CJEM JOURNAL CLUB

Does the administration of intravenous aminophylline improve survival in adults with bradyasystolic cardiac arrest?

Clinical question

Does administration of intravenous aminophylline help restore circulation in patients with bradyasystolic cardiac arrest?

Articles chosen

1. Abu-Laban RB, McIntyre CM, Christenson JM, et al. Aminophylline in bradyasystolic cardiac arrest: a randomised placebo-controlled trial. Lancet 2006;367: 1577-84.
2. Mader TJ, Sminthline HA, Durkin L, et al. A randomized controlled trial of intravenous aminophylline for atropine-resistant out-of-hospital asystolic cardiac arrest. Acad Emerg Med 2003;10(3):192-7.
3. Mader TJ, Smithline HA, Gibson P. Aminophylline in undifferentiated out-of-hospital asystolic cardiac arrest. Resuscitation 1999;41(1):39-45.
4. Mader TJ, Gibson P. Adenosine receptor antagonism in refractory asystolic cardiac arrest: results of a human pilot study. Resuscitation 1997;35(1):3-7.

Clinical bottom line

The identified studies demonstrated that aminophylline had no impact on clinical outcomes in patients who also received standard Advanced Cardiac Life Support. Among adults in bradyasystolic arrest, rates of return of spontaneous circulation (ROSC) or survival (pulseless electrical activity at rates less than 60 beats/min or asystole) were unchanged. The effect of aminophylline when administered within 8 minutes of cardiac arrest is unknown.

The search

Using MEDLINE (1966–Aug. 6, 2006), search ("heart arrest" [MeSH] OR "cardiopulmonary resuscitation" [MeSH]) AND "aminophylline" [MeSH]) AND (clinical [title/abstract] AND trial [title/abstract]) OR clinical trials [MeSH terms] OR clinical trial [publication type] OR random* [title/abstract] OR random allocation [MeSH terms] OR therapeutic use [MeSH subheading]).

Limits: Humans
Yield: 21 results

Non-randomized trials, case reports and review articles were excluded.

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Received: Aug. 14, 2006; revisions received: Aug. 31, 2006; accepted: Aug. 31, 2006

Can J Emerg Med 2007;9(1):26-9

The evidence

Design

These prospective, randomized, double-blinded, placebo-controlled trials were each conducted in the pre-hospital setting. Syringes containing either aminophylline or a matched quantity of saline (placebo) were prepared by a third party in all studies. Block randomization was used in stocking the ambulances in Abu-Laban and colleagues' study, Mader and colleagues' 2003 study (the Baystate Aminophylline Resuscitation Trial, [BART-3]) and Mader and colleagues' 1999 study (BART-2).[1–3] The randomization method was not described for Mader and Gibson's 1997 study (BART-1).[4]

Population

Abu-Laban and colleagues recruited patients >16 years of age with bradyasystole who were unresponsive to intravenous (IV) epinephrine 1 mg and atropine 3 mg.[1] Patients in BART-3 were ≥21 years of age and had to have re-

mained in asystolic arrest for 2 minutes after administration of both atropine and epinephrine (doses not specified).[2] Patients in BART-2 were ≥21 years of age with asystole confirmed in more than 1 lead for at least 15 seconds.[3] Patients in BART-1 were ≥21 years of age with asystole confirmed in more than 1 lead for at least 60 seconds after administration of IV atropine 1 mg and epinephrine 1 mg.[4]

All investigators excluded pregnant patients and patients with arrest secondary to hypothermia or trauma. Also excluded were those with hypersensitivity to the study drug, as well as patients known or suspected to be taking a theophylline product. Abu-Laban and colleagues further excluded dialysis patients, patients whose resuscitation was directed by a paramedic student, and those in whom there was a do-not-resuscitate order.[1] Mader and colleagues, in all 3 of their studies, further excluded patients with liver disease or suspected drug overdose.[2–4] In each study, patients in the treatment and control groups were similar with respect to demographics and predictors of survival.

Intervention

Patients in Abu-Laban and colleagues' study were randomly administered an IV bolus of aminophylline 250 mg or placebo.[1] If there was no change in rhythm after 90 seconds they were given a second dose of the study drug. Resuscitation continued for at least 10 minutes after the study drug was given. In each of Mader and colleagues' studies, patients were treated with prepared syringes randomly assigned to contain either aminophylline 250 mg or placebo.[2–4] In BART-2, the study drug was administered at the same time as the initial doses of epinephrine and atropine, whereas patients in BART-1 and BART-3 were enrolled in the study after failure of initial treatment with epinephrine and atropine.[2–4] The duration of resuscitation after administration of the study drug was not specified in the Mader and colleagues' studies, but patients in BART-3 had to be transported to a hospital.[2]

Outcomes measured

The primary outcome for Abu-Laban and colleagues' study, BART-3, and BART-2 was ROSC, defined as a palpable pulse of any duration.[1–3] The primary outcome in BART-1 was return of electrical activity defined as the occurrence of regular QRS complexes at a rate of ≥40 beats/min for at least 60 seconds, within 5 minutes of the study drug and before the administration of further drugs.[4] Investigators also reported survival to hospital admission and survival to hospital discharge.

Results

Abu-Laban and colleagues' study, BART-3 and BART-2 were analyzed in an intention-to-treat fashion, accounting for all patients who were enrolled.[1–3] Five patients were excluded from analysis in BART-1 because they failed to meet inclusion criteria.[4] The mean response time of the paramedic crew and time to administration of the study drug for each of the studies are listed in Table 1. Ninety-four percent of patients in Abu-Laban and colleagues' active arm received both doses of medication. There were no significant differences between the treatment and control groups with respect to ROSC or survival in any of the studies (Fig. 1, Fig. 2 and Fig. 3).

Comments

Adenosine is an endogenous nucleotide that plays a role in the regulation of myocardial oxygen supply and demand.[5] In periods of cellular hypoxia, production of adenosine increases, leading to accumulation in ischemic cardiac muscle. In what is ordinarily believed to be a cardio-protective mechanism, adenosine acts to increase oxygen supply through coronary vasodilation and diminish oxygen demand by reducing pacemaker activity, blocking conduction at the AV node, and attenuating the response to catecholamines.[5] These actions in the setting of cardiac ischemia may lead to bradycardia or bradyasystole resistant to atropine as it is independent of parasympathetic tone.

Table 1. Mean times for arrival or paramedic crews and administration of the study drug in each arm of the selected studies

	Abu-Laban et al,[1] 2006		Mader et al,[2] (BART-3, 2003)		Mader et al,[3] (BART-2, 1999)		Mader and Gibson,[4] (BART-1, 1997)	
Variable	Study drug	Placebo	Study drug	Placebo	Study drug	Placebo	Study drug	Placebo
Mean time (min) from dispatch to arrival of paramedics	8.9	9.3	5.3	6.2	6.5	6.5	8.8	8.6
Mean time (min) to administration of study drug (or placebo)	14.5*	14.8*	7.2†	6.7†	4.9†	4.6†	16.6*	13.1*

*Mean time from arrival of paramedic crew to administration of study drug or placebo.
†Mean time from diagnosis of asystole to administration of study drug or placebo.

https://doi.org/10.1017/S1481803500014706 Published online by Cambridge University Press

Furthermore, adenosine diminishes the effectiveness of exogenous catecholamines.[5]

Aminophylline is a competitive antagonist of adenosine.[3] Based on an early case series, several case reports, and our understanding of the pathophysiology at the time, aminophylline was thought to be a promising therapy for atropine resistant bradyasystolic arrest.[5–8] However, well-designed randomized controlled trials have not substantiated these hopes.

Because of ethical concerns[1] and a desire to select the appropriate subgroup of patients who were atropine resistant,[2,4] aminophylline was not administered as part of the initial treatment in 3 of the 4 trials. This delay translated to mean times of as long as 16 minutes from diagnosis of rhythm to administration of aminophylline in one study.[4] The likelihood of successful resuscitation diminishes with time, and it is possible that earlier administration of aminophylline might be beneficial. Abu-Laban and colleagues'

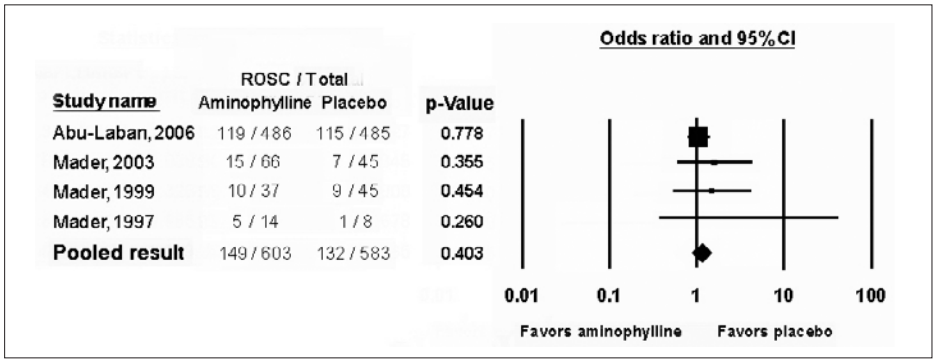

Fig. 1. Forest plot of return of spontaneous circulation (ROSC) in the 4 selected studies. For each trial the square corresponds to the observed odds ratio in the study and is proportionately sized relative to the sample. The horizontal line corresponds to the 95% confidence interval (CI). The central vertical line denotes an odds ratio of 1, reflecting no significant difference between aminophylline and placebo.

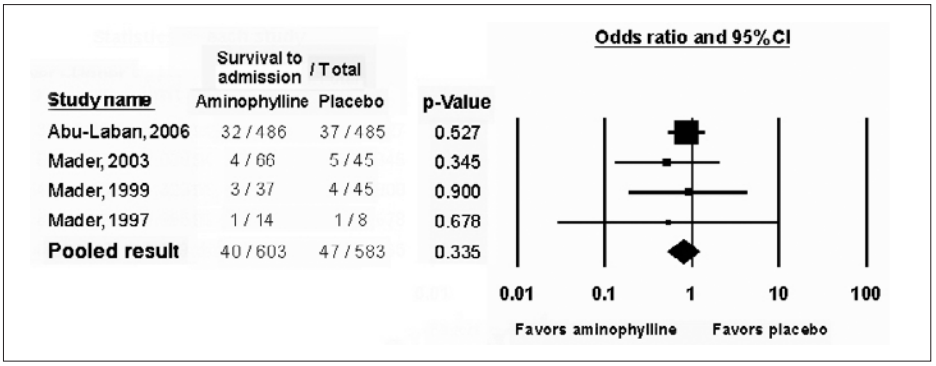

Fig. 2. Forest plot of survival to admission in the 4 selected studies.

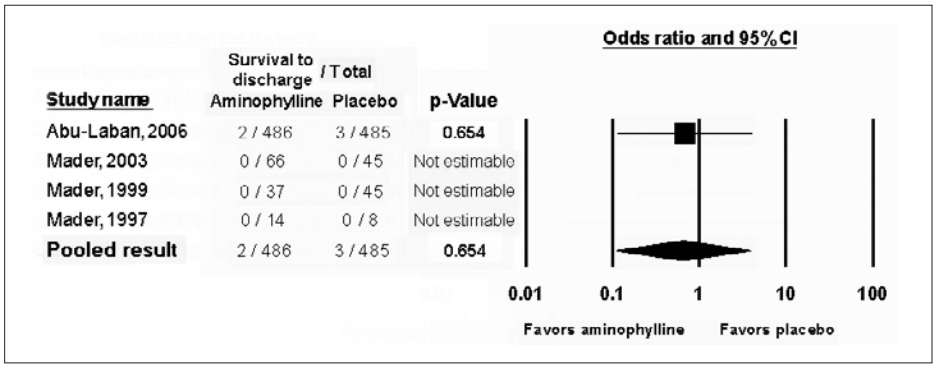

Fig. 3. Forest plot of survival to discharge in the 4 selected studies.

https://doi.org/10.1017/S1481803500014706 Published online by Cambridge University Press

finding of increased tachydysrhythmias after administration of aminophylline does suggest that it has cardiac effects in arrest scenarios, but these do not appear to lead to an increase in survival.[1–4] BART-2 included aminophylline as one of the initial resuscitation drugs and, although underpowered, there was no evidence of benefit even though the mean time from diagnosis of asystole to administration of the drug was less than 5 minutes.[3]

For the purposes of this critically appraised topic, the primary outcome of interest was survival to hospital discharge. The primary outcomes of the studies selected were either ROSC (Abu-Laban and colleagues, BART-2 and -3) or return of electrical cardiac activity (BART-1), neither of which are clinically important when compared with survival.[1–4] Given the low baseline-expected survival in cardiac arrest (<3%), thousands of patients would be needed to demonstrate a statistically significant difference in survival.[1,9] Even so, ROSC is a pre-requisite to survival, and no differences in ROSC were found when comparing aminophylline to placebo.[1–4]

BART-2 and BART-3 were underpowered to detect small differences between groups.[2,3] Abu-Laban and colleagues' trial was powered to detect a smaller absolute difference (8.8%) but still failed to demonstrate a beneficial effect from aminophylline.[1] Optimists might still argue that the drug could be beneficial to a particular subgroup of patients, namely those with an ischemic cardiac event preceding the arrest. A large proportion of Abu-Laban and colleagues' patients were suspected to have suffered a "cardiac" death (82.3%), although the cause of death was not confirmed.

The evidence provided by these trials does not support the addition of aminophylline to standard care for asystole in adults with normothermic, non-traumatic arrest.

Competing interests: None declared.

Key words: cardiac arrest; cardiopulmonary resuscitation; aminophylline

References

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3. Mader TJ, Smithline HA, Gibson P. Aminophylline in undifferentiated out-of-hospital asystolic cardiac arrest. Resuscitation 1999;41:39-45.
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