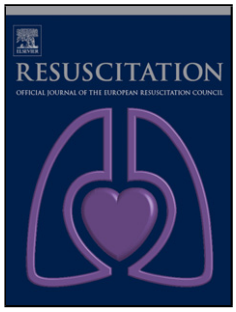

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Refractory ventricular fibrillation treated with esmolol

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ABSTRACT

Aims: This study aimed to evaluate the effects of esmolol treatment for patients with refractory ventricular fibrillation (RVF) in out-of-hospital cardiac arrest (OHCA).

Methods: This single-centre retrospective pre-post study evaluated patients who were treated between January 2012 and December 2015. Some patients had received esmolol (loading dose: 500 μg/kg, infusion: 0–100 μg/kg/min) for RVF (≥3 defibrillation attempts), after obtaining consent from the patient's guardian.

Results: Twenty-five patients did not receive esmolol (the control group), and 16 patients received esmolol. Sustained return of spontaneous circulation (ROSC) was significantly more common in the esmolol group, compared to the control group (56% vs. 16%, p = 0.007). Survival and good neurological outcomes at 30 days, 3months and at 6 months were >2-fold better in the esmolol group, compared to the control group, although these increases were not statistically significant.

Conclusions: The findings of our study suggest that administration of esmolol may increase the rate of sustained ROSC and ICU survival among patients with RVF in OHCA. Further larger-scale, prospective studies are necessary to determine the effect of esmolol for RVF in OHCA.

1. Introduction

Refractory ventricular fibrillation (RVF) which is defined as ventricular fibrillation that is resistant to at least three defibrillation attempts, 3 mg of epinephrine, 300 mg of amiodarone, and does not exhibit return of spontaneous circulation (ROSC) after >10 min of cardiopulmonary resuscitation (CPR), is challengeable to most advanced cardio-pulmonary life support (ACLS) providers. [1] Although patients with ventricular fibrillation-induced cardiac arrest tend to respond more favourably, compared to patients with other aetiologies of cardiac arrest, RVF is associated with a high mortality rate.[2]

Current CPR guidelines recommend the use of vasoactive agents (epinephrine or vasopressin), and then high levels of endogenous and/or exogenous catecholamines may be accumulated in some arrest patients. Epinephrine primarily improves coronary and peripheral flow and pressure, but activation of the beta-1 and beta-2 receptors by epinephrine may cause deleterious effects to the myocardium. Increase in myocardial oxygen requirement may result in ischemic injury and lower ventricular fibrillation threshold. Thus, blocking the beta-adrenergic receptors in the myocardium may provide beneficial effects during cardiac arrest by blocking the beta effects of the high catecholamine concentrations.[3-6] Various Animal studies, case reports and case series have reported successful beta-blocker use in patients with RVF [3-9], but evidence from clinical studies which compare the effect of beta-blocker to the conventional treated group is limited.

This study aimed to compare the clinical outcomes in the RVF patients including ROSC and survival with good neurologic outcome between the esmolol used group and conventional group for RVF patients that suffered from out-of-hospital cardiac arrest (OHCA) using a pre-

post study.

2. Methods

2.1 Design and setting

This retrospective pre-post study evaluated medical records from January 2012 to December 2015. This study's protocol was approved by the institutional review board of our hospital (IRB No:2016I062). All patients had been admitted to the Emergency Medical Center at Hallym University Sacred Heart Hospital, which is a tertiary referral centre that covers a local population of approximately 80,000 patients per year. Every OHCA patients was managed by a resuscitation team that includes emergency medicine physicians, residents, and technicians. The advanced cardiovascular life support protocol (ACLS) at our centre is based on the 2010 and 2015 American Heart Association guidelines. The procedures were performed by a physician or senior resident (grade 3–4) who was certified for ACLS.

2.2 Patients and methods

We enrolled patients who fulfilled the following criteria: (1) age of ≥18 years, (2) OHCA with initial ventricular fibrillation or ventricular tachycardia, and (3) RVF (ventricular fibrillation that was resistant to ≥3 defibrillations, 3 mg of epinephrine, 300 mg of amiodarone, and no ROSC after >10 min of CPR).[1] Patients were excluded if they had (1) severe head trauma or acute active bleeding, (2) severe sepsis, (3) ventricular fibrillation that developed during resuscitation for initial asystole or pulseless electrical activity, (4) terminal-stage malignancy, (5) a history of severe neurological deficits (e.g., dementia, intracranial haemorrhage, or ischemic stroke with a bedridden status), or (6) had received beta-blocker therapy before the cardiac arrest.

The pre-phase (January 2012 to December 2013) of the study included patients with RVF from OHCA who did not receive esmolol, and the post-phase (January 2014 to December 2015) included patients with RVF from OHCA who received esmolol. Esmolol was given after obtaining a verbal informed consent from patient's proxies during the resuscitative effort, and written informed consent was obtained after the resuscitation. The loading dose of esmolol was 500 μg/kg, and this dose was followed by a continuous infusion of 0–100 μg/kg/min. We retrospectively reviewed the patients' initial rhythm, number of defibrillation attempts, kinds and dosage of drugs used, the duration of resuscitation, and clinical outcomes.

2.3 Outcomes and statistical analysis

The primary outcome was defined as sustained ROSC (>20 min of spontaneous circulation without recurrence of cardiac arrest).[10] The secondary outcomes were survival to ICU admission, survival to hospital discharge, and survival with favourable neurological outcomes at 30 days, 3 months, and 6 months. Neurological outcomes were evaluated using the Glasgow-Pittsburgh cerebral performance category (CPC) scale. Good neurological outcomes were defined as a CPC score of 1–2, poor neurological outcomes were defined as a CPC score of 3–4, and brain death was defined as a CPC score of 5. Patients were followed until either discharge or death.

Categorical data were presented as number and frequency. Continuous data were presented as mean and standard deviation, median and interquartile range, or number and range. Inter-group differences were evaluated using the independent two-sample t test, Mann-Whitney U, chi-square test, or Fisher's exact test, as appropriate. All analyses were performed using SPSS software (version 23.0; SPSS Inc., Chicago, IL), MedCalc software (version 15.2.2; MedCalc Ltd., Mariakerke, Belgium), or SAS software (version 9.1; SAS Institute Inc., Cary, NC).

3. Results

All patients received manual chest compressions and the same ACLS treatment. During the study period, we identified 383 patients with OHCA and 183 patients (93 pre-phase and 90 post-phase) had ventricular fibrillation or ventricular tachycardia as their initial rhythm. Among the 93 pre-phase patients with a shockable initial rhythm, we excluded 29 patients who achieved ROSC and 39 patients who were converted to pulseless electrical activity (PEA) or asystole before 3 defibrillation attempts. Thus, 25 patients were finally included in the pre-phase. Among the 90 post-phase patients with a shockable initial rhythm, we excluded 30 patients who achieved ROSC and 36 patients who were converted to PEA or asystole before 3 defibrillation attempts. In addition, we excluded 8 patients because we did not obtain consent for treatment from their guardians. Thus, 16 patients were finally included in the post-phase(Figure 1).

There were no significant differences in the baseline characteristics and ACLS treatments between the esmolol-treated and non-treated groups. Among the 9 patients in the esmolol group who achieved ROSC, the median duration of the esmolol infusion was 9.5 min (range: 7–16 min)(Table 1). Sustained ROSC was significantly more common in the esmolol group, compared to the control group (56% vs. 16%, $p = 0.007$). The esmolol group also exhibited better rates of temporary ROSC and survival to ICU admission. However, there were no significant differences in the rates of survival and good neurological outcomes at 30 days, 3months and 6months between the two groups (Table 2). Three out of the 9 patients who achieved sustained ROSC patients ultimately died within 24 h after their ICU admission, and another 3 patients died within the next 5 days.

When we compared the patients who did and did not achieve sustained ROSC, we found

that the patients with sustained ROSC exhibited a shorter pre-hospital time and were more likely to have received esmolol. And the patients treated with esmolol was significantly more common in the sustained ROSC group, compared to the no sustained ROSC group (69.2% vs. 25%, p=0.007). Amiodarone use was 1.5-fold more common in the sustained ROSC group, although this difference was not statistically significant (Table 3).

4. Discussion

Prolonged RVF-induced cardiac arrest is an extremely critical status that is associated with poor outcomes.[11] Our results indicate that resuscitation using intravenous esmolol might produce good clinical outcomes, as patients who received esmolol exhibited higher rates of temporary ROSC, sustained ROSC, and survival to ICU admission.

Epinephrine is a standard vasoactive drug during CPR regardless of the initial rhythm[12, 13]. It's fast alpha-adrenergic effect can increase the coronary blood flow through systemic arteriolar vasoconstriction.[14-16] Epinephrine is also thought to be crucial to achieve the minimal coronary perfusion pressure (CPP) for successful defibrillation. However, the beta-adrenergic stimulating action of epinephrine may be associated with the deleterious effects on the fibrillated myocardium. During VF, oxygen consumption of myocardium generally increases to more than 4-fold of non-fibrillated myocardium.[17, 18] Epinephrine can heighten the myocardial oxygen consumption through positive inotropic and chronotrophic effects by beta stimulation. Epinephrine may cause serious disequilibrium between oxygen demand and supply in VF patients. Also, beta stimulation of epinephrine is associated high failure of successful defibrillation through promotion of hyperphosporylation of Ryanodine receptor 2 (RyR2) in the myocardium.[19] This can lead to excessive influx of calcium into the cytoplasm

in myocardium and increase the myocardium electrical instability. Epinephrine may also increase right to left shunt and alveolar dead space ventilation in the lung and worsen the oxygen supply to the vital organs. Despite the essential role of the epinephrine for successful ROSC, accumulated use of epinephrine may be associated with myocardial-dysfunction during the post-resuscitation period and poor neurologic outcomes. Recently a large cohort of ROSC patients demonstrated that pre-hospital use of epinephrine was associated with lower chance of survival, and this association increased with the cumulated dosage and delay of the first administration.[12, 13]

Many investigators have suggested that selective block of beta adrenergic receptors can contribute to the reduction of these deleterious effects of epinephrine during CPR. Considering ethical problems in the challengeable use of new drugs during CPR, most of the evidence came from the animal arrest models. In a pig model, co-administration of selective beta blocking agents (esmolol) with epinephrine showed improvement of ROSC and 4 hour-survival compared to the epinephrine only group.[20] Two studies of a rat model revealed that co-administration of selective beta blocking agent (esmolol) improved the success of resuscitation, minimized the myocardial impairment and increased the duration of survival.[21, 22] Bassiakou et al's study demonstrated that beta-blocker (atenolol) could increase coronary blood flow and pressure along with increase of ROSC in the swine model with ventricular fibrillation.[4] For post-resuscitation care, beta blocker (carvedilol) was helpful to improve the myocardial dysfunction, and increased short-term survival in rat models.[23]

Most animal study results agreed that use of beta blocker is beneficial in the setting of arrest with fibrillation and in the post-resuscitation setting. However, use of beta-blocker for arrest victims in the real world setting was a cautious issue to most physicians. There are remarkable differences in function and presence of the beta-adrenoceptors between the

human and animals.[24] Little evidence of beta blocker usage during CPR exits for humans. Only two prospective clinical studies showed better results in treating patients who presented with refractory ventricular arrhythmia.[7, 8]

Our study tried to reveal the efficacy of beta-blockers in real clinical settings. Beta blockers such as carvedilol, esmolol, atenolol were studied and showed beneficial effects on the therapy of VF and post-resuscitation care. Which beta blocker we should use was an important issue before we planned for the use of beta blocker for refractory VF patients. Esmolol was chosen, as it is a cardio selective β blocker with a short elimination half-life (9 minutes). Upon discontinuation of infusion, the effect of beta adrenergic blockade is no longer evident after 10-20min.[25] Thus esmolol may be safely initiated in patients with relative contraindication to beta-blockade such as impaired left ventricular function, sinus node dysfunction, atrioventricular conduction defect.[26] In addition, this drug was widely used in the animal studies, and most studies had shown better results in highly successful defibrillation, longer survival after ROSC, no VF recurrence and protective myocardial function after CPR.[9, 19-22, 27] Most of all, esmolol was well known to act as a suppressor to hyperphosphorylation of RyR2 which was mediated by epinephrine, and can prevent myocardium instability.[19] Therefore, we speculate that esmolol is the optimal beta-blocker to maximize the increased success of treating refractory VF and contributes to increasing ROSC and long-term survival.

In our study, comparing with the conventional treated refractory VF, administration of esmolol increases chances of temporary and sustained ROSC. Over 80% of refractory VF patients recovered the spontaneous circulation and over 50% can be admitted to the ICU after sustained ROSC. Success rate of sustained ROSC reached three fold of that in the non-beta blocker used group. Concerning that refractory VF is not easily treatable because of the

serious stressful status of myocardium by electrical storm, this result seemed to be inspiring. These findings are similar to the previous study findings of Driver et al.,[8] who reported good clinical outcomes in the esmolol group. This study was limited by a small sample size and no statistically significant differences between the two groups (6 of esmolol group VS. 19 of control group). In this study, the esmolol group exhibited higher rates of sustained ROSC (66.7% vs.31.6%), survival to the ICU (66.7% vs. 31.6%), survival to hospital discharge (50% vs. 15.8%), and survival to hospital discharge with good neurological outcomes (50% vs. 10.5%). Both our findings and those of Driver et al. indicate that esmolol was associated with better clinical outcomes.

However, in our study, the esmolol did not show statistically significant improvement in long-term survival and neurological benefits, compared to the control group. This is a remarkable different point between our study and the study of Driver et al. Comparing with the study of Driver et al which showed higher rate of long term survival (3 of 4; 75%), only three among nine ROSC patients (33.3%) survived long term and had good neurologic out come in our study. Esmolol can increase the chance of successful ROSC, but unfortunately, approximately 2/3 of ROSC patients did not survive long-term. We assume that this may be related to the relatively long CPR duration (median time: 51.5 min) in the ROSC group. Despite successful ROSC, most patients may have seriously suffered from whole-body ischaemia-reperfusion syndrome that is called “post-cardiac arrest syndrome”. This unique pathophysiological process involves multiple organs and includes post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response and persistent precipitating pathophysiology. [28] Thus, prolonged CPR may have resulted in reduced survival and irreversible hypoxic brain damage that we observed in the present study.

This study had some limitations. This is a retrospective analysis between the pre- post treated

group which may have selection bias. In addition, this study was only performed at a single hospital and included very small sample of patients despite a long study period. Also, our study results may be limited to be generalised. However, considering that collecting clinical data of RVF treatment is extremely difficult because of the rareness of events and emergent situations, we think that our study result is acknowledgeable. This study successfully revealed that the esmolol using group may be superior to the non-esmolol using group for improving the overall outcomes of RVF. For strong evidence of using esmolol in the RVF arrest, well-designed, prospective and large population studies will be demanded in the future.

4.2 Conclusion

Our findings indicate that esmolol treatment was associated with high rates of sustained ROSC and survival to ICU admission among patients with RVF in OHCA. Further larger-scale, prospective studies are necessary to determine the effect of esmolol for RVF in OHCA

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None.

Conflict of interest statement

None.

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Table 1. Comparisons of baseline characteristics and treatment between the esmolol treated and esmolol non-treated groups

	Esmolol (N = 16)	No esmolol (N = 25)	*p*
Age, median (range), yr	58(45.8-72)	52(43.5-64.5)	0.26
Male, n (%)	14(87.5)	19(76)	0.5
Witnessed by laypersons, n (%)	14(87.5)	17(68)	0.15
Bystander CPR, n (%)	11(68.8)	16(64)	0.75
Initial rhythm VF, n (%)	14(87.5)	21(84)	0.57
Cardiac origin, n (%)	15(93.8)	23(92)	1.0
Time from call to EMS arrival (min), median(IQR)	5(4-7.3)	6(5-11)	0.1
Total pre hospital time (min), median(IQR)	25.5(19.8-30)	25(17-38)	0.82
Total ED CPR time (min), median(IQR)	25.5(16.3-35.3)	29(22-36)	0.47
Total CPR time (min), median (IQR)	55(35.3-70.3)	67(44.5-64.5)	0.5
Defibrillation attempts, median (IQR)	6(6-8.75)	5(5-6.5)	0.08
Adrenaline (mg), median (IQR)	6(3.3-9)	6(5-8)	0.94
Amiodarone (mg), median (IQR)	450(300-450)	300(300-450)	0.22
Sodium bicarbonate (meq), median (IQR)	0(0-40)	0(0-160)	0.15

Table 2. Comparisons of outcomes between the esmolol treated and esmolol non-treated groups

	Esmolol(16)	No esmolol(25)	*p*
Temporary ROSC (%)	13 (81.3)	6 (24)	P < 0.001
Sustained ROSC (%)	9 (56.3)	4 (16)	0.007
Survival to ICU admission (%)	9 (56.3)	4 (16)	0.007
Targeted temperature management (33'C or 36'C) (%)	9(56.3)	4(16)	0.007
Survival at 30 days (%)	3(18.8)	2(8)	0.36
Survival at 3 months (%)	3(18.8)	2(8)	0.36
Survival at 6 months (%)	3(18.8)	2(8)	0.36
Good neurologic outcome at 30days (%)	3(18.8)	2(8)	0.36
Good neurologic outcome at 3 months(%)	3(18.8)	2(8)	0.36
Good neurologic outcome at 6 months (%)	3(18.8)	2(8)	0.36

Table 3. Comparisons of baseline characteristics and treatment between sustained and Non sustained ROSC groups

	Sustained ROSC (N = 13)	No sustained ROSC (N = 28)	*p*
Age, median (range), yr	50(40.5-61)	55(45-69)	0.21
Male, n (%)	10(76.9)	23(82.1)	1.0
Witnessed by laypersons, n (%)	12(92.3)	19(67.9)	0.13
Bystander CPR, n (%)	11(84.6)	16(57.1)	0.16
Initial rhythm VF,n (%)	12(92.3)	23(82.1)	0.65
Cardiac origin, n (%)	12(92.3)	26(92.9)	1.0
Time from call to EMS arrival,min:median(IQR)	5(4-8.25)	6(4-11)	0.56
Total pre hospital time,min:median(IQR)	23.5(13.75-29)	26(19-38)	0.025
Total ED CPR time,min:median(IQR)	22(10.75-58)	23.5(13.75-29)	0.19
Total CPR time, min; median (IQR)	51.5(34-7605)	59(47-65)	0.15
Defibrillation attempts; median (IQR)	4(3-7.5)	4(3-5)	0.52
Adrenaline, mg; median (IQR)	5.5(3-9)	7(5-9)	0.16
Amiodarone, mg; median (IQR)	450(225-450)	300(0-450)	0.06
Sodium bicarbonate, meq; median (IQR)	0(0-40)	0(0-160)	0.31
Treatment with esmolol, n (%)	9/13 (69.2)	7/28 (25)	0.007