Cochrane
Library

Cochrane Database of Systematic Reviews

Aminophylline for bradysystolic cardiac arrest in adults (Review)

Hurley KF, Magee K, Green R

Hurley KF, Magee K, Green R.
Aminophylline for bradysystolic cardiac arrest in adults.
Cochrane Database of Systematic Reviews 2015, Issue 11. Art. No.: CD006781.
DOI: [10.1002/14651858.CD006781.pub3](https://doi.org/10.1002/14651858.CD006781.pub3).

www.cochranelibrary.com

TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	3
BACKGROUND	5
OBJECTIVES	5
METHODS	5
RESULTS	7
Figure 1.	8
Figure 2.	9
Figure 3.	10
Figure 4.	11
DISCUSSION	12
AUTHORS' CONCLUSIONS	12
ACKNOWLEDGEMENTS	12
REFERENCES	13
CHARACTERISTICS OF STUDIES	16
DATA AND ANALYSES	23
Analysis 1.1. Comparison 1: Aminophylline vs. placebo, Outcome 1: Survival to hospital discharge	24
Analysis 1.2. Comparison 1: Aminophylline vs. placebo, Outcome 2: Return of spontaneous circulation	24
Analysis 1.3. Comparison 1: Aminophylline vs. placebo, Outcome 3: Survival to admission	24
Analysis 1.4. Comparison 1: Aminophylline vs. placebo, Outcome 4: Early administration of aminophylline: Survival to hospital discharge	25
Analysis 1.5. Comparison 1: Aminophylline vs. placebo, Outcome 5: Early administration of aminophylline: Survival to hospital admission	25
Analysis 1.6. Comparison 1: Aminophylline vs. placebo, Outcome 6: Early administration of aminophylline: Return of spontaneous circulation	25
Analysis 1.7. Comparison 1: Aminophylline vs. placebo, Outcome 7: Sensitivity analysis: survival to discharge	26
Analysis 1.8. Comparison 1: Aminophylline vs. placebo, Outcome 8: Sensitivity analysis: survival to admission	26
Analysis 1.9. Comparison 1: Aminophylline vs. placebo, Outcome 9: Sensitivity analysis: return of spontaneous circulation	26
APPENDICES	26
WHAT'S NEW	31
HISTORY	32
CONTRIBUTIONS OF AUTHORS	32
DECLARATIONS OF INTEREST	32
SOURCES OF SUPPORT	32
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	32
INDEX TERMS	32

[Intervention Review]

Aminophylline for bradysystolic cardiac arrest in adults

Katrina F Hurley¹, Kirk Magee², Robert Green³

¹Department of Emergency Medicine, IWK Health Centre, Halifax, Canada. ²Department of Emergency Medicine, Dalhousie University, Halifax, Canada. ³Co-appointments in Emergency Medicine and Critical Care, Dalhousie University, Halifax, Canada

Contact: Katrina F Hurley, kfhurley@dal.ca.

Editorial group: Cochrane Heart Group.

Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 9, 2021.

Citation: Hurley KF, Magee K, Green R. Aminophylline for bradysystolic cardiac arrest in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 11. Art. No.: CD006781. DOI: [10.1002/14651858.CD006781.pub3](https://doi.org/10.1002/14651858.CD006781.pub3).

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

In cardiac ischaemia, the accumulation of adenosine may lead to or exacerbate bradysystole and diminish the effectiveness of catecholamines administered during resuscitation. Aminophylline is a competitive adenosine antagonist. Case studies suggest that aminophylline may be effective for atropine-resistant bradysystolic arrest.

Objectives

To determine the effects of aminophylline in the treatment of patients in bradysystolic cardiac arrest, primarily survival to hospital discharge. We also considered survival to admission, return of spontaneous circulation, neurological outcomes and adverse events.

Search methods

For this updated review, we searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, LILACS, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform in November 2014. We checked the reference lists of retrieved articles, reviewed conference proceedings, contacted experts and searched further using Google.

Selection criteria

All randomised controlled trials comparing intravenous aminophylline with administered placebo in adults with non-traumatic, normothermic bradysystolic cardiac arrest who were treated with standard advanced cardiac life support (ACLS).

Data collection and analysis

Two review authors independently reviewed the studies and extracted the included data. We contacted study authors when needed. Pooled risk ratio (RR) was estimated for each study outcome. Subgroup analysis was predefined according to the timing of aminophylline administration.

Main results

We included five trials in this analysis, all of which were performed in the prehospital setting. The risk of bias was low in four of these studies ($n = 1186$). The trials accumulated 1254 participants. Aminophylline was found to have no effect on survival to hospital discharge (risk ratio (RR) 0.58, 95% confidence interval (CI) 0.12 to 2.74) or on secondary survival outcome (survival to hospital admission: RR 0.92, 95% CI 0.61 to 1.39; return of spontaneous circulation: RR 1.15, 95% CI 0.89 to 1.49). Survival was rare (6/1254), making data about neurological outcomes and adverse events quite limited. The planned subgroup analysis for early administration of aminophylline included 37 participants. No one in the subgroup survived to hospital discharge.

Authors' conclusions

The prehospital administration of aminophylline in bradysystolic arrest is not associated with improved return of circulation, survival to admission or survival to hospital discharge. The benefits of aminophylline administered early in resuscitative efforts are not known.

PLAIN LANGUAGE SUMMARY**Aminophylline for cardiac arrest**

Aminophylline is a drug that might help resuscitate patients in cardiac arrest when electrical activity is very slow or absent. Aminophylline may restore blood flow to the heart, improve electrical activity and make other drugs used in resuscitation more effective. We found five studies that included 1254 patients who had this type of cardiac arrest in the prehospital setting. Four of the five studies (1186 patients) were well-designed studies with low risk of bias. Although no adverse events were reported, aminophylline showed no advantage when it was added to the standard resuscitation practice of paramedics when compared with placebo in these patients. It is not known whether giving aminophylline sooner would be helpful.

SUMMARY OF FINDINGS

Summary of findings 1. Aminophylline compared to placebo for bradysystolic cardiac arrest in adults

Aminophylline compared to placebo for bradysystolic cardiac arrest in adults

Patient or population: participants with bradysystolic cardiac arrest in adults

Settings: prehospital

Intervention: aminophylline

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Aminophylline				
Survival to hospital discharge	Study population		OR 0.58 (0.12 to 2.74)	1254 (5 studies)	⊕⊕⊕⊖ moderate ^{a,b}	
	6 per 1000	4 per 1000 (1 to 17)				
	Moderate					
	0 per 1000	0 per 1000 (0 to 0)				
Return of spontaneous circulation	Study population		OR 1.15 (0.89 to 1.49)	1254 (5 studies)	⊕⊕⊕⊕ high ^a	
	234 per 1000	260 per 1000 (214 to 313)				
	Moderate					
	200 per 1000	223 per 1000 (182 to 271)				
Survival to admission	Study population		OR 0.92 (0.61 to 1.39)	1232 (4 studies)	⊕⊕⊕⊖ moderate ^b	
	87 per 1000	80 per 1000 (55 to 116)				
	Moderate					

	100 per 1000	93 per 1000 (63 to 134)			
Early administration of aminophylline: survival to hospital discharge	See comment	See comment	Not estimable	37 (2 studies)	⊕⊕○○ low ^c
Early administration of aminophylline: survival to hospital admission	Study population		OR 0.22 (0.02 to 2.36)	37 (2 studies)	⊕⊕○○ low ^c
	150 per 1000	37 per 1000 (4 to 294)			
	Moderate				
	226 per 1000	60 per 1000 (6 to 408)			
Early administration of aminophylline: return of spontaneous circulation	Study population		OR 1.61 (0.38 to 6.77)	37 (2 studies)	⊕⊕○○ low ^c
	250 per 1000	349 per 1000 (112 to 693)			
	Moderate				
	284 per 1000	390 per 1000 (131 to 729)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aDirks 1999 has unclear risk of bias because of limited information about the methodology on which to base the assessment. However, this represents a small number of participants.

^bBecause of the nature of the event (survival to hospital discharge from cardiac arrest), the 'event' is relatively rare (i.e. fewer than 300 events).

^cThe nature of the outcome required data on the time at which the drug was administered. The subgroup was small and data were available from only 2 of the 5 included studies.

BACKGROUND

Description of the condition

The incidence of out-of-hospital cardiac arrest is estimated to be 58.9 to 78.8 per 100,000 person-years (Hasegawa 2013). People suffering a cardiac arrest may have complete loss of cardiac electrical activity and heart rhythm (asystole), a slow heart rhythm but no cardiac output or a disorganised rhythm (ventricular fibrillation). Bradyasystole, defined as the absence of cardiac electrical activity confirmed in more than one lead or pulseless electrical activity at a rate of less than 60 beats per minute, is the most commonly recorded initial rhythm in cardiac arrest (Herlitz 1994; Sedgwick 1994; Steill 2004; Vaillancourt 2004). Fewer than 10% of patients suffering cardiac arrest (all rhythms) survive to discharge from hospital (Kette 1998; Hasegawa 2013). Overall survival from 'non-shockable' rhythms is estimated to be less than 3% (Thomas 2013). The outlook for asystole, in particular, is more dismal, with fewer than 1% surviving (Steill 2004; Vaillancourt 2004). Interventions to improve outcomes in this group may have a significant impact in terms of lives saved.

Clinical trials on interventions in cardiac arrest have been hindered by variability in data definitions and outcome measures. This has been addressed in part by the Utstein style reporting template for out-of-hospital cardiac arrest from the International Liaison Committee on Resuscitation (ILCOR) (Cummins 1991; Cummins 1997; Jacobs 2004). These guidelines represent an international consensus on the definitions and core data needed to report and study resuscitation for both research purposes and clinical benchmarking. It is interesting to note that ILCOR could not reach a consensus on the definition of asystole or bradyasystole (Jacobs 2004).

Description of the intervention

Aminophylline is a complex of theophylline and ethylenediamine. Aminophylline's active metabolite is theophylline, and pharmacokinetic data quoted in product monographs reference the active metabolite rather than the parent compound. These methylxanthines are metabolised by the liver with about 10% excreted (unchanged) by the kidneys (Micromedex Solutions). The average plasma half-life is 7 to 9 hours in healthy non-smoking adults and 4 to 5 hours in adult smokers (Rudusky 2005). The median half-life in septic patients is prolonged (18.8 hours). The specific pharmacokinetics of aminophylline administered in the setting of cardiac arrest is not known.

Methylxanthines are known to have numerous drug interactions. Prolonged clearance of theophylline has been particularly reported with cimetidine, macrolide antibiotics and ciprofloxacin. Adverse effects in the setting of cardiac arrest have not been reported.

How the intervention might work

Adenosine is an endogenous nucleotide that plays a role in the regulation of myocardial oxygen supply and demand (Mader 2000). In periods of cellular hypoxia, production of adenosine is increased, leading to accumulation in ischaemic cardiac muscle. In what is believed to be a cardioprotective mechanism, adenosine acts to increase oxygen supply through coronary vasodilation and to diminish oxygen demand by reducing intrinsic pacemaker activity, blocking conduction at the atrioventricular (AV) node and attenuating the response to catecholamines (Schrader

1977; Dobson 1983; Wesley 1989; Malcolm 1993; Belardinelli 1995; Mader 2000). These actions in the setting of cardiac ischaemia may lead to bradycardia or bradyasystole resistant to atropine, as it is independent of parasympathetic tone. Furthermore, adenosine diminishes the effectiveness of exogenous catecholamines (Belardinelli 1989; Visentin 1990).

Aminophylline is a competitive nonspecific antagonist of adenosine that enhances cardiac response to beta-agonists and stimulates endogenous catecholamine release (Rudusky 2005). The pathophysiology of bradyasystolic arrest suggests that intravenous aminophylline may be a promising therapy for patients in whom atropine is ineffective (Mader 2000).

Why it is important to do this review

Although reported cases of successful resuscitation with aminophylline generated enthusiasm for this therapy, little has changed with respect to its use in standard care in the last 20 years (Viskin 1993; Perouansky 1998; Lee 2000; Neumar 2010). The adult advanced cardiac life support (ACLS) guidelines in 2010 did not even mention aminophylline (Neumar 2010). To date, there have been no meta-analyses of randomised controlled trials on the use of aminophylline in bradyasystolic arrest. This systematic review of randomised controlled trials compares intravenous aminophylline with placebo in participants with bradyasystolic cardiac arrest to determine whether evidence is available to justify adopting aminophylline as a standard therapy in these patients. The low event rate (survival to hospital discharge) means that a large study or a large meta-analysis is needed to answer this question. We will update this study on an ongoing basis to find new studies.

OBJECTIVES

To determine the effects of aminophylline in the treatment of patients in bradyasystolic cardiac arrest, primarily survival to hospital discharge. We also considered survival to admission, return of spontaneous circulation, neurological outcomes and adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing intravenous aminophylline with the administration of placebo.

Types of participants

Adult participants (16 years of age or older) with non-traumatic, normothermic bradyasystolic cardiac arrest. Bradyasystole must have been present at the time of administration of aminophylline.

Types of interventions

Bradyasystole was defined as the absence of cardiac electrical activity as confirmed in more than one lead or pulseless electrical activity at a rate of fewer than 60 beats per minute. All interventions that compare intravenous aminophylline with placebo during resuscitation from bradyasystolic cardiac arrest were studied, in addition to standard ACLS. Depending on the preceding cardiac rhythms, standard care may include atropine, epinephrine, vasopressin or a combination of these. We did not analyse the

combinations of drugs administered along with aminophylline. However, we planned an a priori subgroup to assess whether aminophylline was administered early or late during resuscitation.

Types of outcome measures

Primary outcome.

- Survival to hospital discharge.

Secondary outcomes.

- Return of spontaneous circulation.
- Survival to hospital admission (survived event).
- Neurological outcome.
- Adverse events.

Survival to hospital discharge, survival to hospital admission and return of spontaneous circulation were defined according to the Utstein style guidelines and templates (Jacobs 2004).

Search methods for identification of studies

We carried out a comprehensive search to identify relevant trials, irrespective of language and publication status.

We initially searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (Issue 4, 2009), MEDLINE, EMBASE, CINAHL and LILACS on 26 November 2009 (Appendix 1; Hurley 2007; Hurley 2013). We performed new searches of CENTRAL, MEDLINE, EMBASE and CINAHL in November 2014 (Appendix 2). We also searched ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; <http://apps.who.int/trialsearch/>), using the terms 'cardiac arrest' OR 'asystole' OR 'bradysystole' as the condition and 'aminophylline' OR 'adenosine antagonist' as the intervention.

We used similar terms to search the grey literature through Google Scholar, the Canada Institute for Scientific and Technical Information (CISTI) Catalogue and the British Library Public Catalogue. We reviewed reference lists of all available primary studies and review articles to identify potentially relevant citations. We also contacted authors of primary studies to inquire about other published or unpublished trials known to them. We contacted scientific advisors for the pharmaceutical companies that manufacture aminophylline (Omega Laboratories and Hospira Healthcare Corporation) for any unpublished results on the use of aminophylline in asystolic arrest. Finally, we reviewed reference lists of relevant trials and review articles as well as conference proceedings from the Canadian Association of Emergency Physicians, the American College of Emergency Physicians, the Society for Academic Emergency Medicine and the American Heart Association (January 1997 to December 2012) and from the European Society of Cardiology (January 2005 to December 2012).

Data collection and analysis

Selection of studies

Two review authors (KFH, RG) screened the full list of titles and abstracts retrieved from the searches, selecting all trials that appeared relevant on the basis of title, abstract and MeSH headings. These two review authors independently reviewed the

full-text articles identified as potentially relevant to select trials for inclusion. We resolved disagreements by discussion or by third party adjudication (KM).

Data extraction and management

Two review authors (KFH, KM) independently extracted data from the trials and entered them into Review Manager 5 (RevMan 2014). Data extraction included the following items.

- Population: age, sex, aetiology of arrest, inclusion and exclusion criteria.
- Intervention: dose and time to administration of aminophylline.
- Control: definition of asystolic arrest, duration of resuscitation after administration of aminophylline, definition of neurological outcome.
- Outcome: return of spontaneous circulation, survival to admission, survival to discharge, neurological outcome, adverse outcomes.
- Design: method of randomisation.

Assessment of risk of bias in included studies

Two review authors (KFH, RG) assessed risk of bias using the criteria recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) (low risk, high risk, unclear).

- Selection: Was the assignment truly randomised? Was the allocation sequence concealed? (selection bias)
- Blinding: Were investigators, participants and caregivers unaware of the treatment assignment? (detection bias and performance bias)
- Losses to follow-up: Were all study participants accounted for and analyses carried out in an intention-to-treat fashion? (attrition bias)
- Reporting: Were all outcomes reported? (reporting bias)

We were not blinded to the identity of study authors or study results.

Measures of treatment effect

We combined data in RevMan 2014. For dichotomous variables, individual and pooled statistics were calculated as risk ratios (RRs) with 95% confidence intervals (CIs). We used a fixed-effect model for data synthesis and assessed heterogeneity using the Chi² test and the I² statistic (Higgins 2003). For continuous outcomes, we calculated individual and pooled statistics as mean differences (MDs) or standardised mean differences (SMDs) and 95% CIs using a random-effects model.

Assessment of reporting biases

We planned to carry out the statistical analyses on an intention-to-treat basis to deal with missing data from individual trials. The data were evaluated for publication bias using graphical and statistical methods. We checked for publication bias using a funnel plot. We assessed the effects of risk of bias in the included studies by using three criteria: method of assignment, blinding and losses to follow-up.

Subgroup analysis and investigation of heterogeneity

We planned two subgroup analyses: comparison of results based on early administration of aminophylline using five minutes as the cut-off point between early and late administration. With respect to use of Utstein style reporting, we considered explicit mention of Utstein style reporting in the study or in correspondence with study authors.

Sensitivity analysis

Where significant heterogeneity ($P < 0.1$) existed, we divided the groups based on our assessment of risk of bias (high versus low).

RESULTS

Description of studies

Results of the search

In our initial review in 2009, structured database searches yielded 285 records. Further online searches through Google and Google Scholar yielded an additional 21 records. After identifying and removing duplicates, we screened 264 records. We retrieved 22 articles for detailed review. Two authors excluded 14 articles: Nine

were Chinese papers that were reported to be randomised trials yet on further inquiry were found not to be prospectively designed (Meng 2001; Ma 2003; Dong 2006; Fu 2006; Jin 2006; Ma 2006; Xiao 2006; Shi 2007; Guo 2008); five articles reported mixed comparisons of aminophylline and epinephrine (Luo 2002; Wu 2002; Luo 2003; Shi 2008; Sun 2009). Two articles were conference abstracts reporting data that were also reported in full text (Mader 2003; Abu-Laban 2006). See details in our [Characteristics of excluded studies](#) table.

The updated search in November 2014 yielded 39 new records, all of which we screened and excluded. We did not retrieve any additional records for inclusion in this review update.

Five studies met inclusion criteria for this review (Mader 1997; Dirks 1999; Mader 1999; Mader 2003; Abu-Laban 2006). One study, published in abstract form only, is awaiting further classification (Snell 2000). Despite repeated attempts to make contact with its authors, we were unable to garner enough additional methodological information to include any of its data in this review.

See [Figure 1](#) for the study flow diagram.

Figure 1. Study flow diagram.

Included studies

We included data from five studies in this meta-analysis, summarising each study's particular features in the [Characteristics of included studies](#) table.

Setting

The five trials included only out-of-hospital arrests and took place in urban, prehospital settings in Canada (n = 971, one study), the United States (n = 215, three studies) and Germany (n = 68, one study). Two studies did not report the specific study period ([Mader 1997](#); [Dirks 1999](#)). The remaining studies were conducted from 1996 to 2003.

Participants

The studies focused on adult participants. [Abu-Laban 2006](#) excluded patients younger than 16 years, and each of Mader's studies excluded patients younger than 21 years ([Mader 1997](#); [Mader 1999](#); [Mader 2003](#)). [Dirks 1999](#) did not specify the exclusion criteria in his published abstract, although communications with the author confirm that the trial excluded patients younger than 16 years. All trials excluded patients with suspected traumatic or hypothermic cardiac arrests. Most studies also excluded patients who were pregnant, using theophylline, known to have hypersensitivity to methylxanthines or known to have liver disease. [Abu-Laban 2006](#) further excluded patients who had evidence of haemorrhage or were on renal dialysis.

Mean age of included participants ranged from 65 to 76.8 years. Females represented a minority (377/1186), although this varied from 28.5% in [Abu-Laban 2006](#) to 45% in [Mader 2003](#). [Dirks 1999](#) did not report these data.

Four studies reported data about the presumed cause of the cardiac arrest ([Dirks 1999](#); [Mader 1999](#); [Mader 2003](#); [Abu-Laban 2006](#)). Three studies reported that suspected ischaemic cardiac events were the most common cause of the arrest, ranging from 64% to 82% ([Dirks 1999](#); [Mader 1999](#); [Abu-Laban 2006](#)). [Mader 2003](#) reported their suspicion that 20.7% of participants had suffered a primary non-ischaemic cardiac event, but that most causes remained "uncertain."

Interventions

All trials compared the administration of IV aminophylline with placebo as an adjunct to standard ACLS resuscitation in bradycardic cardiac arrest. Four studies used 250 mg doses of aminophylline, and one study used 240 mg doses ([Dirks 1999](#)). Four studies required failure of standard ACLS interventions for one to two minutes before the study medication was administered. One study administered aminophylline along with initial doses of epinephrine and atropine ([Mader 1999](#)). Mean time to arrival of the paramedic crew ranged from 5.3 to 9.3 minutes. Because of differences in reporting, it is difficult to comment on the time from the event to administration of aminophylline, although the time from arrival of paramedics to administration of aminophylline ranged from 11 to 16.6 minutes ([Mader 1997](#); [Dirks 1999](#); [Abu-Laban 2006](#)).

Risk of bias in included studies

The assessed risk of bias for each study is detailed in the [Characteristics of included studies](#) table. In general, the included studies were well-designed randomised, placebo-controlled trials. Random sequence generation was aided by computer ([Abu-Laban 2006](#)) or by an investigational drug service ([Mader 1997](#); [Mader 1999](#); [Mader 2003](#)). Use of matched syringes, provided by a third party, assisted with both blinding and allocation concealment ([Mader 1997](#); [Mader 1999](#); [Mader 2003](#); [Abu-Laban 2006](#)). Risks of performance bias, detection bias and attrition bias were low for four studies ([Mader 1997](#); [Mader 1999](#); [Mader 2003](#); [Abu-Laban 2006](#)). The degree of risk associated with randomisation, allocation, blinding and incomplete outcomes data for [Dirks 1999](#) remains 'unclear' because the details about study methodology that were available in the published abstract and in the poster provided by the study's lead author were minimal. Further details about methodology could not be obtained from the study's lead author despite repeated attempts to make contact by email. The risk of selective reporting bias was deemed to be low in all studies ([Mader 1997](#); [Dirks 1999](#); [Mader 1999](#); [Mader 2003](#); [Abu-Laban 2006](#)) because each study reported the outcomes expected from a cardiac arrest study, namely, return of spontaneous circulation, survival to admission, survival to discharge and neurological outcomes. See [Figure 2](#) and [Figure 3](#) for a summary of risk of bias.

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.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias): All outcomes	Incomplete outcome data (attrition bias): All outcomes	Selective reporting (reporting bias)
Abu-Laban 2006	+	+	+	+	+
Dirks 1999	?	?	?	?	+
Mader 1997	+	+	+	+	+
Mader 1999	+	+	+	+	+
Mader 2003	+	+	+	+	+

Effects of interventions

See: [Summary of findings 1 Aminophylline compared to placebo for bradysystolic cardiac arrest in adults](#)

Few disagreements arose between review authors (KFH, RG) in assessing studies for inclusion, assessing risk of bias or extracting data, and they were readily resolved by discussion to reach consensus. With only five studies included in this systematic review,

it is difficult to draw conclusions regarding the funnel plot. For example, only two studies included participants who experienced the primary outcome (survival to hospital discharge). The funnel plot for 'return of spontaneous circulation' was asymmetrical, possibly suggesting a publication bias ([Figure 4](#)). It is unlikely that smaller studies whose results favoured placebo would have significantly affected the pooled results of this analysis. All results discussed below are given as pooled RR and its 95% CI for aminophylline versus placebo.

Figure 4. Funnel plot of comparison: 1 Aminophylline versus placebo, outcome: 1.2 Return of spontaneous circulation.

Survival to discharge

All studies (including 1254 participants) reported survival to hospital discharge—the primary outcome. These findings were homogeneous ($\text{Chi}^2 = 0.08$, degrees of freedom (df) = 1, $P = 0.77$). This event was rare, with only six survivors in total. We are reporting the analyses using a fixed-effect model. As seen in [Analysis 1.1](#), aminophylline was found to have no effect (RR 0.58, 95% CI 0.12 to 2.74). No change in the results was noted when a random-effects model was used. [Dirks 1999](#) reported that their lone survivor was still alive at six months postevent. Four survivors in [Abu-Laban 2006](#) were still alive at one year, and one refused follow-up after discharge from the hospital.

Survival to admission

Data on the secondary outcome—survival to hospital admission—were found to be homogeneous ($\text{Chi}^2 = 2.73$, df = 3, $P = 0.43$). Analysis showed that aminophylline had no effect on this secondary survival outcome ([Analysis 1.3](#): RR 0.92, 95% CI 0.61 to 1.39).

Return of spontaneous circulation

Data on return of spontaneous circulation were also found to be homogeneous ($\text{Chi}^2 = 2.41$, df = 4, $P = 0.66$). Analysis showed that aminophylline had no effect on return of spontaneous circulation ([Analysis 1.2](#): RR 1.15, 95% CI 0.89 to 1.49).

Neurologic outcome

Data about neurological outcomes were limited. [Abu-Laban 2006](#) reported that all five survivors had "excellent neurological and functional outcomes", and [Dirks 1999](#) did not comment about the neurological status of the lone survivor in their study.

Adverse events

None of the trials reported adverse events ([Mader 1997](#); [Dirks 1999](#); [Mader 1999](#); [Mader 2003](#); [Abu-Laban 2006](#)). However, none of the data reporting schema that we reviewed specifically mentioned 'adverse events' as an outcome.

Subgroup analysis

We performed a subgroup analysis on the basis of whether aminophylline was administered early in the resuscitation, using five minutes as the cut-off point. We used data from two studies in this analysis. [Abu-Laban 2006](#) provided raw study data, and we pulled relevant published data from [Mader 1997](#) for an accumulated total of 37 participants. In this small sample of participants, no one survived to hospital discharge ([Analysis 1.4](#)). Three participants survived to admission ([Analysis 1.5](#)), and 11 had return of spontaneous circulation ([Analysis 1.6](#)). We did not find benefit derived from the use of aminophylline in this subgroup analysis. Subgroup data from the other studies were not available.

Sensitivity analysis

The results were unchanged ([Analysis 1.7](#); [Analysis 1.8](#); [Analysis 1.9](#)) when we only selectively pooled data taken from studies with low risk of bias ([Mader 1997](#); [Mader 1999](#); [Mader 2003](#); [Abu-Laban 2006](#)).

DISCUSSION

Summary of main results

This systematic review did not find a survival benefit for the administration of IV aminophylline during adult, out-of-hospital bradysystolic arrest. We did not find statistically significant heterogeneity between studies. Overall, the studies were well designed and the assessed risk of bias was low. Only [Abu-Laban 2006](#) was adequately powered to detect a significant difference in event rates for the primary outcome (return of spontaneous circulation). Because return of spontaneous circulation is a precursor to other survival outcomes, and our analysis demonstrated no significant benefit of aminophylline for this outcome, it is reasonable to conclude that a larger study is unlikely to demonstrate significant survival benefit. Nonetheless, no study was powered to detect a significant difference in our primary outcome—survival to hospital discharge. Given the relative rarity of survival to hospital admission ([Analysis 1.3](#)) and survival to hospital discharge ([Analysis 1.1](#)), drawing conclusions about neurological status and adverse events is problematic as well.

Because the studies included in this review took place in the prehospital setting, the duration of arrest before administration of aminophylline was significant, with mean times from paramedic arrival to administration of study drug as long as 16 minutes ([Mader 1997](#); [Abu-Laban 2006](#)). The subgroup analysis considered the effects of early administration of aminophylline but included only 37 participants with no survivors to hospital discharge (primary outcome). [Mader 1999](#) looked specifically at early administration, with mean times (from diagnosis of asystole to administration of study drug) less than five minutes. However, the mean time from dispatch to arrival to the scene in this population, where 49% of arrests were witnessed, was 6.5 minutes, suggesting that the duration of arrest before aminophylline exceeded ten minutes for most participants. This study accumulated 82 participants, none of whom survived. Hence, the effect of early administration of aminophylline remains unknown.

The unadjusted survival for adult out-of-hospital cardiac arrest in a large population-based registry was 4.9% ([Hasegawa 2013](#)). Patients presenting in 'unshockable' rhythms such as asystole and pulseless electrical activity typically have a poorer prognosis ([Thomas 2013](#)). The survival rate in this meta-analysis, which is derived primarily from a large Canadian study ([Abu-Laban 2006](#)), is in keeping with other published Canadian data ([Steill 2004](#);

[Vaillancourt 2004](#)). Survival from in-hospital adult asystolic arrest appears to be in the range of 10%, with good neurological outcomes reported in 61% of survivors ([Morrison 2013](#)). The improved survival in this population may be attributable, in part, to the rapid onset of resuscitative efforts when a patient suffering a cardiac arrest is both monitored and witnessed ([Brady 2011](#)). Although 73% of in-hospital arrests are both monitored and witnessed, out-of-hospital arrests are witnessed by a health care provider in fewer than 9% of cases ([Brady 2011](#); [Hasegawa 2013](#)). Use of aminophylline has not been studied in the 'in-hospital' cardiac arrest population.

Because of our search strategy, we recovered a number of Chinese language studies, most of which were found through extensive searching in Google and Google Scholar. Some studies have noted the poor quality of reporting of randomised controlled trials in leading medical journals and conference proceedings in China ([Xu 2008](#); [Duan 2009](#); [Chen 2010](#)). One study found that only 6.8% of apparent randomised controlled trials in China were authentic randomised controlled trials ([Wu 2009](#)). We asked the lead author of that study to assess whether the 'apparent' randomised controlled trials that we identified were 'authentic' and found that nine of them were not prospectively designed ([Meng 2001](#); [Ma 2003](#); [Dong 2006](#); [Fu 2006](#); [Jin 2006](#); [Ma 2006](#); [Xiao 2006](#); [Shi 2007](#); [Guo 2008](#)). None of the trials based in China met the criteria to be included in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Although the mechanistic investigations and early case reports were promising, available data from well-designed randomised controlled trials do not warrant the addition of intravenous aminophylline to standard advanced cardiac life support algorithms for out-of-hospital bradysystolic arrest at this time.

Implications for research

Further research on administration of aminophylline in prehospital bradysystolic arrest may not be justified. The low event rate for important outcomes such as survival to discharge dictates the need for larger trials to detect a difference. The data on use of aminophylline early in resuscitative efforts are not adequate to show whether it is effective. Future research directed towards a more carefully selected population of participants, in whom witnessed arrest occurs during prehospital care or in another health care setting where aminophylline can be administered quickly, may more aptly demonstrate its potential.

ACKNOWLEDGEMENTS

The review authors would like to thank Dr Taixiang Wu of the Chinese Cochrane Centre for assisting us in assessing the 'apparent' randomised controlled trials that we found.

REFERENCES

References to studies included in this review

Abu-Laban 2006 {published and unpublished data}

Abu-Laban RB, McIntyre CM, Christenson JM, Van Beek CA, Innes GD, O'Brien R, et al. Aminophylline in bradysystolic cardiac arrest: a randomized placebo-controlled trial. *Academic Emergency Medicine* 2004;**11**(5):435.

* Abu-Laban RB, McIntyre CM, Christenson JM, Van Beek CA, Innes GD, O'Brien RK, et al. Aminophylline in bradysystolic cardiac arrest: a randomised placebo-controlled trial. *The Lancet* 2006;**367**(9522):1577-84. [PMID: 16698410]

Dirks 1999 {published and unpublished data}

Dirks B, Lindner K. Randomized comparison using aminophylline vs. placebo patients in out-of-hospital cardiac arrest with asystole or pulseless electrical activity. *Circulation* 1999;**100**(18 Suppl I):I-314.

Mader 1997 {published data only (unpublished sought but not used)}

Mader TJ, Gibson P. Adenosine receptor antagonism in refractory asystolic cardiac arrest: results of a human pilot study. *Resuscitation* 1997;**35**(1):3-7. [PMID: 9259053]

Mader 1999 {published data only (unpublished sought but not used)}

Mader TJ, Smithline HA, Gibson P. Aminophylline in undifferentiated out-of-hospital asystolic cardiac arrest. *Resuscitation* 1999;**41**(1):39-45. [PMID: 10459591]

Mader 2003 {published data only (unpublished sought but not used)}

Mader TJ, Durkin LJ, Smithline HA, Stevens M. Aminophylline in atropine-resistant asystolic out-of-hospital cardiac arrest. *Academic Emergency Medicine* 2002;**9**(5):357.

* Mader TJ, Smithline HA, Durkin L, Scriver G. A randomized controlled trial of intravenous aminophylline for atropine-resistant out-of-hospital asystolic cardiac arrest. *Academic Emergency Medicine* 2003;**10**(3):192-7. [PMID: 12615581]

References to studies excluded from this review

Dong 2006 {published data only}

Dong L, Jiang J. Clinical study of aminophylline on the treatment of cardiac arrest patient who are invalid with epinephrine. *Practical Clinical Medicine* 2006;**7**(10):33-5. Chinese.

Fu 2006 {published data only}

Fu XH, Zhou GP, Zhu QY, Ma B, Chen C. A clinical survey for aminophylline and epinephrine for 30 patients with cardiac arrest. *Jiangxi Medicine* 2006;**41**(12):981-2. Chinese.

Guo 2008 {published data only}

Guo XF. Effective observation on treatment of 30 cases with respiratory and cardiac arrest by aminophylline. *Journal of*

Henan University of Science & Technology: Medical Science 2008;**26**(1):32-3. Chinese.

Jin 2006 {published data only}

Jin RH, Ma SZ, Li QL. Clinical research on joined application with aminophylline in early period of cardiac arrest. *Lingnan Journal of Emergency Medicine* 2006;**11**(3):161-2. Chinese.

Luo 2002 {published data only}

Luo ZC, Ling ZX, Wang PF. Study on administration of epinephrine combined with vasopressin and aminophylline during cardiopulmonary resuscitation. *Modern Medical and Health* 2002;**18**(3):170-1. Chinese.

Luo 2003 {published data only}

Luo JL, Wang CT, Pan J, An ZQ. Clinical application of ultra-routine dose epinephrine associated with aminophylline in the patients with cardiac arrest. *Modern Medical and Health* 2003;**19**(12):1529-30.

Ma 2003 {published data only}

Ma Y, Meng QY, Qian YY, Zhizhong W, Tong G, Jinming L. Clinical effect of aminophylline associating with epinephrine on the treatment of cardiac arrest. *Chinese Journal of Critical Care Medicine* 2003;**23**(4):232-3. Chinese.

Ma 2006 {published data only}

Ma SZ, Jin RH, Zhang YM. Patients with cardiac arrest early in conjunction with aminophylline and epinephrine effect. *Practical Clinical Medicine* 2006;**7**(5):42-3. Chinese.

Meng 2001 {published data only}

Meng QY, Lai H, Lai SH. Resuscitation using aminophylline in cardiac arrest refractory to epinephrine and atropine: results of a 32 patient study. *Canadian Journal of Cardiology* 2001;**17**(11 Suppl C):210C.

Shi 2007 {published data only}

Shi QB, Huang X, Zhang FX, Wang SY, Wang GE, Sun GL. The application value study of the aminophylline and epinephrine with uniform method at the same time and rapidly combination on cardiopulmonary resuscitation. *China Journal of Postgraduate Medicine* 2007;**30**(1):18-21. Chinese.

Shi 2008 {published data only}

Shi QB, Zhang FX, Wang GE, Jiang FZ, Xu YS, Huang X. Study on the value of the formula of rapid synchronous stepwise increase in dosage of epinephrine combined with aminophylline (7 mg/kg) in cardiopulmonary resuscitation. *Chinese Critical Care Medicine* 2008;**20**(7):409. Chinese. [PMID: 18611339]

Sun 2009 {published data only}

Sun Y. Clinical study on rapidly and synchronously using epinephrine in combination with aminophylline for patients undergoing cardiopulmonary resuscitation. *Chinese Nursing Research* 2009;**23**(2):322-5. Chinese.

Wu 2002 {published data only}

Wu B, Wang J, Hou Z. Study on administration of epinephrine combined with vasopressin and aminophylline during cardiopulmonary resuscitation. *Modern Medicine Health* 2002;**18**(3):170-2. Chinese.

Xiao 2006 {published data only}

Xiao Z, Liu JM, Zhuang JY. The curative effect of epinephrine and aminophylline on cardiopulmonary resuscitation in patients with cardiac arrest onset out of hospital. *Medicine World* 2006;**8**:148-50. Chinese.

References to studies awaiting assessment

Snell 2000 {published data only}

Snell CS, DuPont AM, Niezgodna JA, Cormier S. Aminophylline as an adjunctive therapy to advanced cardiac life support in pre-hospital cardiac arrest. *Academic Emergency Medicine* 2000;**7**(5):509.

Additional references

Belardinelli 1989

Belardinelli L, Linder J, Berne R. The cardiac effects of adenosine. *Progress in Cardiovascular Disease* 1989;**32**(1):73-97.

Belardinelli 1995

Belardinelli L, Shryock JC, Song Y, Wang D, Srinivas M. Ionic basis of the electrophysiological actions of adenosine on cardiomyocytes. *FASEB Journal* 1995;**9**(5):359-65.

Brady 2011

Brady WJ, Gurka KK, Mehning B, Peberdy MA, O'Connor RE, American Heart Association's Get with the Guidelines (formerly, NRCPR) Investigators. In-hospital cardiac arrest: impact of monitoring and witnessed event on patient survival and neurologic status at hospital discharge. *Resuscitation* 2011;**82**(7):845-52. [DOI: [10.1016/j.resuscitation.2011.02.028](https://doi.org/10.1016/j.resuscitation.2011.02.028)]

Chen 2010

Chen Y, Li J, Ai C, Duan Y, Wang L, Zhang M, Hopewell S. Assessment of the quality of reporting in abstracts of randomized controlled trials published in five leading Chinese medical journals. *PLoS One* 2010;**5**(8):e11926.

Cummins 1991

Cummins RO, Chamberlain DA, Abramson NS, Allen M, Baskett P, Becker L, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. Task Force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. *Annals of Emergency Medicine* 1991;**20**(8):861-74.

Cummins 1997

Cummins RO, Chamberlain D, Hazinski MF, Nadkarni V, Kloeck W, Kramer E, et al. Recommended guidelines for reviewing, reporting, and conducting research on in-hospital resuscitation: the in-hospital "Utstein style." American Heart

Association.. *Annals of Emergency Medicine* 1997;**29**(5):650-79. [MEDLINE: PMID: 9140252]

Dobson 1983

Dobson J. Adenosine reduces catecholamine contractile responses in oxygenated and hypoxic atria. *American Journal of Physiology* 1983;**245**:H468-74.

Duan 2009

Duan Y, Li J, Ai C, Chen Y, Chen P, Zhang M, Hopewell S. Quality of trials reported as conference abstracts in China: how well are they reported? *International Journal of Technology Assessment in Health Care* 2009;**25**(4):479-84.

Hasegawa 2013

Hasegawa K, Tsugawa Y, Camargo CA Jr, Hiraide A, Brown DF. Regional variability in survival outcomes of out-of-hospital cardiac arrest: the All-Japan Utstein Registry. *Resuscitation* 2013;**84**(8):1099-107. [DOI: [10.1016/j.resuscitation.2013.03.007](https://doi.org/10.1016/j.resuscitation.2013.03.007)]

Herlitz 1994

Herlitz J, Ekstrom L, Wennerblom B, Axelsson A, Bang A, Holmberg S. Predictors of early and late survival after out-of-hospital cardiac arrest in which asystole was the first recorded arrhythmia on scene. *Resuscitation* 1994;**24**:27-36.

Higgins 2003

Higgins JP, Thompson SG, Deek JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* 5.1.0 [updated March 2011]. Chichester, UK: John Wiley & Sons, Ltd, 2011.

Jacobs 2004

Jacobs I, Nadkarni V, Bahr J, Berg RA, Billi JE, Bossaert L, et al. Cardiac arrest and cardiopulmonary resuscitation outcome reports: update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the international liaison committee on resuscitation (American Heart Association, European Resuscitation Council, Australian Resuscitation Council, New Zealand Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa). *Resuscitation* 2004;**63**(3):233-49. [MEDLINE: PMID: 15582757]

Kette 1998

Kette F, Sbrojavacca R, Rellini G, Tosolini G, Capasso M, Arcidiacono D, et al. Epidemiology and survival rate of out-of-hospital cardiac arrest in north-east Italy: the F.A.C.S. study. Friuli Venezia Giulia Cardiac Arrest Cooperative Study. *Resuscitation* 1998;**36**(3):153-9.

Lee 2000

Lee CC, Dill CE, Carter WA. Restoration of spontaneous circulation from asystole with aminophylline. *American Journal of Emergency Medicine* 2000;**18**(3):350-1.

Mader 2000

Mader TJ, Bertolet B, Ornato JP, Gutterman JM. Aminophylline in the treatment of atropine-resistant bradysystole. *Resuscitation* 2000;**47**(2):105-12.

Malcolm 1993

Malcolm AD, Garratt CJ, Camm AJ. The therapeutic and diagnostic cardiac electrophysiological uses of adenosine. *Cardiovascular Drugs and Therapy* 1993;**7**:139-47.

Morrison 2013

Morrison LJ, Neumar RW, Zimmerman JL, Link MS, Newby LK, McMullan PW Jr, et al, American Heart Association Emergency Cardiovascular Care Committee, Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Strategies for improving survival after in-hospital cardiac arrest in the United States: 2013 consensus recommendations. A consensus statement from the American Heart Association. *Circulation* 2013;**127**(14):1538-63. [DOI: [10.1161/CIR.0b013e31828b2770](https://doi.org/10.1161/CIR.0b013e31828b2770)]

Neumar 2010

Neumar RW, Otto CW, Link MS, Kronick SL, Shuster M, Callaway CW, Kudenchuk PJ, Ornato JP, McNally B, Silvers SM, Passman RS, White RD, Hess EP, Tang W, Davis D, Sinz E, Morrison LJ. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 2010;**122**(18 Suppl 3):S729-67.

Perouansky 1998

Perouansky M, Shamir M, Hershkowitz E, Donchin Y. Successful resuscitation using aminophylline in refractory cardiac arrest with asystole. *Resuscitation* 1998;**38**(1):39-41.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Rudusky 2005

Rudusky BM. Aminophylline: exploring cardiovascular benefits versus medical malcontent. *Angiology* 2005;**56**(3):295-304.

Schrader 1977

Schrader J, Baumann G, Gerlach E. Adenosine as an inhibitor of myocardial effects of catecholamines. *Pflugers Archives - European Journal of Physiology* 1977;**372**(1):29-35.

Sedgwick 1994

Sedgwick ML, Dalziel K, Watson J, Carrington DJ, Cobbe SM. The causative rhythm in out-of-hospital cardiac arrests witnessed by the emergency medical services in the Heartstart Scotland Project. *Resuscitation* 1994;**27**(1):55-9.

Stiell 2004

Stiell IG, Wells GA, Field B, Spaite DW, Nesbitt LP, De Maio VJ, et al, Ontario Prehospital Advanced Life Support Study Group.

Advanced cardiac life support in out-of-hospital cardiac arrest. *New England Journal of Medicine* 2004;**351**(7):647-56.

Thomas 2013

Thomas AJ, Newgard CD, Fu R, Zive DM, Daya MR. Survival in out-of-hospital cardiac arrests with initial asystole or pulseless electrical activity and subsequent shockable rhythms. *Resuscitation* 2013;**84**(9):1261-6. [DOI: [10.1016/j.resuscitation.2013.02.016](https://doi.org/10.1016/j.resuscitation.2013.02.016)]

Vaillancourt 2004

Vaillancourt C, Stiell IG, Canadian Cardiovascular Outcomes Research Team. Cardiac arrest care and emergency medical services in Canada. *Canadian Journal of Cardiology* 2004;**20**(11):1081-90.

Visentin 1990

Visentin S, Wu SN, Belardinelli L. Adenosine-induced changes in atrial action potential: contribution of Ca and K currents. *American Journal of Physiology* 1990;**258**(4 Pt 2):H1070-8.

Viskin 1993

Viskin S, Belhassen B, Roth A, Reicher M, Averbuch M, Sheps D, et al. Aminophylline for bradysystolic cardiac arrest refractory to atropine and epinephrine. *Annals of Internal Medicine* 1993;**118**(4):279-81.

Wesley 1989

Wesley RJ, Belardinelli L. Role of endogenous adenosine in postdefibrillation bradyarrhythmia and hemodynamic depression. *Circulation* 1989;**80**(1):128-37.

Wu 2009

Wu T, Li Y, Bian Z, Liu G, Moher D. Randomized trials published in some Chinese journals: how many are randomized? *Trials* 2009;**10**:46.

Xu 2008

Xu L, Li J, Zhang M, Ai C, Wang L. Chinese authors do need CONSORT: reporting quality assessment for five leading Chinese medical journals. *Contemporary Clinical Trials* 2008;**29**(5):727-31.

References to other published versions of this review

Hurley 2007

Hurley K, Magee K, Green R. Aminophylline for bradysystolic cardiac arrest in adults (Protocol). *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No: CD006781. [DOI: [10.1002/14651858.CD006781](https://doi.org/10.1002/14651858.CD006781)]

Hurley 2013

Hurley KF, Magee K, Green R. Aminophylline for bradysystolic cardiac arrest in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No: CD006781. [DOI: [10.1002/14651858.CD006781.pub2](https://doi.org/10.1002/14651858.CD006781.pub2)]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abu-Laban 2006

Study characteristics		
Methods	Randomised controlled trial Time frame: January 21, 2001 to September 3, 2003	
Participants	Setting: urban EMS system serving population of > 2 million Country: Canada Cause of arrest: presumed (by the paramedic) cardiac in 799 (82.3%) and drug overdose in 80 (8.2%) Control arm — 485 participants Mean age: 65.8 (SD: 17.6) years Sex: 30.7% female Intervention arm — 486 participants Mean age: 65.4 (SD: 17.4) years Sex: 26.3% female	
Interventions	Aminophylline 250 mg IV followed by 10 mL normal saline flush. If the participant remained pulseless and in bradycardia after 90 seconds, a second dose of aminophylline could be administered. Timing: Endotracheal intubation, ventilation with 100% oxygen and appropriate initial ACLS pharmacotherapy (atropine 3 mg and epinephrine 1 mg) had to be carried out without improvement in cardiac rhythm before aminophylline or placebo was administered	
Outcomes	Primary outcome: return of spontaneous circulation Other outcomes considered in this review. <ul style="list-style-type: none">Survival to hospital admission.Survival to hospital discharge.Neurological outcomes: Glasgow Coma Scale, Glasgow-Pittsburgh Cerebral and Overall Performance Scales, Modified Mini-Mental State Exam, Functional Status Questionnaire.	
Notes	Data collected according to Utstein style Mean time from arrival of paramedic crew to administration of aminophylline: 14.5 minutes Mean time from arrival of paramedic crew to administration of placebo: 14.8 minutes	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done by computer"
Allocation concealment (selection bias)	Low risk	Study drug kits were prepared by a third party (Abbott Laboratories) and were distributed to "each ambulance station in batches of eight, and carried on ambulances in batches of two"

Abu-Laban 2006 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	"Study personnel and investigators, caregivers, patients, and their families remained blinded throughout the study period"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	—

Dirks 1999

Study characteristics

Methods	Randomised controlled trial Time frame: not reported
Participants	Setting: urban EMS system serving population of 188,800 Country: Germany Cause of arrest: cardiac in 19 (61.3%) participants in the aminophylline group and in 24 (64.9%) participants in the control group Control arm — 37 participants Mean age: not reported Sex: not reported Intervention arm — 31 participants Mean age: not reported Sex: not reported
Interventions	Aminophylline 240 mg IV Timing: Cardiopulmonary resuscitation (CPR) and appropriate initial ACLS pharmacotherapy (epinephrine 1 mg) had to be carried out without improvement in cardiac rhythm before administration of aminophylline or placebo. Endotracheal intubation, atropine 3 mg and repeated doses of epinephrine were carried out afterwards, if needed
Outcomes	Primary outcome: return of spontaneous circulation Other outcomes considered in this review. <ul style="list-style-type: none">• Survival to hospital admission.• Survival to hospital discharge.
Notes	Data collected according to Utstein style Median time from arrival of paramedic crew to administration of aminophylline: 11 minutes Median time from arrival of paramedic crew to administration of placebo: 15 minutes

Risk of bias

Aminophylline for bradysystolic cardiac arrest in adults (Review)

Dirks 1999 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported in the abstract/poster
Allocation concealment (selection bias)	Unclear risk	Not reported in the abstract/poster
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as "double-blind" but the means of blinding are not reported in the abstract/poster
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported in the abstract/poster
Selective reporting (reporting bias)	Low risk	—

Mader 1997

Study characteristics	
Methods	Randomised controlled trial Time frame: 6 months
Participants	Setting: moderate-sized urban EMS system Country: USA Cause of arrest: not specified Control arm — 8 participants Mean age: 67.5 years Median age: 72.5 years Sex: 25% female Intervention arm — 14 participants Mean age: 76.8 years Median age: 78.5 years Sex: 42.8% female
Interventions	Aminophylline 250 mg IV Timing: appropriate initial ACLS pharmacotherapy (atropine 1 mg and epinephrine 1 mg) had to be carried out without improvement in cardiac rhythm for at least 1 minute before administration of aminophylline or placebo
Outcomes	Primary outcome: return of spontaneous circulation
Notes	The authors did not specify data collection according to Utstein style

Aminophylline for bradycardic cardiac arrest in adults (Review)

Mader 1997 (Continued)

Mean time from arrival of paramedic crew to administration of aminophylline: 16.6 minutes

Mean time from arrival of paramedic crew to administration of placebo: 13.1 minutes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was provided by the investigational drug service"
Allocation concealment (selection bias)	Low risk	"Drug randomization for a given patient was determined by the contents of the syringe assigned to the code bag in the ambulance responding to the call"
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators, caregivers, participants and their families remained blinded throughout the study period. Participants who did not meet inclusion criteria were prospectively excluded from the study (before unblinding)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	—

Mader 1999
Study characteristics

Methods	Randomised controlled trial Time frame: June 1996 to August 1997
Participants	Setting: urban EMS system Country: USA Control arm—45 participants Mean age: 70 years (95% CI 65 to 75) Sex: 36% female Cause of arrest: primary ischaemic cardiac event suspected in 35 (77.8%) Intervention arm—37 participants Mean age: 66 years (95% CI 61 to 71) Sex: 51% female Cause of arrest: primary ischaemic cardiac event suspected in 31 (83.8%)
Interventions	Aminophylline 250 mg IV Timing: Aminophylline or placebo was administered along with appropriate initial ACLS pharmacotherapy (atropine and epinephrine)

Mader 1999 (Continued)

Outcomes	<p>Primary outcome: return of spontaneous circulation</p> <p>Other outcomes considered in this review.</p> <ul style="list-style-type: none"> • Survival to hospital admission • Survival to hospital discharge
Notes	<p>The authors did not specify data collection according to Utstein style, although the 1991 guidelines are cited in the discussion</p> <p>Mean time from diagnosis of asystole to administration of aminophylline: 4.9 minutes</p> <p>Mean time from diagnosis of asystole to administration of placebo: 4.6 minutes</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation was provided by the Baystate Medical Center investigational drug service
Allocation concealment (selection bias)	Low risk	"Aminophylline and placebo were kept in serially numbered identical prefilled single dose syringes"
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators, caregivers, participants and their families remained blinded throughout the study period
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	—

Mader 2003
Study characteristics

Methods	<p>Randomised controlled trial</p> <p>Time frame: February 1999 to August 2000</p>
Participants	<p>Setting: urban EMS system serving population of 250,000</p> <p>Country: USA</p> <p>Cause of arrest: 'uncertain' in most cases</p> <p>Control arm — 45 participants</p> <p>Mean age: 67 years (95% CI 62 to 72)</p> <p>Sex: 36% female</p> <p>Intervention arm — 66 participants</p> <p>Mean age: 65 years (95% CI 61 to 68)</p>

Mader 2003 (Continued)

Sex: 51% female

Interventions	Aminophylline 250 mg IV Timing: Appropriate initial ACLS pharmacotherapy (atropine and epinephrine) had to be carried out without improvement in cardiac rhythm for at least 2 minutes before aminophylline or placebo was administered
Outcomes	Primary outcome: return of spontaneous circulation Other outcomes considered in this review. <ul style="list-style-type: none">• Survival to hospital admission.• Survival to hospital discharge.
Notes	Data on return of spontaneous circulation collected according to Utstein style Mean time from diagnosis of asystole to administration of aminophylline: 7.2 minutes Mean time from diagnosis of asystole to administration of placebo: 6.7 minutes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was provided by the Baystate Medical Center investigational drug service. "A single allocation sequence was constructed using a permuted block design with a blocking factor of four."
Allocation concealment (selection bias)	Low risk	A third party prepared "identically appearing pre-filled syringes of aminophylline and placebo and sequentially numbered them according to the allocation sequence. Each ambulance was stocked with the study syringe, which was replaced with the next sequentially numbered syringe after it was used."
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators, caregivers, participants and their families remained blinded throughout the study period
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	—

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Dong 2006	No prospective design of protocol
Fu 2006	No prospective design of protocol
Guo 2008	No prospective design of protocol
Jin 2006	No prospective design of protocol

Aminophylline for bradyasystolic cardiac arrest in adults (Review)

Study	Reason for exclusion
Luo 2002	Mixed comparison of epinephrine (control) with epinephrine, vasopressin and aminophylline (intervention)
Luo 2003	Mixed comparison of epinephrine (control) with higher doses of epinephrine combined with aminophylline (intervention)
Ma 2003	No prospective design of protocol
Ma 2006	No prospective design of protocol
Meng 2001	No prospective design of protocol
Shi 2007	No prospective design of protocol
Shi 2008	Mixed comparison using escalating doses of epinephrine combined with aminophylline
Sun 2009	Study population unclear (not specified beyond 'cardiac arrest'. Mixed comparison of standard dose epinephrine, high dose epinephrine and standard dose epinephrine in conjunction with simultaneous administration of aminophylline. No placebo apparent
Wu 2002	Mixed comparison of epinephrine (control) with epinephrine, vasopressin and aminophylline (intervention)
Xiao 2006	No prospective design of protocol

Characteristics of studies awaiting classification *[ordered by study ID]*

[Snell 2000](#)

Methods	Randomised controlled trial Time frame: 18 months
Participants	Setting: prehospital, community setting Country: USA Cause of arrest: not reported Control arm — 36 participants Mean age: not reported Sex: not reported Intervention arm — 36 participants Mean age: not reported Sex: not reported
Interventions	Aminophylline 250 mg IV Timing: administered in addition to standard ACLS therapy, after the initial dose of epinephrine
Outcomes	Primary outcomes: return of spontaneous circulation and survival to ICU admission

Snell 2000 (Continued)

Notes

Published in abstract form only (conference proceedings)

"Eligible patients included adults in non-traumatic cardiopulmonary arrest with an arrhythmia requiring epinephrine by ACLS protocol."

The authors do not specify the types of cardiac rhythms that were considered eligible for study enrolment. All pulseless rhythms may be treated with epinephrine. We suspect that a subset of the participants in this study would fit our population of interest (those with bradysystole). We were not able to get more information or study data from the authors.

DATA AND ANALYSES

Comparison 1. Aminophylline vs. placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Survival to hospital discharge	5	1254	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.12, 2.74]
1.2 Return of spontaneous circulation	5	1254	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.89, 1.49]
1.3 Survival to admission	5	1254	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.61, 1.37]
1.4 Early administration of aminophylline: Survival to hospital discharge	2	37	Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5 Early administration of aminophylline: Survival to hospital admission	2	37	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.02, 2.36]
1.6 Early administration of aminophylline: Return of spontaneous circulation	2	37	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [0.38, 6.77]
1.7 Sensitivity analysis: survival to discharge	4	1186	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.11, 3.99]
1.8 Sensitivity analysis: survival to admission	4	1186	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.52, 1.25]
1.9 Sensitivity analysis: return of spontaneous circulation	4	1186	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.86, 1.48]

Analysis 1.1. Comparison 1: Aminophylline vs. placebo, Outcome 1: Survival to hospital discharge

Analysis 1.2. Comparison 1: Aminophylline vs. placebo, Outcome 2: Return of spontaneous circulation

Analysis 1.3. Comparison 1: Aminophylline vs. placebo, Outcome 3: Survival to admission

Analysis 1.4. Comparison 1: Aminophylline vs. placebo, Outcome 4: Early administration of aminophylline: Survival to hospital discharge

Study or Subgroup	Aminophylline		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Abu-Laban 2006	0	14	0	17		Not estimable	
Mader 1997	0	3	0	3		Not estimable	
Total (95% CI)		17		20		Not estimable	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

Analysis 1.5. Comparison 1: Aminophylline vs. placebo, Outcome 5: Early administration of aminophylline: Survival to hospital admission

Study or Subgroup	Aminophylline		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Abu-Laban 2006	0	14	2	17	62.6%	0.21 [0.01, 4.84]	
Mader 1997	0	3	1	3	37.4%	0.24 [0.01, 8.62]	
Total (95% CI)		17		20	100.0%	0.22 [0.02, 2.36]	
Total events:	0		3				
Heterogeneity: Chi ² = 0.00, df = 1 (P = 0.96); I ² = 0%							
Test for overall effect: Z = 1.25 (P = 0.21)							
Test for subgroup differences: Not applicable							

Analysis 1.6. Comparison 1: Aminophylline vs. placebo, Outcome 6: Early administration of aminophylline: Return of spontaneous circulation

Study or Subgroup	Aminophylline		Placebo		Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
	Events	Total	Events	Total			
Abu-Laban 2006	4	14	4	17	88.6%	1.30 [0.26, 6.52]	
Mader 1997	2	3	1	3	11.4%	4.00 [0.13, 119.23]	
Total (95% CI)		17		20	100.0%	1.61 [0.38, 6.77]	
Total events:	6		5				
Heterogeneity: Chi ² = 0.34, df = 1 (P = 0.56); I ² = 0%							
Test for overall effect: Z = 0.65 (P = 0.52)							
Test for subgroup differences: Not applicable							

Analysis 1.7. Comparison 1: Aminophylline vs. placebo, Outcome 7: Sensitivity analysis: survival to discharge

Analysis 1.8. Comparison 1: Aminophylline vs. placebo, Outcome 8: Sensitivity analysis: survival to admission

Analysis 1.9. Comparison 1: Aminophylline vs. placebo, Outcome 9: Sensitivity analysis: return of spontaneous circulation

APPENDICES

Appendix 1. Search strategies 2009

CENTRAL

#1 MeSH descriptor heart arrest explode all trees

Aminophylline for bradycardic cardiac arrest in adults (Review)

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

#2 heart next arrest*
 #3 cardiac next arrest*
 #4 cardiopulmonary next arrest*
 #5 sudden next cardiac next death
 #6 asystol*
 #7 MeSH descriptor Cardiopulmonary Resuscitation explode all trees
 #8 resuscitat*
 #9 Bradycardiasystol*
 #10 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)
 #11 MeSH descriptor aminophylline explode all trees
 #12 aminophyllin*
 #13 MeSH descriptor Adenosine explode all trees with qualifier: AI
 #14 adenosine next antagonist*
 #15 adenosine next inhibitor*
 #16 (Adenosine near/6 Block*)
 #17 (#11 or #12 or #13 or #14 or #15 or #16)
 #18 (#10 and #17)

MEDLINE

#1 "Death, Sudden, Cardiac"[Mesh] OR "Cardiopulmonary Resuscitation"[Mesh] OR "Heart Arrest"[Mesh] (29885)
 #2 "sudden cardiac death" or "cardiopulmonary resuscitation" or "heart arrest" or "cardiac arrest" or asystol* (43164)
 #3 #1 OR #2 (47970)
 #4 "Aminophylline"[Mesh] OR "Adenosine/antagonists and inhibitors"[Mesh] (4723)
 #5 Aminophylline (4984)
 #6 #4 OR #5 (5816)
 #7 #3 AND #6 (57)
 #8 #3 AND #6 Limits: Humans (41)

EMBASE

#1. 'sudden death'/exp OR 'resuscitation'/exp OR 'heart arrest'/exp (85,049)
 #2. 'sudden cardiac death'/exp OR 'sudden cardiac death' OR 'cardiopulmonary resuscitation'/exp OR 'cardiopulmonary resuscitation' OR 'heart arrest'/exp OR 'heart arrest' OR 'cardiac arrest'/exp OR 'cardiac arrest' OR asystol* (94,133)
 #3. #1 OR #2 (94,133)
 #4. 'aminophylline'/exp OR 'adenosine receptor blocking agent'/exp (18,617)
 #5. 'aminophylline'/exp OR aminophylline (12,594)
 #6. #4 OR #5 (19,106)
 #7. #3 AND #6 (268)
 #8. #7 AND [humans]/lim (204)

CINAHL

S1 (MH "Death, Sudden, Cardiac") or (MH "Resuscitation, Cardiopulmonary+") or (MH "Heart Arrest") (7943)
 S2 "sudden cardiac death" or "cardiopulmonary resuscitation" or "heart arrest" or "cardiac arrest" or asystol* (6080)
 S3 S1 or S2 (9378)
 S4 (MH "Aminophylline") or (MH "Adenosine/AI") (111)
 S5 aminophylline (130)
 S6 S4 or S5 (149)

S7 (S4 or S5) and (S3 and S6) (15)

LILACS

Search words included combinations of:

asystole (405) or bradyasystole (0) or cardiac arrest (399) or heart arrest (399)

AND

aminophylline (77) or (adenosine AND antagonist) (10)

Yeild: 1 citation

Appendix 2. Search strategies 2014

CENTRAL (search restricted to years 2012-2014)

#1 MeSH descriptor Heart Arrest explode all trees

#2 (heart next arrest*)

#3 (cardiac next arrest*)

#4 (cardiopulmonary next arrest*)

#5 "sudden cardiac death"

#6 (asystol*)

#7 MeSH descriptor Cardiopulmonary Resuscitation explode all trees

#8 (resuscitat*)

#9 (Bradyasystol*)

#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)

#11 MeSH descriptor Aminophylline explode all trees

#12 aminophyllin*

#13 MeSH descriptor Adenosine explode all trees

#14 (adenosine next antagonist*)

#15 (adenosine next inhibitor*)

#16 (Adenosine near/6 Block*)

#17 (#11 OR #12 OR #13 OR #14 OR #15 OR #16)

#18 (#10 AND #17)

MEDLINE (OVID)

Cochrane sensitive-maximising RCT filter applied (Handbook 2011)

1. Heart Arrest/

2. heart arrest*.tw.

3. cardiac arrest*.tw.

4. cardiopulmonary arrest*.tw.

5. "sudden cardiac death".tw.

6. asystol*.tw.

7. exp Cardiopulmonary Resuscitation/
8. resuscitat*.tw.
9. Bradysystol*.tw.
10. or/1-9
11. exp Aminophylline/
12. aminophyllin*.tw.
13. Adenosine/ or Adenosine A1 Receptor Antagonists/ or Receptor, Adenosine A1/
14. adenosine antagonist*.tw.
15. adenosine inhibitor*.tw.
16. or/11-15
17. randomized controlled trial.pt.
18. controlled clinical trial.pt.
19. randomized.ab.
20. placebo.ab.
21. drug therapy.fs.
22. randomly.ab.
23. trial.ab.
24. groups.ab.
25. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. exp animals/ not humans.sh.
27. 25 not 26
28. 10 and 16 and 27
29. (201203* or 201204* or 201205* or 201206* or 201207* or 201208* or 201209* or 201210* or 201211* or 201212* or 2013* or 2014*).ed.
30. 28 and 29

EMBASE (OVID)

Cochrane RCT filter (Handbook 2011)

1. Heart Arrest/
2. heart arrest*.tw.
3. cardiac arrest*.tw.
4. cardiopulmonary arrest*.tw.
5. "sudden cardiac death".tw.
6. asystol*.tw.
7. exp Cardiopulmonary Resuscitation/
8. resuscitat*.tw.
9. Bradysystol*.tw.

Aminophylline for bradysystolic cardiac arrest in adults (Review)

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

10. or/1-9
11. exp Aminophylline/
12. aminophyllin*.tw.
13. Adenosine/ or Adenosine A1 Receptor Antagonists/ or Receptor, Adenosine A1/
14. adenosine antagonist*.tw.
15. adenosine inhibitor*.tw.
16. or/11-15
17. random\$.tw.
18. factorial\$.tw.
19. crossover\$.tw.
20. cross over\$.tw.
21. cross-over\$.tw.
22. placebo\$.tw.
23. (doubl\$ adj blind\$).tw.
24. (singl\$ adj blind\$).tw.
25. assign\$.tw.
26. allocat\$.tw.
27. volunteer\$.tw.
28. crossover procedure/
29. double blind procedure/
30. randomized controlled trial/
31. single blind procedure/
32. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33. (animal/ or nonhuman/) not human/
34. 32 not 33
35. 10 and 16 and 34
36. (201203* or 201204* or 201205* or 201206* or 201207* or 201208* or 201209* or 201210* or 201211* or 201212* or 2013* or 2014*).dd.
37. (2012* or 2013* or 2014*).em.
38. 36 or 37
39. 35 and 38

CINAHL (EBSCO)

- S1 (MH "Heart Arrest+")
- S2 "heart arrest*"
- S3 "cardiac arrest*"
- S4 "sudden cardiac death"

S5 asystol*

S6 (MH "Resuscitation, Cardiopulmonary+")

S7 resuscitat*

S8 Bradyasystol*

S9 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8

S10 (MH "Aminophylline")

S11 aminophyllin*

S12 (MH "Adenosine+")

S13 "adenosine antagonist*"

S14 "adenosine inhibitor*"

S15 Adenosine N6 Block*

S16 S10 or S11 or S12 or S13 or S14 or S15

S17 S9 and S16

S18 (singl* blind*)

S19 (doubl* blind*)

S20 (tripl* blind*)

S21 (trebl* blind*)

S22 (trebl* mask*) or (tripl* mask*) or (doubl* mask*) or (singl* mask*)

S23 (randomi?ed control* trial*)

S24 (MH "Random Assignment")

S25 (random* allocat*)

S26 (MH "Placebos")

S27 (MH "Quantitative Studies")

S28 (allocat* random*)

S29 S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28

S30 S17 and S29

S31 EM 20120301-20141116

S32 S30 and S31

WHAT'S NEW

Date	Event	Description
21 September 2021	Review declared as stable	No new studies since review first published in 2013 (latest search February 2020).

HISTORY

Protocol first published: Issue 4, 2007

Review first published: Issue 8, 2013

Date	Event	Description
25 August 2015	New citation required but conclusions have not changed	No new studies were identified for inclusion. Our conclusion remain the same.
17 November 2014	New search has been performed	The search strategy was updated in November 2014. No new studies were found.
8 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Served as guarantor of the review: Dr Hurley

Drafted the protocol: Drs Hurley and Magee

Searched for trials: Dr Hurley

Obtained copies of trials: Dr Hurley

Selected which trials to include: Drs Hurley, Green and Magee

Extracted data from trials: Drs Hurley, Green and Magee

Entered data into RevMan: Drs Hurley and Magee

Carried out the analysis: Drs Hurley and Magee

Interpreted the analysis: Drs Hurley, Magee and Green

Drafted the final review: Drs Hurley, Green and Magee

Updated the review: Dr Hurley

DECLARATIONS OF INTEREST

KH: none known

KM: The author received a speaking fee from Fresenius Kabi for presenting at the European Society of Anaesthesia Symposium 2014 in Sweden on Propofol for Emergency Department Procedural Sedation and Analgesia.

RG: none known

SOURCES OF SUPPORT

Internal sources

- Dalhousie University, Canada

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Aminophylline [*therapeutic use]; Bradycardia [complications]; Cardiostonic Agents [*therapeutic use]; Injections, Intravenous; Out-of-Hospital Cardiac Arrest [*drug therapy] [etiology] [mortality]; Randomized Controlled Trials as Topic; Survival Analysis

MeSH check words

Aged; Female; Humans; Male