placebo.
Outcomes	Primary end points: • safety end point was that G-CSF would not decrease 30-day rupture-free survival • efficacy end point was that G-CSF would improve baseline to 30-day left ventricular ejection fraction (LVEF) improvement relative to placebo Secondary end points: • survival at 12 months; rates of rehospitalization for CHF through 12 months; improvement in LVEF from baseline to 12 months; infarct wall thickness at 30 days; reinfarction within 30 days; and maximum white blood cell (WBC), CD34+, CD117+ counts (measured daily until hospital discharge) during days 2 to 7 after treatment.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Ellis 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	Used a permutated block design
Allocation concealment (selection bias)	Low risk	By densely opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double blinded. The nurses and physicians caring for the patient were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	In the hematology and core echocardiographic laboratories, technicians and physicians were fully blinded to treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Stated that no patient was lost to follow up through 30 days.
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in methods are reported in results. Selective reporting would be difficult to rule out.

Ince 2005a

Study characteristics	
Methods	Study design: stated as randomized Method of randomization: closed-envelope method Losses to follow up: Not reported
Participants	Country: Germany Participants: 50 randomized Mean age: 49 and 50 years for control and treatment groups respectively Sex (M/F): 23/2 and 23/2 for control and treatment groups respectively Inclusion criteria: Patients between 18 and 65 years of age and with first STEMI comprising 3 of 12 ECG leads were eligible Exclusion criteria: Cardiogenic shock (defined as systolic blood pressure 80mm Hg requiring intravenous pressors or intra-aortic balloon counterpulsation), major bleeding requiring blood transfusion, a history of leukopenia, thrombocytopenia, hepatic or renal dysfunction, evidence of malignant disease, or unwillingness to participate were criteria for exclusion.
Interventions	Treatment group: subcutaneous G-CSF at a dose of 10 microgram/kg body weight over a period of 6 days. Control group: not stated.
Outcomes	Baseline ejection fraction (LVEF) and volumes were calculated by use of the area-length method; coronary angiograms were evaluated for binary restenosis, (in-stent) late lumen loss, and minimal lumen diameter of the target lesion.
Notes	
Risk of bias	

Bias	Authors' judgement	Support for judgement

Ince 2005a *(Continued)*

Random sequence generation (selection bias)	Low risk	Patients were randomly allocated.
Allocation concealment (selection bias)	Low risk	Patients were randomized by use of the closed envelope.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label application of G-CSF.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded evaluation by expert readers unaware of patient group assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated.
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in methods are reported in results. Selective reporting would be difficult to rule out.

Leone 2007

Study characteristics	
Methods	Study design: stated as randomized Method of randomization: Not stated Losses to follow up: one patient in the treatment group
Participants	Country: Germany Participants: 41 randomized Mean age: 56 and 53 years for control and treatment groups respectively Sex (M/F): 13/1 and 27/0 for control and treatment groups respectively Inclusion criteria: Patients with a first large anterior AMI and a LV ejection fraction 50% despite successful percutaneous revascularization of the infarct-related artery Exclusion criteria: Cardiogenic shock, uncontrolled myocardial ischemias or arrhythmias, malignancies, severe infections, hematologic diseases, splenomegaly on abdominal echocardiography, and age 80 years.
Interventions	Treatment group: Subcutaneous G-CSF at a dose of 10 microgram/kg body weight over a period of 5 days. Control group: Conventional therapy.
Outcomes	Left ventricular function studies.
Notes	
Risk of bias	
Bias	**Authors' judgement**	**Support for judgement**

Leone 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Patients were randomly allocated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blind to the treatment outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient in the treatment group was lost to follow up
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in methods are reported in results. Selective reporting would be difficult to rule out.

Ripa 2006

Study characteristics	
Methods	Study design: stated as randomized Method of randomization: sequentially numbered, sealed envelopes Losses to follow up: 8 patients
Participants	Country: Denmark Participants: 78 randomized Mean age: 54 and 57 years for control and treatment groups respectively Sex (M/F): 34/5 and 28/11 for control and treatment groups respectively Inclusion criteria: Patients treated successfully with primary PCI within 12 hours after the onset of symptoms were included in the study. STEMI was diagnosed from typical chest pain at rest lasting 30 minutes, the presence of cumulative ST-elevations 0.4 mV in 2 contiguous leads on a standard 12-lead ECG, and a significant rise in serum markers of myocardial infarction. Only patients who were between 20 and 70 years of age with a culprit lesion located in the proximal section of a large coronary artery branch, plasma creatine kinase-MB more than 100 g/L, or development of significant Q waves in the ECG were included. Exclusion criteria: Patients with prior myocardial infarction, significant stenosis in a nonculprit coronary vessel, ventricular arrhythmia after PCI requiring treatment, pregnancy, unprotected left main stem lesion, diagnosed or suspected cancer, New York Heart Association class 3 to 4 heart failure symptoms, or known severe claustrophobia.
Interventions	Treatment group: subcutaneous G-CSF at a dose of 10 microgram/kg body wt over a period of 6 days Control group: similar volume of placebo (isotonic sodium-chloride)
Outcomes	Primary end point was change in regional systolic wall thickening from day 1 to 6 months evaluated with cardiac MRI.

Ripa 2006 *(Continued)*

	Secondary end points were: (1) change in ejection fraction, end-systolic and end-diastolic volumes, and infarct size by MRI and (2) change in ejection fraction and end-systolic and end-diastolic volumes by echocardiography. Safety end points were (1) death of any cause, reinfarction, and new revascularization; (2) other adverse events; (3) in-stent restenosis; and (4) changes in inflammatory parameters (C-reactive protein and erythrocyte sedimentation rate).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double-blind, randomized, placebo-controlled study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double-blind, randomized, placebo-controlled study
Incomplete outcome data (attrition bias) All outcomes	Low risk	8 participants, 2 and 6 in the treatment and control groups respectively
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in methods are reported in results. Selective reporting would be difficult to rule out.

Takano 2007

Study characteristics

Methods	Study design: stated as randomized Method of randomization: sequentially numbered, sealed envelopes Losses to follow up: 5 patients
Participants	Country: Japan Participants: 40 randomized Mean age: 63 and 61 years for control and treatment groups respectively Sex (M/F): 18/4 and 14/4 for control and treatment groups respectively Inclusion criteria: Patients were eligible if they were admitted within 12 hours after onset of AMI with total occlusion of LAD alone and underwent successful PCI with bare metal stent implantation Exclusion criteria: previous MI; angiographically significant lesions in right coronary artery and/or left circumflex coronary artery; persistent severe heart failure (greater than Killip class II); uncontrolled myocardial ischemia or ventricular tachycardia; culprit lesion of infarct related artery not feasible for PCI; age older than 80 years; malignant disease; serious current infection or hematological disorder.

Takano 2007 *(Continued)*

Interventions	Treatment group: subcutaneous G-CSF at a dose of 2.5 microgram/kg body weight over a period of 5 days. Control group: patients were subcutaneously injected with saline.
Outcomes	Primary end point was the changes between global LVEF, LVESV and LVEDV at baseline and those after 6 months follow-up. Secondary end points were a change in defect scores and the difference in the incidence of major adverse cardiac events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated
Allocation concealment (selection bias)	Low risk	Minimization method
Blinding of participants and personnel (performance bias) All outcomes	High risk	After randomization, study processes were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Randomization was done by a blinded independent coordinator
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 participants, 2 and 3 in the treatment and control groups respectively
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in methods are reported in results. Selective reporting would be difficult to rule out.

Valgimigli 2005

Study characteristics

Methods	Study design: stated as randomized Method of randomization: Computer based Losses to follow up: Not stated
Participants	Country: Italy Participants: 20 randomized Mean age: 61 and 62 years for control and treatment groups respectively Sex (M/F): 8/2 and 8/2 for control and treatment groups respectively Exclusion criteria: previous MI, any haematological disorder, age less than 21 or more than 80, and Killip class more than 1.
Interventions	Treatment group: subcutaneous G-CSF at a dose of 5 microgram/kg body weight over a period of 4 days

Valgimigli 2005 *(Continued)*

	Control group: placebo
Outcomes	Major side effects, angiographic analysis to assess the rate of restenosis, LV function parameters
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated
Allocation concealment (selection bias)	Low risk	Computer-based randomization
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Single blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in methods are reported in results. Selective reporting would be difficult to rule out.

Zohlnhöfer 2006

Study characteristics

Methods	Study design: stated as randomized Method of randomization: Sealed envelope Losses to follow up: 18 participants
Participants	Country: Germany Participants: 114 randomized Mean age: 59 and 59 years for control and treatment groups respectively Sex (M/F): 46/12 and 44/12 for control and treatment groups respectively Inclusion criteria: Patients were required to have had successful reperfusion by percutaneous coronary intervention (performed 12 hours from symptom onset) and an infarct size of at least 5% of the left ventricle in single-photon emission computed tomography with technetium Tc 99m sestamibi (performed before randomization) Exclusion criteria: age younger than 18 years or older than 80 years, congestive heart failure defined as Killip class higher than II, electrical or hemodynamic instability, a history of prior myocardial infarction, autoimmune diseases, fructose intolerance, malignancies, incompatibility of G-CSF, and known or suspected pregnancy.

Zohlnhöfer 2006 *(Continued)*

Interventions	Treatment group: subcutaneous G-CSF at a dose of 10 microgram/kg body wt over a period of 5 days Control group: placebo
Outcomes	The primary end point was the reduction of infarct size measured as the difference in left ventricular infarct size at baseline (study entry) and follow-up by single-photon emission computed tomography. Secondary end points were improvement in LVEF from baseline to follow-up by MRI as well as angiographic restenosis defined as a diameter stenosis of 50% or greater by follow-up angiography. Other measures assessed were left ventricular volumes by MRI, LVEF, and number of hypokinetic chords by angiography. We also monitored for the occurrence of the following major adverse cardiac events: death, recurrent myocardial infarction, and reintervention in the infarct-related artery.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly allocated
Allocation concealment (selection bias)	Low risk	Sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated as double blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Stated as double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 participants lost to follow up, 7 and 11 in the treatment and control groups respectively
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in methods are reported in results. Selective reporting would be difficult to rule out.

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

Study	Reason for exclusion
De Lezo 2007	The study had more than one active arm of investigation which was out of the scope of the current review.
Engelmann 2006	In this study, patients with subacute MI were included, not AMI.
Gloekler 2009	The study investigates patients with coronary artery disease, not AMI.
Guo 2008	The study included patients with MI and leukopenia.
Huttmann 2006	The study included patients with chronic heart failure, not AMI.

Study	Reason for exclusion
Hyun-Jae 2003	The study Included patients with chronic heart failure, not AMI.
Joseph 2008	The study was not randomized.
Kang 2006	The study had more than one active arm of investigation which was out of the scope of the current review.
Kuethe 2004	The study was not randomized.
Kuo 2009	The study was not randomized.
Li 2004	The study included patients with old MI, not AMI.
Meier 2009	The study included patients with coronary artery disease, not AMI.
Suarez 2004	The study had more than one active arm of investigation which was out of the scope of the current review.
Subramaniyam 2009	The study included patients with peripheral artery disease not AMI
Suzuki 2006	The study included patients with coronary heart disease, not AMI.
Wnag 2005	The study included patients with severe chronic Ischaemic heart disease, not AMI.
Wolfram 2007	The study included patients with coronary artery disease, not AMI.
Zbinden 2005	The study included patients with coronary artery disease, not AMI.

DATA AND ANALYSES

Comparison 1. GCSF versus placebo

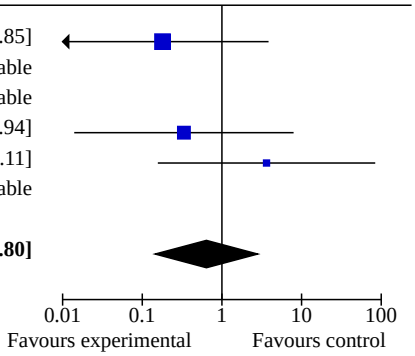
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mortality	6	341	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.15, 2.80]
1.2 Left Ventricular Ejection Fraction	7	354	Mean Difference (IV, Random, 95% CI)	3.41 [-0.61, 7.44]
1.3 Incidence of reinfarction	4	244	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.15, 6.86]
1.4 Incidence of restenosis	6	343	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.65, 1.46]
1.5 Incidence of revascularization	2	192	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.56, 1.57]
1.6 Left Ventricular End-Systolic Volume	5	285	Mean Difference (IV, Fixed, 95% CI)	-1.35 [-4.68, 1.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7 Left Ventricular End-Diastolic Volume	6	343	Mean Difference (IV, Random, 95% CI)	-4.08 [-8.28, 0.12]

Analysis 1.1. Comparison 1: GCSF versus placebo, Outcome 1: Mortality

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ellis 2006	0	12	1	6	50.0%	0.18 [0.01 , 3.85]
Ince 2005a	0	25	0	25		Not estimable
Leone 2007	0	14	0	27		Not estimable
Ripa 2006	0	39	1	39	38.4%	0.33 [0.01 , 7.94]
Takano 2007	1	18	0	22	11.6%	3.63 [0.16 , 84.11]
Zohlnhöfer 2006	0	56	0	58		Not estimable
Total (95% CI)		**164**		**177**	**100.0%**	**0.64 [0.15 , 2.80]**
Total events:	1		2			

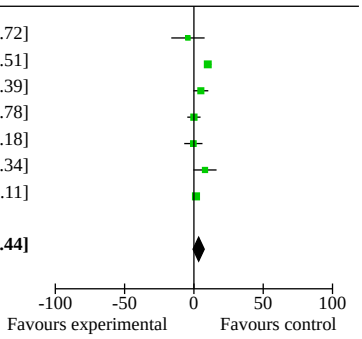
Heterogeneity: Chi² = 2.00, df = 2 (P = 0.37); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.55)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: GCSF versus placebo, Outcome 2: Left Ventricular Ejection Fraction

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ellis 2006	4.5	11.3	6	8.8	9.9	6	7.2%	-4.30 [-16.32 , 7.72]
Ince 2005a	6	4	25	-4	5	25	18.7%	10.00 [7.49 , 12.51]
Leone 2007	5	9	13	0	6	27	14.8%	5.00 [-0.39 , 10.39]
Ripa 2006	8	14	39	8	6	39	15.7%	0.00 [-4.78 , 4.78]
Takano 2007	3.6	10.2	18	4	11	22	13.1%	-0.40 [-6.98 , 6.18]
Valgimigli 2005	22	10	10	14	9	10	10.8%	8.00 [-0.34 , 16.34]
Zohlnhöfer 2006	2	4.9	56	0.5	3.8	58	19.6%	1.50 [-0.11 , 3.11]
Total (95% CI)			**167**			**187**	**100.0%**	**3.41 [-0.61 , 7.44]**

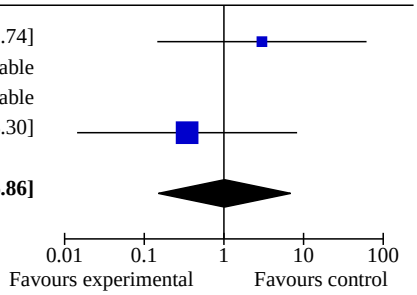
Heterogeneity: Tau² = 20.87; Chi² = 38.07, df = 6 (P < 0.00001); I² = 84%
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: GCSF versus placebo, Outcome 3: Incidence of reinfarction

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ellis 2006	1	6	0	6	25.3%	3.00 [0.15 , 61.74]
Ripa 2006	0	39	0	39		Not estimable
Takano 2007	0	18	0	22		Not estimable
Zohlnhöfer 2006	0	56	1	58	74.7%	0.35 [0.01 , 8.30]
Total (95% CI)		**119**		**125**	**100.0%**	**1.02 [0.15 , 6.86]**
Total events:	1		1			

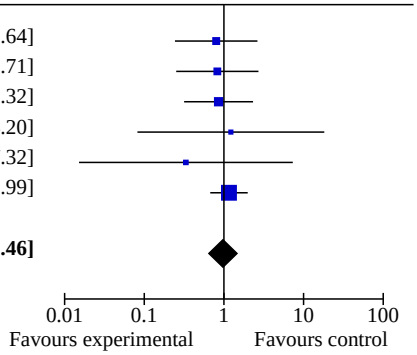
Heterogeneity: Chi² = 0.94, df = 1 (P = 0.33); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.99)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: GCSF versus placebo, Outcome 4: Incidence of restenosis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ince 2005a	4	25	5	25	13.9%	0.80 [0.24 , 2.64]
Leone 2007	3	14	7	27	13.3%	0.83 [0.25 , 2.71]
Ripa 2006	6	39	7	39	19.5%	0.86 [0.32 , 2.32]
Takano 2007	1	18	1	22	2.5%	1.22 [0.08 , 18.20]
Valgimigli 2005	0	10	1	10	4.2%	0.33 [0.02 , 7.32]
Zohlnhöfer 2006	19	56	17	58	46.5%	1.16 [0.67 , 1.99]
Total (95% CI)		**162**		**181**	**100.0%**	**0.97 [0.65 , 1.46]**
Total events:	33		38			

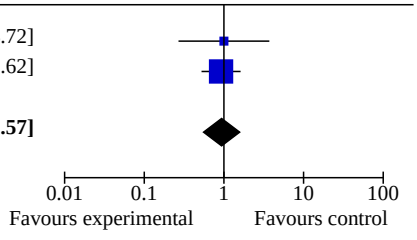
Heterogeneity: Chi² = 1.12, df = 5 (P = 0.95); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: GCSF versus placebo, Outcome 5: Incidence of revascularization

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ripa 2006	4	39	4	39	18.4%	1.00 [0.27 , 3.72]
Zohlnhöfer 2006	16	56	18	58	81.6%	0.92 [0.52 , 1.62]
Total (95% CI)		**95**		**97**	**100.0%**	**0.94 [0.56 , 1.57]**
Total events:	20		22			

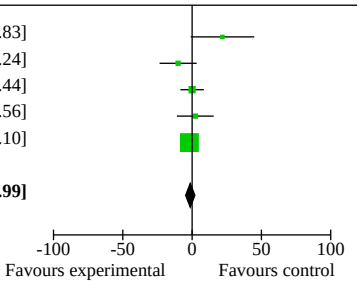
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.25 (P = 0.80)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: GCSF versus placebo, Outcome 6: Left Ventricular End-Systolic Volume

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Ellis 2006	31.2	25	6	9.3	14	6	2.1%	21.90 [-1.03 , 44.83]
Leone 2007	7	24	14	17.12	12	27	6.2%	-10.12 [-23.48 , 3.24]
Ripa 2006	6	20	39	6	18	39	15.6%	0.00 [-8.44 , 8.44]
Takano 2007	4.7	23	18	2.4	19	22	6.3%	2.30 [-10.96 , 15.56]
Zohlnhöfer 2006	1.5	4	56	3.4	15	58	69.7%	-1.90 [-5.90 , 2.10]
Total (95% CI)			**133**			**152**	**100.0%**	**-1.35 [-4.68 , 1.99]**

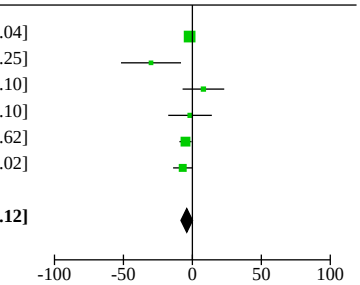
Heterogeneity: Chi² = 6.07, df = 4 (P = 0.19); I² = 34%
Test for overall effect: Z = 0.79 (P = 0.43)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: GCSF versus placebo, Outcome 7: Left Ventricular End-Diastolic Volume

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ince 2005a	1	3	25	3	4	25	37.0%	-2.00 [-3.96 , -0.04]
Leone 2007	-3	33	14	27	35	27	3.4%	-30.00 [-51.75 , -8.25]
Ripa 2006	17	33	39	9	35	39	6.5%	8.00 [-7.10 , 23.10]
Takano 2007	0.3	31	18	2	16	22	6.0%	-1.70 [-17.50 , 14.10]
Valgimigli 2005	6	5	10	11	5	10	28.0%	-5.00 [-9.38 , -0.62]
Zohlnhöfer 2006	-2	18	56	5	20	58	19.1%	-7.00 [-13.98 , -0.02]
Total (95% CI)			**162**			**181**	**100.0%**	**-4.08 [-8.28 , 0.12]**

Heterogeneity: Tau² = 11.40; Chi² = 10.99, df = 5 (P = 0.05); I² = 55%
Test for overall effect: Z = 1.90 (P = 0.06)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Summary table of risk of bias

Bias element	Overall risk of bias
Random sequence generation (selection bias)	Low risk
Allocation concealment (selection bias)	Low risk
Blinding of participants and personnel (performance bias)	High risk
Blinding of outcome assessment (detection bias)	Low risk
Incomplete outcome data (attrition bias)	Low risk
Selective reporting (reporting bias)	Unclear risk

APPENDICES

Appendix 1. Search strategies

CENTRAL (*The Cochrane Library*)

#1 MeSH descriptor Myocardial Infarction explode all trees
#2 myocard* next infarct*
#3 ami
#4 coronary near/3 occlusion*
#5 cardiac next infarct*
#6 heart next attack*
#7 heart near/2 infarct*
#8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Granulocyte Colony-Stimulating Factor explode all trees
#10 MeSH descriptor Granulocyte-Macrophage Colony-Stimulating Factor explode all trees
#11 G-CSF
#12 Colony next Stimulating next Factor*
#13 neupogen
#14 filgrastim
#15 pegfilgrastim
#16 lenograstim
#17 molgramostim
#18 (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17)
#19 (#8 AND #18)

MEDLINE (OVID)

1. exp Myocardial Infarction/
2. myocard* infarct*.tw.
3. ami.tw.
4. (coronary adj3 occlusion*).tw.
5. cardiac infarct*.tw.
6. heart attack*.tw.
7. (heart adj2 infarct*).tw.
8. or/1-7
9. exp Granulocyte Colony-Stimulating Factor/
10. exp Granulocyte-Macrophage Colony-Stimulating Factor/
11. G-CSF.tw.
12. Colony-Stimulating Factor*.tw.
13. neupogen.tw.
14. filgrastim.tw.
15. pegfilgrastim.tw.
16. lenograstim.tw.
17. molgramostim.tw.
18. or/9-17
19. 8 and 18
20. randomized controlled trial.pt.
21. controlled clinical trial.pt.
22. randomized.ab.
23. placebo.ab.
24. drug therapy.fs.
25. randomly.ab.
26. trial.ab.
27. groups.ab.
28. or/20-27
29. exp animals/ not humans.sh.
30. 28 not 29
31. 19 and 30

EMBASE (OVID)

1. exp heart infarction/
2. ami.tw.
3. cardiac infarct*.tw.
4. (coronary adj3 occlusion*).tw.
5. heart attack*.tw.
6. (heart adj2 infarct*).tw.
7. myocard* infarct*.tw.

8. or/1-7
9. granulocyte colony stimulating factor/
10. recombinant granulocyte colony stimulating factor/
11. granulocyte macrophage colony stimulating factor/
12. recombinant granulocyte macrophage colony stimulating factor/
13. G-CSF.tw.
14. Colony Stimulating Factor*.tw.
15. neupogen.tw.
16. filgrastim.tw.
17. pegfilgrastim.tw.
18. lenograstim.tw.
19. molgramostim.tw.
20. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 8 and 20
22. random$.tw.
23. factorial$.tw.
24. crossover$.tw.
25. cross over$.tw.
26. cross-over$.tw.
27. placebo$.tw.
28. (doubl$ adj blind$).tw.
29. (singl$ adj blind$).tw.
30. assign$.tw.
31. allocat$.tw.
32. volunteer$.tw.
33. crossover procedure/
34. double blind procedure/
35. randomized controlled trial/
36. single blind procedure/
37. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36
38. (animal/ or nonhuman/) not human/
39. 37 not 38
40. 21 and 39
41. limit 40 to embase

BIOSIS Previews (ISI Web of Science)

#19 #18 AND #17
#18 TS=(random* or blind* or placebo* or trial or trials or mask* or singl* or doubl* or trebl* or tripl*)
#17 #16 AND #8
#16 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9
#15 TS=molgramostim
#14 TS=lenograstim
#13 TS=pegfilgrastim
#12 TS=filgrastim
#11 TS=neupogen
#10 TS=G-CSF
#9 TS="Colony Stimulating Factor*"
#8 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#7 TS="cardiac infarct*"
#6 TS="myocard* infarct*"
#5 TS="heart attack*"
#4 TS=ami
#3 TS=(heart SAME infarct*)
#2 TS=(coronary SAME occlusion*)
#1 TS=cardiac infarct*

Science Citation Index Expanded and Conference Proceedings Citation Index – Science (ISI Web of Science)

#21 #20 OR #19
#20 #17 AND Document Type=(Meeting Abstract OR Meeting Summary OR Meeting-Abstract)
#19 #18 AND #17
#18 TS=(random* or blind* or placebo* or trial or trials or mask* or singl* or doubl* or trebl* or tripl*)

#17 #16 AND #8
#16 #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9
#15 TS=molgramostim
#14 TS=lenograstim
#13 TS=pegfilgrastim
#12 TS=filgrastim
#11 TS=neupogen
#10 TS=G-CSF
#9 TS="Colony Stimulating Factor*"
#8 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#7 TS="cardiac infarct*"
#6 TS="myocard* infarct*"
#5 TS="heart attack*"
#4 TS=ami
#3 TS=(heart SAME infarct*)
#2 TS=(coronary SAME occlusion*)
#1 TS=cardiac infarct*

WHAT'S NEW

Date	Event	Description
21 September 2021	Review declared as stable	This Cochrane Review has had low usage is therefore not a priority for updating.

HISTORY

Protocol first published: Issue 11, 2010
Review first published: Issue 5, 2013

Date	Event	Description
11 June 2013	Amended	Affiliatin detail for Aria Roohi and Bobak Moazzami amended

CONTRIBUTIONS OF AUTHORS

KM is the contact author and the guarantor of the review. He was responsible for drafting the protocol, obtaining copies of studies, selecting which studies to include, extracting data from studies, entering data into RevMan, and drafting the final review and will update the review. AR was responsible for drafting the protocol, obtaining copies of the studies, selecting which studies to include, extracting data from studies and drafting the final review. BM was responsible for drafting the protocol, extracting data from studies, entering data into RevMan, and drafting the final review and will update the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

INDEX TERMS

Medical Subject Headings (MeSH)

Granulocyte Colony-Stimulating Factor [administration & dosage] [*therapeutic use]; Hematopoietic Stem Cell Mobilization [*methods] [mortality]; Myocardial Infarction [mortality] [*therapy]; Randomized Controlled Trials as Topic; Recurrence

MeSH check words

Humans