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Meta-analysis review

Is epinephrine still the drug of choice during cardiac arrest in the emergency department of the hospital? A meta-analysis

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ABSTRACT

Epinephrine is the first-line emergency drug for cardiac arrest and anaphylactic reactions but is reported to be associated with many challenges resulting in its under- or improper utilization. Therefore, in this meta-analysis, the efficacy and safety of epinephrine as a first-line cardiac emergency drug for both out-of-hospital and in-hospital patients was assessed. Pertinent articles were searched in central databases like PubMed, Scopus, and Web of Science, using appropriate keywords as per the PRISMA guidelines. Retrospective and prospective studies were included according to the predefined PICOS criteria. RevMan and MedCalc software were used and statistical parameters such as odds ratio and risk ratio were calculated. Twelve clinical trials with a total of 208,690 cardiac arrest patients from 2000 to 2022 were included, in accordance with the chosen inclusion criteria. In the present meta-analysis, a high odds ratio (OR) value of 3.67 (95 % CI 2.32–5.81) with a tau^2 value of 0.64, a chi^2 value of 12,446.86, df value of 11, I^2 value of 100 %, Z-value 5.53, and a p-value < 0.00001 were reported. Similarly, the risk ratio of 1.89 (95 % CI 1.47–2.43) with a tau^2 value of 0.19, chi^2 value of 11,530.67, df value of 11, I^2 value of 100 %, Z-value of 4.95, and p-value < 0.000001. The present meta-analysis strongly prefers epinephrine injection as the first cardiac emergency drug for both out--of-hospital and in-hospital patients during cardiac arrest.

Keywords: cardiac arrest, epinephrine/adrenaline, cardiopulmonary resuscitation, cardiac-emergency medicine, intravenous injection, intracardiac injection

INTRODUCTION

Cardiac arrest is a global public health concern and accounts for about 15–20 % of all deaths (1). Cardiac arrest means the sudden loss of heart function and lack of blood flow throughout the body, which leads to loss of breathing and consciousness (2, 3). Patients with cardiac arrest experience severe pain, difficulty breathing, and become unconscious

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in a short period of time as a result of these dramatic metabolic changes, and if not treated, they die (4, 5). It happens to owe to the sudden disturbance in the electrical activity of the heart that leads to arrhythmia, irregular heartbeats and loss of blood flow to different regions of the body.

To treat sudden in-hospital or out-of-hospital cardiac arrest patients, the first-aid treatment is the injection of cardiac emergency drugs like adrenaline (epinephrine), amiodarone, lidocaine, atropine, *etc*. (6, 7). These drugs can be injected into the patient like intracardiac, intramuscular, intra-osseous or intravenous injections (6–9), the latter being preferred owing to fast drug delivery and rapid onset of drug effects (10). Epinephrine is the generic or official name of adrenaline, a hormone produced by our adrenal cortex, and also acts as a neurotransmitter. Epinephrine is a potential sympathomimetic drug which acts on alpha-1 receptors and increases the heart rate, contraction of smooth muscles and myocardial contractility. In cardiac arrest, it significantly improves the heart rate and spontaneous circulation of patients with favourable neurological outcomes. It also acts on the kidney *via* beta-1 receptors and increases the release of renin. Different randomized controlled trials, prospective and retrospective studies, recommend epinephrine as the first cardiac emergency drug. It is a preferred drug for cardiac arrest because it can rapidly increase the blood flow to the heart and proximately restore the heartbeat (11).

Several research groups recommended epinephrine against cardiac arrest (12–23). Huan *et al*. (24), in their systematic review and meta-analysis, also suggested epinephrine as the preferred drug for the treatment of out-of-hospital cardiac arrest. In their review article, Wyer *et al*. (25) stated that epinephrine is more useful than vasopressin because it ensures a higher proportion of survivability to hospital discharge and more favorable neurological outcomes. In their systematic reviews and meta-analyses, the research groups led by Ludwin, Srisurapanont and Morales-Cane (26–28) reported that with a higher rate of spontaneous circulation and longer survival after cardiopulmonary resuscitation (CPR), epinephrine/adrenaline is the medication of choice for adults as compared to other drugs like vasopressin, atropine, *etc*. Similarly, Lundin, Gallimore and Papastylianou with their co-workers (29–31) in their review studies pointed to epinephrine/adrenaline as a useful medication in the treatment of cardiac arrest.

Although all of the above studies reported the potential benefits and high efficiency of epinephrine as a first-line cardiac emergency drug, some studies, such as Sinha *et al*. (32) and Amacher *et al*. (33), suggest that more studies and research are needed to establish epinephrine as a first line cardiac emergency drug. Also, studies like the PARAMEDIC-2 trial of Jung *et al*. (34) suggest that rethinking is needed about the role of epinephrine in cardiac arrest. Epinephrine is the choice of treatment for cardiac arrest and life-threatening anaphylactic reactions, but is associated with many issues like allergic reactions, chest pain, vomiting, nervousness, breathing issues, tachycardia, *etc*. Gough *et al*. (35) reported in their review that epinephrine can impair cerebral microcirculatory flow. Unless epinephrine has great potential to save life, due to these issues and challenges reported by many research articles its use is limited.

Because of contradictory views regarding the use of epinephrine as the first-line cardiac emergency drug, the meta-analysis based on the selected studies (different randomized controlled trials, cohorts, prospective and retrospective studies) was undertaken in the present study, as a new contribution to the knowledge of the efficacy of epinephrine in cardiac arrest.

SOURCES AND METHODES

In the present study the guidelines of PRISMA (preferred reporting items for systematic reviews and meta-analyses) normative recommendations were followed.

Search techniques

This meta-analysis is based on a thorough search of the databases Medline (through PubMed), Cinahl (*via* Ebsco), Scopus and Web of Science, from 2000 to 2022. The keywords used were: cardiac arrest, epinephrine, adrenaline, intravenous injection, intracardiac injection, cardiopulmonary resuscitation, cardiac-emergency medication, meta-analyses, and various RCTs on epinephrine to search for relevant studies. All included papers were chosen in accordance with the PRISMA standards, and studies were chosen at random, regardless of language, publication status or study type (prospective, retrospective or clinical trial). The selected studies yielded a demographic summary of the patients as well as event data. The entire texts of the sources' papers were collected, and abstracts were included only if they contained enough information for the meta-analysis.

Outdated studies were removed, and valuable research was incorporated in accordance with the inclusion criteria.

Criteria for inclusion and exclusion

The trials that employed epinephrine for the treatment of both in-hospital and out-of--hospital cardiac arrest patients were considered. The studies were chosen between the years 2000 and 2022. We considered only full-text data in the current study, excluding publications with insufficient data, studies reporting the use of medications other than epinephrine, and related studies published before 2000.

Analytical standard and source of heterogeneity evaluation

The following factors contributed to the investigated heterogeneity: use of full-text publications *versus* abstracts, distinct age groups and patient numbers, variable length of therapy, different study outcomes, and comparison with different controls. Deek's funnel plot, Cochran Q statistic, and I^2 index in the random bivariate mode were produced using RevMan software to study heterogeneity. The included studies' risk of bias was assessed, and the related risk of bias summary and risk of bias graph were created using RevMan software (36).

Analytical statistics

The Mantel Haenszel method (37) with random bivariate effects was used to calculate statistical parameters like diagnostic odds ratio, and relative risk with a 95 % confidence interval using RevMan software (38) along with their respective forest plots. The tau^2 value, chi^2 value, I^2 value, and Z-value were used to assess heterogeneity in the included studies. A *p*-value of 0.05 was deemed statistically significant. The DerSimonian Lair approach was used to determine the diagnostic odds ratio. RevMan software was used to do a meta-analysis on a 2 × 2 table. A pooled diagnostic odds ratio with a 95 % confidence

interval was determined, and forest plots were created accordingly. Begg's and Egger's tests were used to examine the publication bias of the included studies (39), and a funnel plot was created by graphing the log risk ratio of each research against its standard error using MedCalc software (40). The medicine's efficacy was determined by comparing the positive outcomes of epinephrine and the control drug using the Box and Whisker Plot (41).

RESULTS AND DISCUSSION

Outcomes of literature search for meta-analysis

Through electronic searches of several databases, we discovered a total of 1,012 studies. We eliminated 145 studies by reading their titles and abstracts and 867 records were reviewed. Furthermore, we removed 604 studies due to faulty references and duplication, leaving only 263 for final screening. Out of these 263 studies, 185 were removed due to

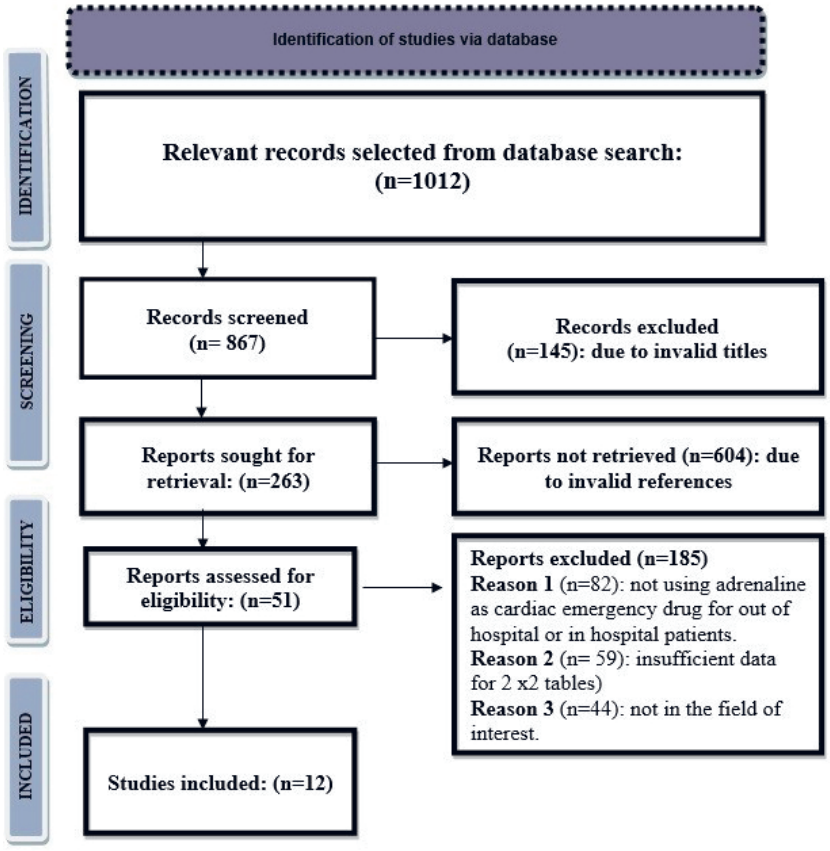

Fig. 1. PRISMA diagram of the study group.

Table I. Quality assessment for included studies

Ref.	12	13	14	15	16	17	18	19	20	21	22	23
Did the studies avoid inappropriate exclusions?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Did all patients receive the same reference standard?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Were all patients included in the analysis?	no	no	no	no	no	no	no	no	no	no	no	no
Was the sample frame appropriate to address the target population?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Were study participants sampled in an appropriate way?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Were the study subjects and the setting described in detail?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Were valid methods used for the identification of the condition?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Was the condition measured in standard, reliable ways for all participants?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Was there an appropriate statistical analysis?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

inclusion criteria, and the eligibility of the remaining 51 was further evaluated. The main reasons for omission were insufficient evidence and insufficient comparative criteria for creating 2 × 2 tables for review. Finally, for the meta-analysis, 12 studies that met the inclusion criteria, *i.e.*, the use of epinephrine for cardiac arrest, were used, as shown in Fig. 1. According to the specified inclusion criteria, twelve studies included a total of 208,690 cardiac arrest patients during the years 2000 to 2022. Adult patients of various ages were chosen at random and treated with either an intravenous injection of epinephrine or the control drug, which in most cases was vasopressin. The number of patients who had positive outcomes was retrieved as event data and statistically examined in both circumstances.

Risk of bias assessment

Table I reports on the quality or risk of bias assessment for the included studies. The RevMan software was used to do the risk of bias analysis, and we discovered that the risk of bias was minimal, as indicated in the related risk of bias summary in Fig. 2 and the risk of bias graph in Fig. 3.

Table II gives the total sample size, in-hospital or out-of-hospital patients, epinephrine and control medication doses used, study outcomes, number of patients with positive outcomes, and related *p*-values for the statistical significance of the data.

Meta-analysis results

RevMan software was used to conduct a meta-analysis. The software MedCalc was used to measure publication bias. The funnel plot

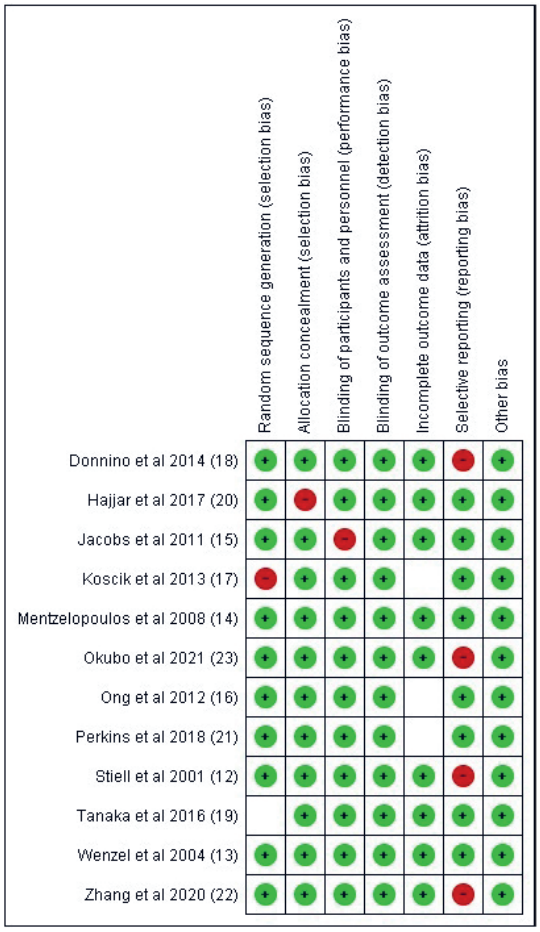

Fig. 2. Risk of bias summary.

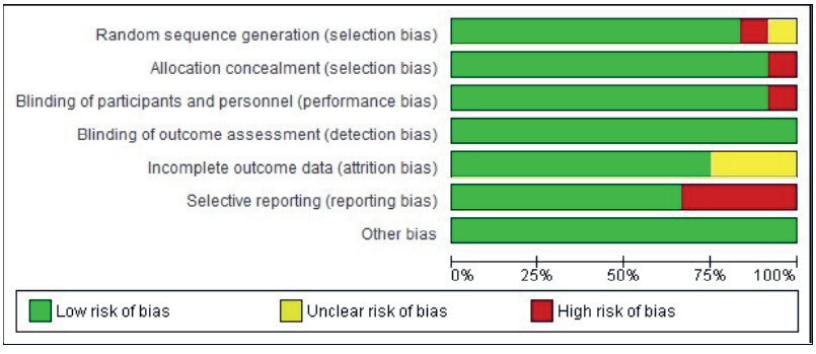

Fig. 3. Risk of bias graph.

Table II. Included studies information

Study type	Number of patients	Clinical trial purpose	Drug used in patients out of total		Dose	Administration route	Outcome(s)	Recommendation	*p*-value	Ref.
Randomised controlled trial	200	Treatment of in-patient cardiac arrest	Epinephrine	96/200	1 mg	*i.v.*	Survival to hospital discharge, neurological function	Epinephrine	0.03	12
			Vasopressin	104/200	40 U	*i.v.*				
Randomised controlled trial	1,186	Treatment of out-of-hospital cardio-pulmonary resuscitation	Epinephrine	597/1,186	1 mg	*i.v.*	Survival to hospital and survival to hospital discharge	Vasopressin followed by epinephrine	0.02	13
			Vasopressin	589/1,186	40 U	*i.v.*				
Prospective, randomized, double-blind, placebo-controlled, trial	100	Treatment of in-patient cardiac arrest	Epinephrine	39/48	1 mg	*i.v.*	Return of spontaneous circulation for 15 min, survival to hospital discharge	Combined vasopressin and epinephrine	0.02	14
			Vasopressin	27/52	20 IU	*i.v.*				
Randomized controlled trial	534	Treatment of out-of-hospital cardiac arrest patients	Epinephrine	272/564	1 mg	*i.v.*	Survival to hospital discharge, neurological outcome, pre-hospital ROSC	Epinephrine	0.04	15
			Placebo	262/534	0.9 %	*i.v.*				
Randomized controlled trial	727	Treatment of cardiac arrest patients presenting to or in ED	Epinephrine	353/727	1 mg	*i.v.*	Survival to hospital discharge or survival upto 30 days post-arrest	Combined vasopressin and epinephrine	0.03	16
			Vasopressin	374/727	40 IU	*i.v.*				
Retrospective analysis	809	Treatment of out-of-hospital cardiac arrest patients	Epinephrine	686/809	1 mg	*i.v.*	Return of spontaneous circulation, survival to hospital discharge	Earlier administration of epinephrine	0.03	17
			No epinephrine	123/809	–	–				
Retrospective analysis	119,978	Treatment of in-hospital patients of cardiac arrest	Epinephrine	25,095/119,978	1 mg	*i.v.*	Survival to hospital discharge. sustained return of spontaneous circulation, 24-h survival, favorable neurologic status at hospital discharge	Earlier administration of epinephrine	0.02	18
			No epinephrine	94,883/119,978	–	–				

Study type	Number of patients	Clinical trial purpose	Drug used in patients out of total		Dose	Administration route	Outcome(s)	Recommendation	*p*-value	Ref.
Prospective, population-based observational study	119,639	Treatment of out-of-hospital cardiac arrest patients	Epinephrine	20,420/119,639	1 mg	*i.v.*	Cerebral performance category, return of spontaneous circulation	Early epinephrine administration within 19 min	0.04	19
			Control	99,219/119,639	1 mg	*i.v.*				
Prospective, randomized, double-blind trial	330	For vasoplegic shock after cardiac surgery	Norepinephrine	151/330	1 mg	Infusion	Requirement for mechanical ventilation for longer than 48 h, stroke, deep wound infection, acute renal failure within 30 days	Vasopressin	0.02	20
			Vasopressin	149/330	40 IU	Infusion				
Randomized, double-blind controlled trial	8,014	Treatment of out-of-hospital cardiac arrest patients	Epinephrine	4,015/8,014	1 mg	*i.v.* or *i.o.*	Rate of survival until hospital discharge, favourable neurologic outcome	Epinephrine	0.02	21
			Saline placebo	3,999/8,014	0.9 %					
Retrospective cohort study	35,733	Treatment of out-of-hospital cardiac arrest	Epinephrine	27,758/35,733	1 mg	*i.v.*	Survival to hospital discharge, pre-hospital return of spontaneous circulation, favourable neurological outcome	Epinephrine administration by *i.v.*	0.01	22
			Epinephrine	7,975/35,733	1 mg	*i.o.*				
Cohort study	41,079	Treatment of out-of-hospital cardiac arrest	Epinephrine with shockable cardiac rhythm	10,088/41,079	1 mg	*i.v.*	Survival to hospital discharge and favorable functional status at hospital discharge	Recommend epinephrine for both cases	0.02	23
			Epinephrine with non-shockable cardiac rhythm	30,991/41,079	1 mg					

ED – emergency department, *i.o.* – intraosseous, *i.v.* – intravenous, ROSC – returns of spontaneous circulation

(Fig. 4) and the results of the Egger's, Begg and Mazumdar tests show that the current meta-analysis has a low probability of publication bias. The Egger regression test determines the degree of asymmetry of the funnel plot to assess the publication bias. The Begg and Mazumdar rank correlation test illustrates the relationship between effect size ranks and variances. If the *p*-value is greater than 0.05, the results were considered statistically significant with a minimal chance of publication bias. Because the *p*-value for both statistical tests in our meta-analysis is greater than 0.05, *i.e.*, 0.357 for Egger's test and 0.68 for Begg's test, it confirms the low probability of publication bias (42).

The odds ratios of the included studies were calculated using RevMan software and the Mantel-Haenszel test with random effects to compare the efficacy of epinephrine as a first-aid treatment for in-hospital and out-of-hospital cardiac arrest patients to the control medicines. Fig. 5 depicts the forest plot of odd ratios and data heterogeneity. We found a pooled odds ratio (OR) of 3.67 (95 % CI 2.32–5.81), a chi^2 value of 12,446.86, a df value of 11, an I^2 value of 100 %, a Z-value of 5.53 and *p*-value of 0.00001. When compared to other medications, an odds ratio greater than one indicates that epinephrine is more effective than control drugs like vasopressin, or placebo, at treating patients after cardiac arrest and

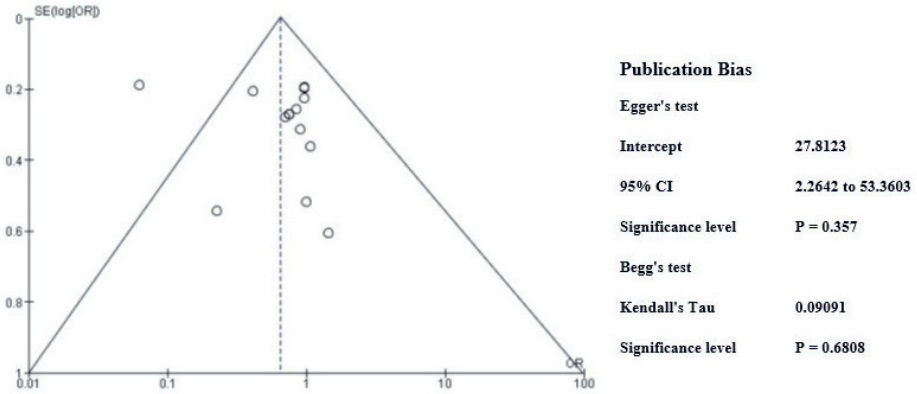

Fig. 4. Funnel plot for publication bias.

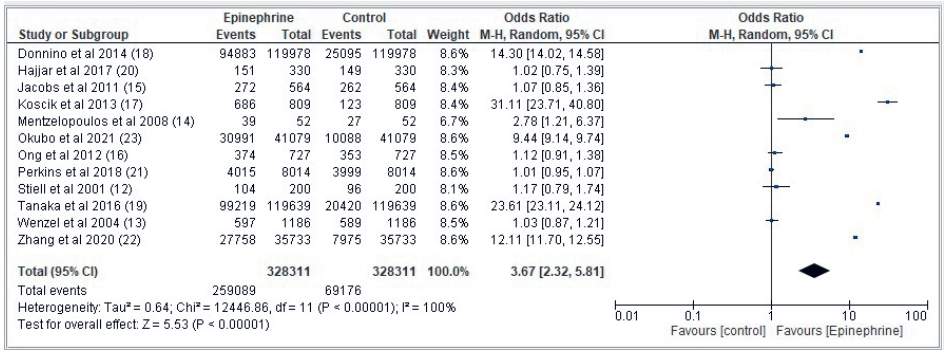

Fig. 5. Forest plot odds ratio.

restoring blood flow and heart rate. All of these findings are statistically significant, and the evidence suggests that epinephrine should be used as a first-line cardiac emergency medicine to successfully enhance the myocardial force of contraction, heart rate and blood flow in cardiac arrest patients (43, 44).

The risk ratio of each included study was estimated using RevMan software, and the corresponding forest plot is presented in Fig. 6. The pooled risk ratio was 1.89 (95 % CI 1.47-2.43) with $tau^2 = 0.19$, $chi^2 = 11{,}530.67$, df = 11, $I^2 = 100\%$, $Z = 4.95$ and $p = 0.000001$. These values point to data collection at random and the usage of categorical study variables. A risk ratio greater than one suggests that epinephrine has a higher likelihood of curing cardiac arrest patients than the control medicine vasopressin because it is more capable of restoring spontaneous blood circulation and recovering the heartbeat of patients with improved neurological outcomes (45). The heterogeneity value in meta-analysis shows the diversity in research outcomes between different studies chosen for meta-analysis, and the populations samples or findings picked, are random and distinct (46). The high I^2 index of 100 % in both the odds ratio and the risk ratio confirms the great heterogeneity. It depicts

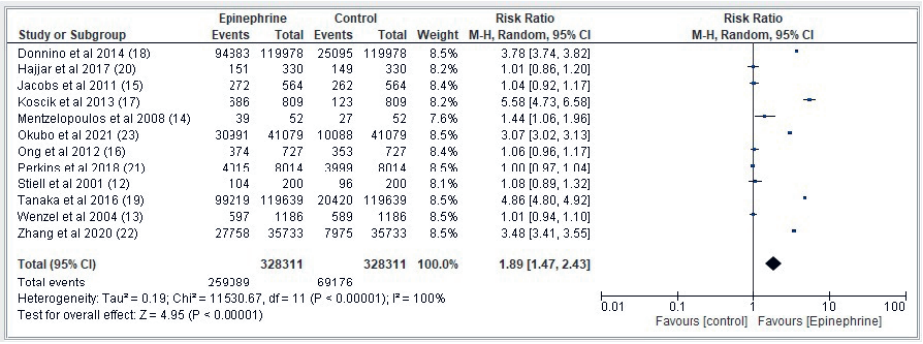

Fig. 6. Forest plot risk ratio of epinephrine *versus* control.

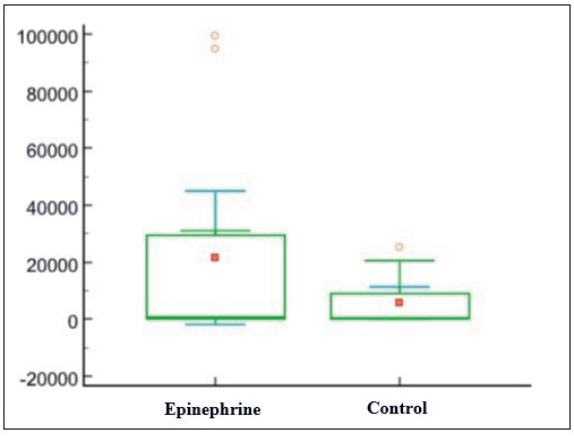

Fig. 7. Box and Whisker plot.

the spread of effect sizes in a meta-analysis (47). The Z-value represents the significant weighted average effect and is statistically significant when the *p*-value is less than 0.05 (48). The *p*-value indicates the likelihood of achieving the substantial observed effect. In both the odds ratio and risk ratio calculations, we achieved high Z-values with *p*-values less than 0.05, demonstrating the statistical importance of our findings. The efficiency of epinephrine was assessed by comparing the positive outcomes of epinephrine and the control medicine, and epinephrine was shown to be more effective, as shown in Fig. 7, the Box and Whisker plot.

Limitations of the meta-analysis

The diversity of control drugs utilized to treat cardiac arrest in comparison to epinephrine skews the outcomes of this study. Numerous studies indicate that epinephrine is not as effective as other common cardiac emergency medications. This has an impact on the statistics as well. Data from other relevant studies validating the usage of epinephrine in comparison to other emergency drugs may potentially provide further information for proposing its use with greater precision. Complete data on a patient's case history, physical examination, and pathological testing can improve the efficacy of proposing epinephrine as a first-line cardiac emergency drug for cardiac arrest by demonstrating the variability of the patient's condition.

CONCLUSIONS

Despite a lot of disputes and many cardiac emergency drugs available for the treatment of both out-of-hospital and in-hospital patients during cardiac arrest, epinephrine is still the most preferred first-choice drug. In the present meta-analysis, we statistically analyzed the relevant studies related to the use of intravenous injection of epinephrine, vasopressin or saline placebo during cardiac arrest. Actually, a high pooled odds ratio (OR) value of 3.67 (95 % CI 2.32–5.81) with a tau^2 value of 0.64, a chi^2 value of 12446.86, df value of 11, I^2 value of 100 %, Z-value 5.53, and a *p*-value < 0.00001, and the risk ratio of 1.89 (95 % CI 1.47–2.43) with tau^2 value of 0.19, chi^2 value of 11530.67, df value 11, I^2 value 100 %, Z-value of 4.95, and *p*-value < 0.000001, speak on behalf of high efficiency of epinephrine for the treatment of cardiac arrest as compared to control drugs, with a high survival rate, rapid recovery of blood flow, heartbeat and heart functions. Taking into account all of our statistically significant meta-analysis results we strongly recommend epinephrine as the first cardiac emergency medicine, however, it should be injected at the recommended site and dosage only, to avoid any risk or side effects.

The datasets used and/or analyzed during the current study are available on request.

Acknowledgements. – In the present study the guidelines of PRISMA (preferred reporting items for systematic reviews and meta-analyses) normative recommendations with the university registration number WU#/IRB/2021/1184, were followed. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committees.

Conflict of interest. – The authors declare no competing interests.

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Authors contributions. – Conceptualization, M.H. and S.D.; data curation, Q.K.; formal analysis and writing-reviewing and editing, M.O.; validation and writing the draft, Y.Z.

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