報 告

Efficacy of Vasopressin Administration in the Resuscitation of Out-of-hospital Cardiopulmonary Arrest Patients

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Abstract

BACKGROUND: The National Institute of Health (NIH) guidelines highly recommend using vasopressin as well as adrenaline for resuscitation. However, as health insurance does not cover resuscitation with vasopressin in Japan, it has not yet been introduced. As a part of a National Hospital Organizations' multi-center study, we conducted a follow-up study of out-of-hospital cardiopulmonary arrest (CPA) cases using vasopressin at 14 emergency and critical care centers.

METHODS: The CPA patients (patients from 18 to 79 years old) with witnesses were alternately assigned to receive injections of either a combination of vasopressin and adrenaline or adrenaline alone.

RESULTS: A total of 84 informed and consenting patients were examined over 2 years: 47 patients (M/F＝29/18, age 69.7±13.4) received 40 mg of vasopressin as soon as possible after the first dose of 1 mg adrenaline, followed by administration of 1 mg adrenaline if needed; 37 patients (M/F＝21/16, age 68.4±12.2) received only adrenaline 1 mg every 3 minutes. No significant differences were seen between the combination-therapy and adrenaline only groups in baseline characteristics. Among the combination-therapy group, 18 out of 47 patients (38.2%) showed return of spontaneous circulation (ROSC); however no one survived more than 1 month. In the meantime, 9 out of 37 patients in the adrenaline-only group (24.3%) showed ROSC, and 2 patients survived more than 1 month. As compared with adrenaline alone, the rates of ROSC and long term survival for the combination-therapy group showed no significance.

CONCLUSIONS: Resuscitation using vasopressin is less likely to effect significant changes in the improvement of CPA patients compared with adrenaline alone.

Key Words: cardiopulmonary arrest, vasopressin, resuscitation

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Table 1 Criteria for registration and exclusion

(Criteria for registration)

1. From 18 to 79 years old
2. Cases with out-of- hospital Cardiopulmonary Arrest (CPA).
3. Cases with witnesses.
4. It was not important if bystander cardiopulmonary resuscitation (CPR) had been performed or not.
5. It was not important if defibrillation had been performed before arrival at the hospital or not.
6. The cause of CPA could be either intrinsic or extrinsic.
7. Informed consent from the patient himself/herself or his/her family for participation in this study was essential.

(Criteria for exclusion)

1. Patients in whom adrenaline had been administered before arrival at the hospital.
2. Patients who had already been involved in other studies or clinical trials.
3. Patients who were suspected of having committed any crime.
4. In addition to the exclusions listed above, patients for whom the doctors in charge considered CPA was inappropriate.

Introduction

According to current reports, vasopressin may be more effective for resuscitation than adrenaline alone[1)2)]. In fact, guidelines by the National Institute of Health (NIH) highly recommend the use of vasopressin as well as adrenaline for resuscitation[3)]. However, health insurance does not cover resuscitation with vasopressin in Japan so it has not yet been introduced. For that reason, a study was needed to be designed to assess the effects of the combination of vasopressin and adrenaline to investigate its practical use for advanced medical treatment. The present study was a prospective and multicenter clinical study for 2 years among Japanese National Organization Hospitals and National Centers. The aim of this study was to prove the efficacy of vasopressin by collecting and accumulating the data obtained at the institutions mentioned above.

Methods

Study design : Two-year prospective cohort study (human subjects).

Study Patients : This study was conducted on patients who had an out-of-hospital cardiac arrest and were admitted to our emergency and critical care center. Table 1 shows the criteria for registration.

The patients who met the conditions above were registered for this study together with written informed consent to participate. Informed consents of the patients' families were not required impromptu because of the urgent situation. In order not to delay the treatment, we carried out the informed consent process after the treatment. Informed consent was required to inform patients' families about the efficacy of vasopressin for resuscitation which has been proved by large-scale examinations overseas.

This study was approved by the Ethics board of Kumamoto Medical Center, National Hospital Organization and all the other co-researchers' institutions. The patients' data for this study were of course completely protected and we took particular attention when handling the data to maintain complete confidentiality.

Study Protocol : Treatment assignments were precisely and alternately generated into the following two groups ; (1)Combination-treatment Group : Patients used both adrenaline and vasopressin, (2) Adrenaline-only Group : Patients used only adrenaline. The combination-treatment group re-

Table 2 Baseline characteristics of the vasopressin combination treated group and adrenaline only group

	N(M/F)	Age±SD	Bystander CPR(%)	Defibrillation(%)
Vasopressin combination treated group	47 (29/18)	69.7±13.4	14 (29.8%)	8 (17.0%)
Adrenaline only group	37 (21/16)	68.4±12.2	15 (40.5%)	5 (13.5%)

Table 3 Breakdown of causes of CPA in the two groups

	Intrinsic causes	Extrinsic causes
Vasopressin combination treated group (n=47)	Acute myocardial infarction 9 Acute heart failure 5 Rupture of aorta 3 Dissection of aorta 2 Subarachnoid hemorrhage 2 Cerebral hemorrhage 2 Cancer 2 Renal failure 1 Sepsis 1 Unknown 14	Suffocation 4 Trauma 1 Heat stroke 1
Adrenaline only group (n=37)	Acute myocardial infarction 7 Acute heart failure 3 Rupture of aorta 3 Ventricular fibrillation 1 Subarachnoid hemorrhage 1 Cerebral hemorrhage 1 Pulmonary thrombosis 1 Renal failure 1 Cancer 1 Unknown 10	Trauma 4 Suffocation 3 Drowning 1

ceived 40mg of vasopressin as soon as possible after the first dose of 1 mg adrenaline, followed by administration of 1 mg adrenaline every 3 minutes if spontaneous circulation was not restored. The adrenaline-only group received 1 mg of adrenaline every 3 minutes. The primary end point was return of spontaneous circulation (ROSC) during hospital admission; the secondary end point was 1-month survival.

Statistical Analysis: The chi-square test was used for statistical analysis, and a P value of <0.05 was considered statistically significant.

Results

A total of 84 patients were examined over 2 years, of whom 47 patients (M/F=29/18, age 69.7±13.4) received the combination-therapy and 37patients (M/F=21/16, age 68.4±12.2) received adrenaline alone. There was no significant difference in the baseline characteristics between the two groups. The breakdown of the causes of CPA in the two groups is shown in Table 3. Patients whose causes were not identified were classified into "Unknown". Among the combination-therapy group, 18 out of 47 patients (38.2%) showed return of spontaneous circulation (ROSC);

Table 4 Comparison of the ROSC rate and prognosis in the vasopressin combination treated group and adrenaline only group

	ROSC(%)	1 month survival(%)	3 months survival(%)
Vasopressin combination treated group (n=47)	18 (38.2)	0 (0)	0 (0)
Adrenaline only group (n=37)	9 (24.3)	2 (5.4)	1 (2.7)

ROSC: return of spontaneous circulation

however no one survived more than 1 month, whereas 9 out of 37 patients in the adrenaline-only group (24.3%) showed ROSC, and 2 patients survived more than 1 month (Table 4). These data indicated that there were no apparent significant differences between these two therapeutic approaches.

Discussion

Vasopressin has a cyclic polypeptide structure (molecular weight 1084, Half-life 8-18minutes) consisting of 9 amino acid and similar to Oxytocin. It is also called antidiuretic hormone (ADH) because of its function in regulating the body's retention of water. Vasopressin receptors are classified into three subtypes; Arginine vasopressin receptor 1 A (AVPR 1 A), Arginine vasopressin receptor 1 B (AVPR 1 B) and Arginine vasopressin receptor 2 (AVPR 2). AVPR 1 A is expressed in vascular smooth muscle cells, hepatocytes, platelets, brain cells, and uterine cells, and functions as a non-adrenergic vasoconstrictor.

Prengel indicated that vasopressin with or without epinephrine and norepinephrine resulted in higher myocardial and cerebral perfusion than epinephrine alone[4]. According to the results obtained by Volker Wenzel et al., a total of 1219 patients underwent randomization ; 33 were excluded because of missing study-drug codes[1]. Among the remaining 1186 patients, 589 were assigned to receive vasopressin and 597 to receive epinephrine. The two treatment groups had similar clinical profiles. There were no significant differences in the rates of hospital admission between the vasopressin group and the epinephrine group either among patients with ventricular fibrillation (46.2 percent vs. 43.0 percent, P=0.48) or among those with pulseless electrical activity (33.7 percent vs. 30.5 percent, P=0.65). Among patients with asystole, however, vasopressin use was associated with significantly higher rates of hospital admission (29.0 percent, vs. 20.3 percent in the epinephrine group; P=0.02) and hospital discharge (4.7 percent vs. 1.5 percent, P=0.04). Among 732 patients in whom spontaneous circulation was not restored with the two injections of the study drug, additional treatment with epinephrine resulted in significant improvement in the rates of survival to hospital admission and hospital discharge in the vasopressin group, but not in the epinephrine group (hospital admission rate, 25.7 percent vs. 16.4 percent; P=0.002 ; hospital discharge rate, 6.2 percent vs. 1.7 percent; P=0.002). Cerebral performance was similar in the two groups.

Following the result of the European vasopressin study, Krismer also recommended a combination of adrenaline and vasopressin, and we adopted this treatment for resuscitation in the present study[2].

However, Callaway studied 167 in the vasopressin group and 158 in the placebo group and reported that there were no significant differences between the two groups in both the rate of return of pulse (31% vs. 30%) and the hospital admission rate (19% vs. 23%)[5]. Furthermore, according to Gueugniaud, who administrated two successive combination injections of 1 mg adrenaline and 40 IU of vasopressin, followed by an additional ad-

ministration of 1 mg of adrenaline, no significant differences between the two groups, 1442 in the vasopressin group and 1452 in the epinephrine alone group, were shown in the rate of return spontaneous circulation (28.6% vs. 29.5%), hospital admission (20.7% vs. 21.3%), and survival to hospital discharge[6].

The 2005 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations concluded that there is insufficient evidence to support or refute the use of vasopressin as an alternative to, or in combination with, adrenaline in any cardiac arrest rhythm[3].

The present study was a two-year prospective and large-scale multicenter study, and the aim of this study was to prove the efficacy of the use of vasopressin for resuscitation by collecting and accumulating data; however, we obtained fewer patients than expected. Nevertheless, we were successfully able to examine a total of 84 patients, and based on our results we concluded that there were no significant differences between the vasopressin combination and the adrenaline only groups. Unfortunately, in regard to the long-term survival rate, few patients survived to hospital discharge and the study population was not large enough to judge the efficacy. Further study will be required in the future with much larger patient populations.

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[Reference]

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バソプレシンを併用した蘇生法による院外心肺停止患者の蘇生効果

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要旨　バソプレシンによる心肺蘇生法はアメリカ国立衛生研究所（NIH）の心肺蘇生法ガイドラインにてアドレナリンと同様に推奨されている．しかし日本ではバソプレシンを心肺蘇生に使用する保険適応がなく，使用されていない．そこで国立病院機構多施設共同研究として，国立病院機構病院救命救急センター14施設で，心肺蘇生にバソプレシンを併用したCPA症例の予後調査を行った．目撃のある院外心肺停止症例（18歳以上80歳未満）を交互法でバソプレシンおよびアドレナリン併用群とアドレナリンのみによる対照群に割り付けた．バソプレシン併用群では初回アドレナリン1mg投与時に，バソプレシン40mg静注を同時投与し，その後はアドレナリン1mgのみを3分おきに投与した．対照群はアドレナリン1mgのみを3分おきに投与した．2年間で当研究に組み入れられた患者は，バソプレシン群は47症例（M/F＝29/18，年齢69.7±13.4），対照群は37症例（M/F＝21/16，年齢68.4±12.2）で，両群間の患者背景に有意差は認められなかった．バソプレシン群では18例で心拍再開し，再開率38.2%であったが，1カ月以上の生存者は0例であった．一方対照群では，9例で心拍再開し，再開率24.3%で，1カ月以上の生存者は2例であった．バソプレシン群の心拍再開率は，対照群に比べ有意（$P<0.05$）に高かった．しかし，長期生存率では有意差は認められなかった．

キーワード　心肺停止，バソプレシン，心肺蘇生