Why epinephrine should not always be used in pediatric cardiac arrest?

To the editor We read the article by Nadolny et al[1] with great interest. The authors showed that the use of epinephrine was not associated with higher resuscitation efficiency. Epinephrine is an endogenous catecholamine with a high affinity for α1-, β1-, and β2-receptors present in cardiac and vascular smooth muscle cells.[2] The current recommendations on pediatric resuscitation suggest administering epinephrine in both shockable and nonshockable rhythms.[3] Although a recent meta-analysis on epinephrine use in adults confirms its strong benefit in short-term outcomes, it also demonstrates no effect on favorable neurological outcome at discharge.[4] Studies on the use of epinephrine during pediatric cardiopulmonary resuscitation are scarce. According to the resuscitation guidelines, in children receiving cardiopulmonary resuscitation for bradycardia with poor perfusion, epinephrine was associated with worse outcomes, although the study does not eliminate the potential for confounding.[3]

Another important study worth mentioning is an article by Matsuyama et al,[5] which focuses on prehospital administration of epinephrine in pediatric patients with out-of-hospital cardiac arrest (OHCA). The authors observed that prehospital administration of epinephrine was associated with return of spontaneous circulation, although there were no significant differences in 1-month survival or favorable neurological outcome between patients who received epinephrine and those who did not. We therefore recommend that in their next study, Nadolny et al[1] consider an assessment of the effect of epinephrine and other resuscitation treatments during OHCA depending on the first observed cardiac rhythm.

We conducted a meta-analysis to assess the efficacy of epinephrine use during pediatric cardiac arrest. The methodological approach of this systematic review is presented in Supplementary material.

Up to October 18, 2020, a total of 492 citations from 4 databases met our search criteria. Finally, 5 articles were included in the analysis (Supplementary material).

Survival to hospital discharge (SHD) was reported in 4 studies. This parameter was variable and equaled 37.1% for the epinephrine group and 44.8% for the control group (odds ratio [OR], 1.56; 95% CI, 0.49–4.95; $P = 0.45$; $I^2 = 94\%$). Subgroup analysis by the site of cardiac arrest revealed that epinephrine use during in-hospital cardiac arrest (IHCA) was associated with lower SHD rate compared with the control group (38.2% vs 48.5%, respectively; OR, 0.54; 95% CI, 0.3–0.95; $P = 0.03$) (Supplementary material). An inverse relationship was observed for OHCA (26.3% vs 5.4%, respectively; OR, 5.32; 95% CI, 1.96–14.42; $P = 0.001$).

Favorable neurological outcome at hospital discharge (defined as a Pediatric Cerebral Performance Category of 1 [normal or no cerebral disability] or 2 [mild cerebral disability]) also differentiated OHCA from IHCA. In OHCA, the use of epinephrine was associated with a better neurological result compared with the control group (3.6% vs 2.6%, respectively; OR, 1.39; 95% CI, 0.55–3.5; $P = 0.49$). In IHCA, in turn, there was a relationship between the use of epinephrine and a worse neurological outcome at hospital discharge (21.6% vs 28.5%, respectively; OR, 0.69; 95% CI, 0.61–0.78; $P < 0.001$).

In conclusion, while this meta-analysis supports the use of epinephrine in OHCA, it also challenges our knowledge and the current practice to use it in pediatric IHCA. The included studies concordantly strongly suggest that epinephrine use in pediatric resuscitation for IHCA may not only be inefficient but actually lead to deleterious outcomes. The authors of a recent study[2] point out that the study design does not allow to account for all possible confounders, and suggest the use of more granular data. Unfortunately, no registry analysis can substitute randomized clinical trials as doubts and concerns regarding confounders will always cast a shadow over the legibility of the drawn conclusions.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/kardiologiapolska.

ARTICLE INFORMATION

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ACKNOWLEDGMENTS The study was supported by the ERC Research NET and the Polish Society of Disaster Medicine.

CONFLICT OF INTEREST None declared.

HOW TO CITE Trela M, Szarpak Ł, Filipiak KJ, et al. Why epinephrine should not always be used in pediatric cardiac arrest? Kardiol Pol. 2021; 79: 220-221. doi:10.33963/KP.15754

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3 Soar J, Donnino MW, Maconochie I, et al. 2018 International consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations summary. Resuscitation. 2018; 133: 194-206.

4 Ludwin K, Safiejko K, Smereka J, et al. Systematic review and meta-analysis appraising efficacy and safety of adrenaline for adult cardiopulmonary resuscitation. Cardiol J. 2020 Nov 3. [Epub ahead of print].

5 Matsuyama T, Komukai S, Izawa J, et al. Pre-hospital administration of epinephrine in pediatric patients with out-of-hospital cardiac arrest. J Am Coll Cardiol. 2020; 75: 194-204.

Authors' reply Sudden cardiac arrest is a major problem, not only in medicine but also in social and economic terms. According to the data of the European Resuscitation Council, there are 350 000 to 700 000 cases of sudden cardiac arrest in Europe every year. Resuscitation in accordance with the guidelines of the scientific societies, performed by the witnesses of the occurrence (often with the guidance of an emergency medical dispatcher) or by members of the medical rescue team, results in higher patient survival rates and better neurological prognoses, also as far as administration of medication is concerned. Epinephrine has been used in cardiorespiratory resuscitation for a few decades now; however, the previous randomized trials have not unequivocally proved its effectiveness in sudden out-of-hospital cardiac arrest (OHCA).

It was with intense interest that we read the letter by Trela et al[1] concerning the administration of epinephrine in cases of sudden OHCA. The authors carried out a meta-analysis in this regard and arrived at the conclusion that the administration of epinephrine is beneficial, although some studies prove its inefficiency or even harmful effects. It is worth emphasizing that this study concerns pediatric patients.

The current guidelines of the European Resuscitation Council indicate that both in adult and pediatric patients it is recommended to administer epinephrine in cases of sudden cardiac arrest, both in shockable and nonshockable rhythms.[2]

In a retrospective analysis evaluating cases of sudden OHCA (n = 26 783) in the entire Polish population (38.5 million), treated by emergency medical service staff, with an observation period of 12 months (data retrieved from the POL-OHCA registry), we proved that the administration of epinephrine does not increase the rate of patient survival until hospital admission or transport to hospital by helicopter emergency medical service (HEMS) (P = 0.15). Nevertheless, it is worth emphasizing that the rates of administration of medicines are particularly high. In the group of patients who survived until hospital admission or transport by HEMS it was 98.1%, and in the group of patients whose medical rescue was discontinued, it was 98.4%. This proves that the quality of resuscitation activities performed by members of the emergency medical services is high.[3] Unfortunately, the study did not analyze the 30-day, 6-month, and 1-year survival rates or, most importantly, the neurological outcomes of the patients.

In a study by Obremska et al[4], which compared dialyzed and nondialyzed patients with sudden OHCA, the analysis revealed that the administration of epinephrine in the studied groups did not have a significant impact (P = 0.35). Furthermore, in both groups dialysis did not affect the survival of patients until transfer to hospital (P = 0.88).

It is worth referring to an extensive study, PARAMEDIC2 (Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest), initiated by the International Liaison Committee on Resuscitation.[5] This randomized double-blind trial involved more than 80 000 patients with sudden OHCA in the UK. Epinephrine at a dose of 1 mg or placebo was administered intravenously or intraosseously every 3 to 5 minutes. Median value for the time from the call for an ambulance to the commencement of administration was 21 minutes (median value for the time from the call to the arrival of the ambulance, 6.6 min); average total dose of epinephrine amounted to 4.9 mg. In the epinephrine

group, more patients returned to spontaneous circulation during resuscitation (36.3% vs 11.7% in the placebo group). Additionally, 30-day survival was higher in the epinephrine group (3.2% vs 2.4% in the placebo group; $P = 0.02$). Survival to hospital discharge in a favorable neurological state was similar (2.2% vs 1.9%, respectively), and a higher percentage of discharged patients in the epinephrine group had more severe neurological disorders (31% vs 17.8%, respectively).[5]

This may be explained by the potential toxic effect of epinephrine on brain cells through disturbances in microcirculation. It is also possible that epinephrine "restarts" the heart at a moment during which the damage to neurons is already irreversible.

In our opinion, these results question the practical benefits of epinephrine use. Therefore, an analysis of the effectiveness of epinephrine in cases of sudden OHCA requires further clinical trials to be conducted on large randomized groups.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

HOW TO CITE Nadolny K, Zyśko D, Ładny JR, Gałązkowski R. Why epinephrine should not always be used in pediatric cardiac arrest? Authors' reply. Kardiol Pol. 2021; 79: 221-222. doi:10.33963/KP.15755

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