Atropine Sulfate for Patients With Out-of-Hospital Cardiac Arrest due to Asystole and Pulseless Electrical Activity

The Survey of Survivors After Out-of-hospital Cardiac Arrest in KANTO Area, Japan (SOS-KANTO) Study Group

Background: The 2005 guidelines for cardiopulmonary resuscitation (CPR) have recommended that administration of atropine can be considered for non-shockable rhythm, but there are insufficient data in humans.

Methods and Results: The effects of atropine were assessed in 7,448 adults with non-shockable rhythm from the SOS-KANTO study. The primary endpoint was a 30-day favorable neurological outcome after cardiac arrest. In the 6,419 adults with asystole, the epinephrine with atropine group (n=1,378) had a significantly higher return of spontaneous circulation (ROSC) rate than the epinephrine alone group (n=5,048) with an adjusted odds ratio of 1.6 (95% confidence interval (CI) 1.4–1.7, P<0.0001), but the 2 groups had similar 30-day favorable neurological outcome with an adjusted odds ratio of 0.6 (95%CI 0.2–1.7, P=0.37). In the 1,029 adults with pulseless electrical activity (PEA), the 2 groups had similar rates of ROSC and 30-day favorable neurological outcome, and the epinephrine with atropine group had a significantly lower 30-day survival rate than the epinephrine alone group with an adjusted odds ratio of 0.4 (95%CI 0.2–0.9, P=0.016).

Conclusions: Administration of atropine had no long-term neurological benefit in adults with out-of-hospital cardiac arrest due to non-shockable rhythm. Atropine is not useful for adults with PEA. (*Circ J* 2011; 75: 580–588)

Key Words: Asystole; Atropine; Cardiac arrest; Neurological outcome; Pulseless electrical activity (PEA)

Cardiac arrest is a major public health problem in the world. Recent guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care have shown that basic CPR and early defibrillation are of primary importance, and drug administration for advanced cardiac life support (ALS) is of secondary importance during cardiac arrest.1–3 There have been recent 2 clinical studies on ALS in patients with out-of-hospital cardiac arrest. A multicenter, controlled clinical study by Stiel et al demonstrated that standard ALS, which includes endotracheal intubation and/or intravenous drug administration, does not improve the rate of survival to hospital discharge.4 A randomized controlled study by Olasveengen et al demonstrated that ALS with intravenous drug administration, which includes epinephrine, atropine and/or amiodarone, is not associated with long-term survival benefits.5 However, these 2 clinical studies did not focus on the use of atropine for medications of non-shockable rhythm with asystole or PEA. Administration of atropine has been used universally in the medications of ALS, but there is little evidence to show that it improves long-term survival in humans. However, the use of atropine improves short-term survival and is inexpensive and easy to administer.1 Literature to refute the use of atropine for asystole and PEA is equally sparse and of limited quality.1 Asystole can be precipitated or exacerbated by excessive vagal tone, and administration of a vagolytic medication is consistent with a physiologic approach.6 Moreover, recent CPR guidelines have reported that administration of atropine remains a first line drug for acute symptomatic bradycardia (Class 2a; weight of evidence is in favor of usefulness/efficacy). On the basis of these findings, administration of atropine can be considered for patients with cardiac arrest with asystole or PEA (Class Indeterminate; no recommendation until further research).1

We therefore assessed the efficacy of the use of atropine in 7,448 adults with non-shockable rhythm from the SOS-KANTO study, which was a prospective, multicenter, observational trial in patients with out-of-hospital cardiac arrest. We expected that intravenous administration of atropine during ALS would be beneficial to short-term survival, while it would not be beneficial to long-term neurologically intact survival.
SOS-KANTO Atropine for Cardiac Arrest

Methods

Study Patients
The survey of survivors after out-of-hospital cardiac arrest in the Kanto area of Japan (SOS-KANTO) was a prospective, multicenter observational trial consisting of 9,592 patients who suffered out-of-hospital cardiac arrest and were transported to the 58 emergency hospitals participating in the SOS-KANTO by emergency medical service personnel.\textsuperscript{7-10} The present study patients were enrolled from the SOS-KANTO trial when they met the following criteria: aged 18 years or older; persistent cardiac arrest on arrival at the emergency room (ER); asystole or PEA after the first administration of epinephrine in the ER. Exclusion criteria were a return of spontaneous circulation (ROSC) before the second administration of epinephrine, administration of vasopressin or high-dose epinephrine, extracorporeal CPR, documented terminal illness and the presence of a do-not-resuscitate order.

Study Design and Data Collection
The design and data collection of the SOS-KANTO study has been reported previously.\textsuperscript{7-10} The study was approved by the SOS-KANTO Research Ethics Board, and the requirement for informed consent was waived according to the guidelines of the Japanese government.\textsuperscript{11} The treatment for out-of-hospital cardiac arrest were managed according to the Guidelines 2000 for CPR and emergency cardiovascular care.\textsuperscript{2} A 1-mg dose of epinephrine every 3–5 min was administered intravenously if cardiac arrest persisted. Although the use of atropine was not standardized, the dose of atropine for asystole or PEA arrest was 1 mg intravenous, which could be repeated every 3–5 min (maximum total of 3 mg) if asystole or PEA arrest persisted. The use of other resuscitation drugs (eg, vasopressin, antiarrhythmics and buffers), inclusive of the high-dose epinephrine, were not standardized if the first administration of 1-mg dose of epinephrine failed. Extracorporeal CPR and hypothermia for post-resuscitation care were also not standardized. It was up to the attending physicians to stop the ALS efforts.

Study Endpoints
The primary endpoint was a favorable neurological outcome at 30 days after cardiac arrest defined according to the Glasgow-Pittsburgh cerebral-performance category of 1 (good performance) or 2 (moderate disability) on a 5-category scale; the other categories were 3 (severe disability), 4 (a vegetative state) and 5 (death).\textsuperscript{2,12} The secondary endpoints were ROSC, survival to hospital admission and survival at 30 days after cardiac arrest. Neurological outcomes were defined by physicians that were not connected to this study.

Figure 1. Study profile. ROSC, return of spontaneous circulation; ER, emergency room; PEA, pulseless electrical activity; VF/ pulseless VT, ventricular fibrillation/pulseless ventricular tachycardia; IV, intravenous; CPR, cardiopulmonary resuscitation.
Statistical Analysis
Baseline characteristics were compared using the chi-square test for categorical variables and the Mann-Whitney U test for continuous variables, as appropriate. Odds ratios and their 95% confidence interval (CI) were calculated for the study endpoints. A multiple logistic-regression analysis was carried out for independent predictors of the study endpoints, including age, cause of cardiac arrest, witnessed arrest, bystander CPR attempt, number of defibrillatory shock and administration of atropine. All analyses were performed using the SPSS software package (version 16.0 J SPSS).

All authors had full access to the study data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results
During the study period, resuscitation was attempted in 9,592 patients who lapsed into out-of-hospital cardiac arrest. Of those, 2,144 patients were not eligible. This study therefore included 7,448 adult patients with persistent asystole or PEA cardiac arrest. Of these, 6,419 patients had cardiac arrest due to asystole; 5,048 (79%) were administered epinephrine alone and 1,371 (21%) were administered epinephrine with atropine. One patient was lost to follow-up in the epinephrine alone group and 2 were lost to follow-up in the epinephrine with atropine group for study endpoints at 30 days after cardiac arrest. The number of cardiac arrest due to PEA was 1,029; 688 (67%) were administered epinephrine alone and 341 (33%) were administered epinephrine with atropine. Two patients were lost to follow-up in the epinephrine with atropine group for study endpoints at 30 days after cardiac arrest (Figure 1).

Characteristics of patients with asystole are presented in Table 1. At baseline, significant differences were seen between the epinephrine with atropine group and the epinephrine alone group in the proportions of cardiac cause, witnessed arrest, bystander CPR attempt, gasping breathing, initial recorded cardiac rhythm, defibrillatory shock during CPR and tracheal intubation.

Characteristics of patients with PEA are presented in Table 2. At baseline, significant differences were seen between the epinephrine with atropine group and the epinephrine alone group in the proportions of initial recorded cardiac rhythm, defibrillatory shock during CPR and tracheal intubation.

Table 3 shows the study outcomes with unadjusted odds ratios of ROSC, survival to hospital admission, 30-day survival and 30-day favorable neurological outcome. In the patients with asystole, the epinephrine with atropine group
had significantly higher rates of ROSC and survival to hospital admission than the epinephrine alone group (ROSC: 32.5% vs. 19.1%, P<0.001, survival to hospital admission: 18.0% vs. 12.0%, P<0.001). The 2 groups had similar rates of 30-day survival and 30-day favorable neurological outcome (30-day survival: 1.3% vs. 1.3%, P=0.83, 30-day favorable neurological outcome: 0.24% vs. 0.22%, P=0.84). In the multiple logistic-regression analysis (Figures 2A–D), the adjusted odds ratio after the administration of epinephrine and atropine compared with epinephrine alone was 1.82 (95%CI 1.58–2.09; P<0.001) for ROSC, 1.55 (95%CI 1.31–1.83; P<0.001) for survival to hospital admission, 1.01 (95%CI 0.59–1.72; P=0.986) for 30-day survival and 0.69 (95%CI 0.19–2.48; P=0.571) for 30-day favorable neurological outcome. Other independent predictors were age, cardiac cause, witnessed arrest and attempted defibrillation shocks for ROSC, cardiac cause, witnessed arrest, bystander CPR attempt and defibrillation shock attempt for survival to hospital admission.
**Figure 2.** Adjusted odds ratios of patients with asystole (n=6,416). The adjusted odds ratio after the administration of epinephrine and atropine compared with epinephrine alone was 1.82 (95% CI 1.58–2.09; P<0.001) for ROSC (**A**), 1.55 (95% CI 1.31–1.83; P<0.001) for survival to hospital admission (**B**), 1.01 (95% CI 0.59–1.72; P=0.986) for 30-day survival (**C**) and 0.69 (95% CI 0.19–2.48; P=0.571) for 30-day favorable neurological outcome (**D**). ROSC, return of spontaneous circulation; CI, confidence interval; CPR, cardiopulmonary resuscitation.
### A ROSC

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<td>Atropine</td>
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### B Survival to hospital admission

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### C Survival at 30 days

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### D Favorable Neurological Outcome at 30 Days

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**Figure 3.** Adjusted odds ratios of patients with pulseless electrical activity (PEA) (n=1,027). The adjusted odds ratio after the administration of epinephrine and atropine compared with epinephrine alone was 0.95 (95%CI 0.73–1.24, P=0.708) for ROSC (A), 0.87 (95%CI 0.65–1.16; P=0.339) for survival to hospital admission (B), 0.40 (95%CI 0.22–0.86; P=0.016) for 30-day survival (C) and 0.51 (95%CI 0.10–2.48; P=0.040) for 30-day favorable neurological outcome (D). ROSC, return of spontaneous circulation; CI, confidence interval; CPR, cardiopulmonary resuscitation.
sion, and witnessed arrest for survival at 30 days and favorable outcome at 30 days. When gasping breathing, tracheal intubation, therapeutic hypothermia and coronary reperfusion therapy were included in the analysis for 30-day favorable neurological outcome, the result did not change.

In the subgroup of patients with PEA, no significant differences were seen between the 2 groups in the rates of ROSC, survival to hospital admission and 30-day favorable neurological outcome, but the epinephrine with atropine group had a lower rate of 30-day survival than the epinephrine alone group (3.2% vs. 7.1%; P=0.010). In the multiple logistic-regression analysis (Figures 3A–D) for the subgroup of patients with PEA, the adjusted odds ratio after the administration of epinephrine and atropine compared with epinephrine alone was 0.95 (95%CI 0.73–1.24; P=0.708) for ROSC, 0.87 (95%CI 0.65–1.16; P=0.339) for survival to hospital admission, 0.40 (95%CI 0.22–0.86; P=0.016) for 30-day survival and 0.51 (95%CI 0.10–2.48; P=0.040) for 30-day favorable neurological outcome. Other independent predictors were non-cardiac cause for ROSC and survival to hospital admission. When gasping breathing, tracheal intubation, therapeutic hypothermia and coronary reperfusion therapy were included in the analysis for 30-day favorable neurological outcome, the result did not change.

Discussion

This was the first multicenter, controlled study of administration of atropine during ALS in adult patients with out-of-hospital cardiac arrest due to non-shockable rhythm (asystole or PEA). This study demonstrated that resuscitation outcomes of administration of atropine differed between the adults with asystole and those with PEA. In the 6,416 patients with asystole, administration of atropine was beneficial to short-term survival, but did not improve long-term survival (Table 3, Figure 2). In the 1,029 adults with PEA arrest, administration of atropine was not associated with any survival benefits. In fact, atropine was not useful to long-term survival in patients with PEA arrest (Table 3, Figure 3). In the patients with asystole, the epinephrine with atropine group had favorable conditions for resuscitation (eg, higher proportions of cardiac cause, witnessed arrest, bystander CPR attempt, gasping breathing and VF as an initial recorded cardiac rhythm) compared with the epinephrine alone group (Table 1), and a multiple logistic-regression analysis showed that the administration of atropine was an independent predictor of ROSC and survival to hospital admission (Figure 2). In contrast, the epinephrine with atropine group in patients with PEA had favorable conditions for resuscitation (eg, higher proportions of VF as an initial recorded cardiac rhythm) compared with the epinephrine alone group (Table 2), but a multiple logistic-regression analysis showed that the administration of atropine was an independent predictor of death at 30 days (Figure 3).

Atropine reverses cholinergic-mediated decreases in heart rate, systemic vascular resistance and blood pressure. Atropine has similar antagonist activity for all 5 muscarinic receptor subtypes. Thus far, the postsynaptic muscarinic receptors supported to transduce parasympathetic impulses to the heart have been assigned to the M2 subtype because mRNA for M1 or M3 receptors could not be found in heart muscle cells in experimental studies and in adult animals. The direct effect of activation of M2 receptors in the heart is to decrease myocardial activity; that is, negative chronotropic, dromotropic and inotropic effects occur. M2 receptors inhibit adenylate cyclase activity and enhance K+ currents, both of which lead to decreased activation of myocardial cells. In pacemaker cells, this slows the rate of spontaneous depolarization. A negative inotropic effect decreases myocardial oxygen demand. These cardiodepressant effects are a predictable consequence of mimicking the parasympathetic nervous system and are consistent with energy conservation.

Several small studies in adults have shown that administration of atropine is not associated with any consistent benefits after in-hospital or out-of-hospital cardiac arrests. In patients with asystole, a retrospective review found that 6 of 43 patients receiving asystole treated with atropine survived to hospital admission compared to 0 of 41 patients who did not receive atropine. A case series of adults in cardiac arrest documented conversion from asystole to sinus rhythm in 7 of 8 patients, and 3 of 8 patients were discharged from the hospital. A prospective controlled non-randomized study of out-of-hospital arrest found that 2 of 11 patients with asystole or pulseless idioventricular rhythms treated with atropine survived to hospital admission compared with 2 of 10 patients who did not receive atropine. These findings suggest that there are insufficient data on patients with out-of-hospital cardiac arrest due to asystole. The present study showed that administration of atropine during ALS for adults with asystole was associated with short-term survival benefits. When the ideal treatment for post cardiac arrest syndrome is established, administration of atropine for adults with asystole may have long-term survival benefits.

There are few studies of PEA arrest in humans. In an animal model of PEA, no difference was seen in resuscitation outcomes between standard-dose atropine and placebo groups. In the present study, administration of atropine during ALS for adults with PEA had no short-term survival benefits and had harmful influence on long-term survival. The primary reason of these results was considered as follows.

PEA is defined as any of a heterogeneous group of organized electrocardiographic rhythms without sufficient mechanical contraction of the heart to produce a palpable pulse or measurable blood pressure. Although several clinical studies have shown that administration of atropine improves heart rate, signs and symptoms in both in-hospital and out-of-hospital adults with acute symptomatic bradycardia, atropine is not indicated in bradycardia from high degree (second degree with Mobitz or third degree) atrioventricular block. Atropine exerts its antibrady cardiac effects at the atrioventricular node and is unlikely to be effective if this block is at or below the Bundle of His. In such instances atropine can rarely accelerate sinus rate and atrioventricular node conduction. PEA is consisted in the QRS complex with wide versus narrow, and witnessed arrest for survival at 30 days and favorable outcome at 30 days. When gasping breathing, tracheal intubation, therapeutic hypothermia and coronary reperfusion therapy were included in the analysis for 30-day favorable neurological outcome, the result did not change.
rected. Therefore, further clinical studies are needed for adults with PEA with a wide QRS complex or narrow QRS complex.

**Study Limitations**

First, it was not a randomized controlled trial. It is difficult to conduct a randomized controlled trial for patients with out-of-hospital cardiac arrest in Japan.

Second, the treatment for asystole or PEA arrest were managed according to the ALS algorithm of the Guidelines 2000 for CPR and emergency cardiovascular care.① If the treatment for asystole or PEA arrest were managed according to the 2005 CPR algorithm, inclusive of basic CPR and defibrillation, the resuscitation outcomes might change slightly. However, the algorithm of administration of atropine for asystole or PEA arrest was the same, and the dose of atropine for asystole or PEA was 1 mg intravenous, which could be repeated every 3–5 min (maximum total of 3 mg) if asystole or PEA persisted.

Third, administration of atropine for adults with asystole or PEA arrest was not standardized. The attending physicians were entrusted with the use of atropine. In fact, the epinephrine with atropine group compared with epinephrine alone had favorable conditions for resuscitation. A multiple logistic-regression analysis showed that the administration of atropine for patients with asystole was an independent predictor of ROSC and survival to hospital admission, but the administration of atropine for PEA was an independent predictor of 30-day death after out-of-hospital cardiac arrest. Further adjusted studies of atropine are needed for patients with out-of-hospital cardiac arrest.

Fourth, it was up to the attending physicians to stop the ALS efforts.

Fifth, the time interval from cardiac arrest to administration of atropine was long. The resuscitation outcomes may change when the drugs with epinephrine and atropine were administered at the time of circulatory phase, but the 2 groups had similar call-to-drug-administration interval of longer than 30 min.

Finally, post-resuscitation care was not standardized. Therapeutic hypothermia, coronary reperfusion therapy and/or glucose control might be useful options for the treatment of post cardiac arrest syndrome in adults with out-of-hospital cardiac arrest due to non-shockable rhythm.33,34 In this study, there were a few adults treated with mild hypothermia and/or coronary reperfusion therapy and the proportion of each treatment was similar in the 2 groups (Tables 1 and 2).

**Conclusion**

We conclude that administration of atropine for ALS had no long-term neurological benefit in patients with out-of-hospital cardiac arrest due to non-shockable rhythm. Atropine is not useful for patients with PEA.

**Acknowledgments**

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**Disclosure**

We declare that we have no conflict of interest.

References


**Appendix**

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**Author Contributions**

K. Nagao and T. Yagi, as principal investigators, participated in the study conception, design, conduct, data collection, data management, data analyses, interpretation of the results and multiple revisions of the manuscript and contributed to the final manuscript. K. Nagao obtained funding. T. Sakamoto, K. Koseki, M. Igashira, S. Ishimatsu, A. Sato, S. Hori, S. Kanasaka, Y. Hamabe, D. Saito and S. Kitamura participated in the study conception, design, conduct, data collection, data management and interpretation of the results. K. Nagao, T. Yagi and D. Saito carried out the statistical analysis. All authors approved the final version.

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