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Randomised Controlled Trial

The effect of epinephrine and methylprednisolone on cardiac arrest patients☆

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ABSTRACT

Background: Cardiopulmonary resuscitation (CPR) involves organized procedures performed on patients with cardiac arrest. CPR method and techniques can determine neurological outcomes of the patients. The aim of this study is to investigate the effect of epinephrine in combination with methylprednisolone on neurological complications and the need for vasopressor after resuscitation in patients with cardiac and respiratory arrest.

Methods: In this randomized control clinical trial, patients referred to (XXX) who suffered from cardiac arrest and required CPR were included. Patients were divided into two groups; intervention (methylprednisolone + epinephrine) and placebo (epinephrine + placebo). Patients' information was completed in a questionnaire based on demographic information, main objectives and important variables (neurological complication and the need for vasopressor) and SPSSv21 was used for statistical analysis.

Results: A total of 347 patients were included in the study. The intervention and control group were not significantly different in terms of gender, age systolic and diastolic blood pressure, $p > 0.05$. CPC scores were also not significantly different among the two groups, $p > 0.05$.131 patients (37.8%) needed vasopressor after the intervention and 216 patients (62.2%) did not need vasopressor. The two groups were significantly different in terms of intervention ($P = 0.021$).

Conclusion: Glucocorticoid, methylprednisolone does not reduce the risk of neurological complications following CPR in cardiac arrest patients.

1. Introduction

Cardiac arrest is referred to a condition where heart function ceases resulting in loss of breath and consciousness [1,2]. Cardiopulmonary resuscitation (CPR) is performed to reverse cardiac arrest [3]. Approximately, 55.3 million individuals are reported to emergency department with cardiac arrest worldwide [4].

Neurological complication are commonly reported after cardiopulmonary arrest and its prevalence in various studies have been reported between 30 and 60%, which can cause changes in memory or psychomotor function that impair recovery, decrease quality of life and delayed return to normal routine [5]. Brain damage from cardiopulmonary arrest manifests itself in a wide range of disorders, including stroke, encephalopathy, and cognitive impairment. The most common manifestation of brain injury is stroke, which affects 1–3% of patients after cardiopulmonary arrest [6], but cognitive impairment is the most common neurological disorder in 65–30% of patients in the first month 20–45% of patients are seen after the fifth month [7,8].

Numerous studies have shown that adrenal insufficiency and high levels of plasma adrenocorticotropic hormone and antidiuretic hormone cause shock and increased mortality in patients, and therefore adrenal insufficiency in patients with return of spontaneous circulation (ROSC) following cardiac arrest will cause poor outcomes [9,10]. Treatment of adrenal insufficiency with corticosteroids, can reduce mortality and

Abbreviations: CPR, Cardiopulmonary resuscitation; ROSC, return of spontaneous circulation.

☆ The study was approved by the Ethics Committee and the Vice Chancellor for Research of Kermanshah University of Medical Sciences (**IRCT20130812014333N127**).

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dysfunction of vital organs and improves neurological complications [11–13]. In cardiac arrest, cortisol levels decrease during and after resuscitation, and studies have shown that ROSC and the prognosis of patients improves with combinational use of steroid and epinephrine in CPR [14,15].

2. Methods

In this randomized control clinical trial, patients referred to (XXX) from January 2020–December 2020 with respiratory arrest and need cardiopulmonary resuscitation were enrolled. The study was approved by the Ethics Committee and the Vice Chancellor for Research of (XXX). Inclusion criteria: All patients over 18 years of age who did not have a previous neurological problem and their next-to-kin consented to participate in the study. Exclusion criteria was patients under 18 years of age, with out-of-hospital cardiac arrest, those with neurological problems before resuscitation that interfered with CPC score after resuscitation, patients who could not be injected with resuscitation drug due to lack of peripheral blood vessels. There were no patients who did not have successful resuscitation or had cardiac arrest again 20 min after successful resuscitation.

According to the formula, the minimum sample size with 95% confidence and 80% power, also based on the percentage of CPC percentage of 13.9% vs 5.1%, the minimum sample size in each group was estimated 171 people. In order to increase the accuracy of the study, 171 samples were included in the intervention group treated with methylprednisolone and 176 samples in the placebo group. Finally, a total of 347 patients with cardiac arrest were included in the study.

$$n = \frac{\left(z\left(1-\frac{a}{2}\right)+z(1-\beta)\right)^2((p1\ x\ q1)+(p2\ x\ q2))}{(p2-p1)^2}$$

Patients were randomly divided into two groups of intervention and placebo based on a table of random numbers. For both groups, resuscitation was performed according to the AHA protocol chest compressions, shock and administration of epinephrine and antiarrhythmic if indicated.

Patients in both groups received epinephrine at a dose of 1 mg per CPR cycle, lasting approximately 3 min per cycle. For the intervention group, during the first cycle of resuscitation or during the second injection of epinephrine (3–5 min later), 125 mg of methylprednisolone was also injected intravenously, and in the placebo group, saline was injected as a placebo and resuscitation was continued. Methylprednisolone and saline were prepared in similar syringes and the clinician administered the injection only according to the specified code (blinded).

In addition to the special experts of this study (clinical experts), physicians, nurses, laboratory staff and those in charge of pharmaceutical affairs were trained. For this purpose, a special design manual was written and distributed. Training sessions and exchange of views were held with different groups before the commencement of the research.

Demographic information, history of previous illness, heart rate, the need for shock, and vital signs after resuscitation were recorded for all patients. During the first 24 h after resuscitation of neurological complications and blood pressure, patients were examined for CPC score (Cerebral performance category).

CPC score was defined as.

CPC 1: complete recovery or mild disability.
CPC 2: Conscious with moderate disability (conscious and not dependent on daily activities but with disorders such as paresis-seizures and cognitive impairments).
CPC 3: Severe dysfunction CPC 4: Coma or persistent vegetative state
CPC 5: Death.

The score were evaluated three times and the most frequent one was selected to reduce inter-rater differences.

2.1. Data analysis

The data was analyzed using SPSSv22. Descriptive statistics indices in the form of frequency and mean and standard deviation were used to present the data. The normality of data distribution was assessed using Kolmogorov-Smirnov test. T-test was used to evaluate the differences between quantitative variables in the presence of normal data distribution and Mann-Whitney-U statistical test was used in case of non-normal distribution. The relationship between qualitative variables was evaluated using chi-square and Fisher's exact test. P value less than 0.05 was considered statistically significant.

The design was approved by the Ethics Committee of (XXX).

The work has been reported in line with the CONSORT criteria [16].

Unique identifying number (UIN) of your study. 6905.

3. Results

347 patients were included in the study with 171 in intervention and 176 in placebo group. The mean age of the patients included in the study was 67.57 ± 17.87 years. To evaluate the normality of age data in the study population, Kolmogorov-Smirnov test was used. The test results showed that the age of the patients did not follow the normal distribution ($P = 0.036$). However, there was no statistically significant difference in the two groups in terms of age ($P = 0.255$), so the two groups were age-matched.

The results of the present study showed that, in the total population of the studied patients, 118 (34%) were female and 229 (66%) were male. There was no statistically significant difference in terms of gender between the intervention and placebo groups ($P = 0.163$).

A total of 288 (83%) patients had asystole rhythm (83%), 39 patients (11.2%) had PEA rhythm (pulse free electrical activity), 12 patients (3.5%) VT rhythm and 8 patients (2.3%) had VF rhythm. The two groups have a similar trend in terms of rhythm during resuscitation. In the placebo group 4 patients had successful asystole rhythm and resuscitation, also 4 patients had VT rhythm and successful resuscitation. In the intervention group 6 patients had successful resuscitation, all of which had an asystole rhythm (Table 1).

The mean systolic blood pressure in the study population was 74.50 ± 10.17 mmHg. The results of Kolmogorov-Smirnov test showed that systolic blood pressure data did not follow the normal distribution after resuscitation ($P < 0.001$). The two groups did not have a statistically significant difference ($P = 0.337$) in systolic blood pressure after resuscitation.

The results showed that the mean diastolic blood pressure in the study population was 47.32 ± 7.19 mmHg. The results of Kolmogorov-Smirnov test showed that diastolic blood pressure data did not follow the normal distribution after resuscitation ($P < 0.001$).

The two groups did not differ significantly in terms of diastolic pressure ($P = 0.133$).

The results showed that, in total 318 deaths (91.6%) CPC 5 were reported, 9 cases were of severe dysfunction CPC 4, CPC 3 (2.6%), 6 cases of coma (1.7%), 7 (2%) cases of CPC 2, moderate dysfunction (2%) and 7 cases of normal brain function (2%), CPC 1 were observed.

Table 1
Frequency and percentage of rhythm frequency during resuscitation in two groups of intervention and placebo.

Rhythm during resuscitation	intervention (Epinephrine + methylprednisolone)%	placebo (Epinephrine + placebo)%
Asystole	145 (84.8%)	143 (81.2%)
VT	3 (1.8%)	9 (5.1%)
VF	4 (2.3%)	4 (2.3%)
PEA	19 (11.1%)	20 (11.4%)
Total	171 (100%)	176 (100%)

The two groups did not differ significantly in terms of CPC score, Table 2 A total of 7 patients had normal life after resuscitation, of which 2.3% were in the intervention group and 1.7% in the placebo group.

The mean age of patients with successful CPR was 58.5 ± 14.31 years and in the failed CPR group was 70.4 ± 17.9 years (Table 3), which was significantly different ($P < 0.001$).

In total, 131 patients (37.8%) needed vasopressor after the intervention. The results of Chi-square test showed that the two groups were statistically different in terms of need for vasopressor ($P = 0.021$), Table 4.

4. Discussion

The aim of this study was to compare the effect of epinephrine in combination with methylprednisolone on neurological complications and the need for vasopressor after resuscitation in 347 patients with cardiopulmonary arrest over 18 years of age.

A 2011 study by Jaber et al. reported the success rate of in-hospital cardiopulmonary resuscitation. In this study, the success rate of resuscitation in patients with VT and VF rhythms was higher than other rhythms, including PEA during cardiac arrest [17].

Methylprednisolone is a moderately active glucocorticoid and, like other drugs, has side effects including increased blood pressure. In the present study, the effect of epinephrine in combination with methylprednisolone in patients with cardiac arrest on systolic and diastolic blood pressure and the need for vasopressor during 24 h after resuscitation was not significantly different to placebo group. Slightly high-dose epinephrine rarely increases spontaneous return of blood flow and increases the chances of early survival. In several clinical trials in more than 9000 patients with cardiac arrest, high-dose epinephrine showed no improvement in survival, discharge or improvement in neurological results compared to standard doses. In the present study, epinephrine as a placebo group was evaluated and compared [18].

Based on the results of CPC score in the present study, 318 deaths (91.6%), 9 severe dysfunction (2.6%), 6 coma (1.7%), 7 moderate dysfunction (2%) and 7 cases of good brain function (2%) were observed, and no significant difference in CPC score was observed among patients in the two groups, indicating that the addition of methylprednisolone had no significant effect on patients' CPC score. No, a total of 7 patients had normal life after resuscitation, of which 2.3% were in the intervention group and 1.7% in the placebo group. Consistent with our findings, in the study of Haji Bagheri et al. [19]. and in the study of Dolatabadi et al. [20] conducted in Iran, the mortality rate after resuscitation was more than 90% and the rate of hospital discharge was less than 7% is reported. Zandbergon EG et al., reported that the difference in success rates for CPR at home and hospital, with many patients receiving BLS (basic life support) before entering the hospital, leading to an increase in success and reduction in complications [21].

In many studies, the simultaneous effect of epinephrine and several drugs for reduction in neurological complications and the need for vasopressor has been considered. In a study by Torabi et al. comparison with epinephrine and vasopressin showed that, it was concluded that, due to reduced incidence of tachycardia in patients receiving vasopressin, vasopressin may in certain conditions, such as in combination with other drugs improve asystole rhythm [22].

Mentzelopoulos et al. [23] investigated the effects of the combination of vasopressin, epinephrine and methylprednisolone (n = 130) with the epinephrine and placebo group (n = 138). Intervention group showed greater rate for return of spontaneous circulation (83.9%), compared to control (65.9%) along with more survival to hospital discharge rate (13.9 vs 5.1). However, the rate of adverse events were not different in the two groups. In 2018, a study by Belletti A et al. reported that the combination of adrenaline, vasopressin and methylprednisolone was not associated with reduced neurological complications [24]. Similarly, Bolvardi et al. conducted a clinical trial to evaluate the effects of prednisolone on neurological complication in patients with cardiopulmonary arrest. The study evaluated CPC score following 24 h of the treatment. Findings of the study concluded that the rate of successful CPR and CPC score were not significantly different in the prednisolone and placebo groups. The findings are parallel with those reported from our study. However, 48-h effect of the treatment can give better findings, since it can take more than 48 h for brain edema to resolve, which might require multiple doses of the drugs. S

In the present study, the combination of methylprednisolone and epinephrine did not cause any neurological complications compared to epinephrine and placebo. However, in the total number of patients studied, the need of vasopressor was significantly more in intervention group (epinephrine + methylprednisolone). Mentzelopoulos et al. [25], investigated effect of methylprednisolone in 100 patients with cardiac arrest who needed resuscitation. Post-resuscitation vasopressin epinephrine and methylprednisolone improved survival, hemodynamics, and oxygen saturation and organ-failure free days.

The ideal result of a resuscitation operation is one hundred percent return of the patient to life. However, there are several factors involved in the success or failure of this such as underlying diseases, the length of cardiac arrest until the start of resuscitation, the availability of trained staff, and pharmacological and non-pharmacological method employed.

Some of the limitations of our study include lack of data regarding baseline hormone levels, myocardial functioning after arrest and 1-year follow up data and sample size. Our study doesn't long term neurologic outcomes in these patients, which has been recommended based on recent guidelines [26]. Future studies including these variables and additional role of vasopressin are therefore, required in this field.

One of the major challenges during the study was getting enough staff who could perform CPR based on standard protocols and is experienced. For this, we recruited trained medical staff with at least 3 years

Table 2
Frequency and percentage of CPC Score in two groups of intervention and placebo.

CPC score	intervention (Epinephrine + methylprednisolone)%	placebo (Epinephrine + placebo)%
Death (score = 5)	157 (91.8%)	161 (91.5%)
Coma (score = 4)	3 (1.8%)	3 (1.7%)
severe dysfunction	5 (2.9%)	4 (2.3%)
moderate dysfunction	2 (1.2%)	5 (2.8%)
normal brain function	4 (2.3%)	3 (1.7%)

8 cells (80.0%) have expected count less than 5. The minimum expected count is 2.96.

Table 3
Percentage of success in CPR based on CPC Score in the intervention and placebo groups.

CPC score	intervention (Epinephrine + methylprednisolone) %	placebo (Epinephrine + placebo) %
successful	6 (3.5%)	8 (4.54%)
Failed	165 (96.5%)	168 (94.45%)

Table 4
Frequency and percentage of need for vasopressor in two groups of intervention and placebo.

needed vasopressor	intervention (Epinephrine + methylprednisolone) %	placebo (Epinephrine + placebo) %	p-value
Yes	75 (43.9%)	56 (31.8%)	0.021
No	96 (56.1%)	120 (68.2%)	

of experience at our center and the protocols and procedures of the study was briefed to them. Students and internees were not utilized to perform any medical procedure, in order to avoid discrepancies in the data.

5. Conclusion

The findings of our study indicated that the addition of glucocorticoid for CPR doesn't not alter neurological complication among cardiac arrest patients. The need of vasopressor was significantly more in intervention group.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Please state any conflicts of interest

The authors deny any conflict of interest in any terms or by any means during the study.

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Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent

Not applicable.

Author contributions

Dr. Shahrouz Tabrizi: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Dr. Nasrin Bahrami, Dr. Amir Hossein Meisami and Dr. Haniyeh Azadifar: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Dr.Hooman Rafiei: Coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

Registration of research studies

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Guarantor

Dr. Hooman Rafiei.

References

[1] R. Alizadeh, Z. Aghsaeifard, M. Sadeghi, P. Hassani, P. Saberian, Effects of prehospital traige and diagnosis of ST segment elevation myocardial infarction on mortality rate, Int. J. Gen. Med. 13 (2020) 569–575.
[2] M. Ahmadinejad, I. Ahmadinejad, L.H. Maghsoudi, A. Soltanian, M. Safari, Complications in patients with cardiac penetrating trauma, Cardiovasc. Haematol. Disord. - Drug Targets 21 (4) (2021) 212–216.
[3] M. Nikravan-Mofrad, Comprehensive CPR Book in Adult, Tehran Noore-danesh Publication, 2001, pp. 1–5.
[4] T. Colak, B.O. Tekten, Factors affecting survival and neurological outcomes for patients who underwent cardiopulmonary resuscitation, J. Pakistan Med. Assoc. (2020) 2020.
[5] M. McCoyd, T. McKiernan, Neurologic complications of cardiac arrest, Handb. Clin. Neurol. 119 (2014) 25–39.
[6] C.W. Hogue, T. Sundt, B. Barzilai, K.B. Schecthman, V.G. Dávila-Román, Cardiac and neurologic complications identify risks for mortality for both men and women undergoing coronary artery bypass graft surgery, J. Am. Soc. Anesthesiologists 95 (5) (2001) 1074–1078.
[7] U. Sofi, T. Kokroo, E. Velasquez, M. Kline, Predictive indices of survival in patients undergoing cardiopulmonary resuscitation, Chest 116 (4) (1999) 245S–S.
[8] M. Aryafar, R. Bozorgmehr, R. Alizadeh, F. Gholami, A cross-sectional study on monitoring depth of anesthesia using brain function index among elective laparotomy patients, Int. J. Surg. Open 27 (2020) 98–102.
[9] Z. Aghsaiefard, Z. Hossenifard, R. Alizadeh, T. Ramim, The relationship between hemoglobin level with PTH level and dialysis adequacy in chronic hemodialysis patients, Tehran Univ. Med. J. 76 (4) (2018) 257–264.
[10] Z. Aghsaeifard, R. Alizadeh, N. Bagheri, Association between neutrophil gelatinase-associated lipocalin (NGAL) and iron profile in chronic renal disease, Arch. Physiol. Biochem. (2020) 1–5.
[11] Effects of immunosuppressive drugs on rat renal ischemia reperfusion injury, in: C. Parra, P. Salas, J. Dominguez (Eds.), Transplantation Proceedings, Elsevier, 2010.
[12] R. Alizadeh, Z.A. Fard, Renal effects of general anesthesia from old to recent studies, J. Cell. Physiol. 234 (10) (2019) 16944–16952.
[13] R. Alizadeh, Z. Aghsaie Fard, Renal impairment and analgesia: from effectiveness to adverse effects, J. Cell. Physiol. 234 (10) (2019) 17205–17211.
[14] G.L. Büchele, E. Silva, G.A. Ospina-Tascon, J.-L. Vincent, D. De Backer, Effects of hydrocortisone on microcirculatory alterations in patients with septic shock, Crit. Care Med. 37 (4) (2009) 1341–1347.
[15] M. Ahmadinejad, A. Shirzadi, A. Soltanian, I. Ahmadinejad, S. Sootodeh, The impact of intercostal nerve block on the necessity of a second chest x-ray in patients with penetrating trauma: a randomised controlled trial, Int. J. Surg. Open 29 (2021) 24–28.
[16] K.F. Schulz, D.G. Altman, D. Moher, CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials, Ann. Intern. Med. 152 (11) (2010) 726–732.
[17] Y. Jaberi, L. Changizian, S. Mazlomzadeh, Predictors of outcome in in-hospital cardio-pulmonary resuscitation, J. Adv. Med. Biomed. Res. 19 (75) (2011) 48–57.
[18] A.H. Travers, T.D. Rea, B.J. Bobrow, D.P. Edelson, R.A. Berg, M.R. Sayre, et al., Part 4: CPR overview: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, Circulation 122 (18_suppl_3) (2010) S676–S684.
[19] M.A. Hajbaghery, G. Mousavi, H. Akbari, Factors influencing survival after in-hospital cardiopulmonary resuscitation, Resuscitation 66 (3) (2005) 317–321.
[20] A.A. Dolatabadi, A. Setayesh, M. Zare, A. Hosseinnejad, F. Bozorgi, D. Farsi, Descriptive analysis of contributing factors in outcomes of emergency department CPRs, Crit. Care 9 (1) (2005) 1.
[21] S.H. Montazar, M. Amooei, M. Sheyoei, M. Bahari, Results of CPR and contributing factor in emergency department of sari imam Khomeini hospital, 2011-2013, J. Mazandaran University. Med. Sci. 24 (111) (2014) 53–58.
[22] M. Torabi, Effect of Vasopressin and Epinephrine in Cardiac Arrest Outcome in Patients with Asystole Rhythm, 2015.
[23] S.D. Mentzelopoulos, S. Malachias, C. Chamos, D. Konstantopoulos, T. Ntaidou, A. Papastylianou, et al., Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial, JAMA 310 (3) (2013) 270–279.
[24] A. Belletti, U. Benedetto, A. Putzu, E.A. Martino, G. Biondi-Zoccai, G.D. Angelini, et al., Vasopressors during cardiopulmonary resuscitation. a network meta-analysis of randomized trials, Crit. Care Med. 46 (5) (2018) e443–e451.
[25] S.D. Mentzelopoulos, S.G. Zakynthinos, M. Tzoufi, N. Katsios, A. Papastylianou, S. Gkisioti, et al., Vasopressin, epinephrine, and corticosteroids for in-hospital cardiac arrest, Arch. Intern. Med. 169 (1) (2009) 15–24.
[26] R.G. Geocadin, C.W. Callaway, E.L. Fink, E. Golan, D.M. Greer, N.U. Ko, et al., Standards for studies of neurological prognostication in comatose survivors of cardiac arrest: a scientific statement from the American heart association, Circulation 140 (9) (2019) e517–e542.