THERAPEUTIC ADVANCES in
Cardiovascular Disease

Systematic Review

Efficacy and safety of intracoronary epinephrine for the management of the no-reflow phenomenon following percutaneous coronary interventions: a systematic-review study

Ther Adv Cardiovasc Dis

2023, Vol. 17: 1–9

DOI: 10.1177/17539447231154654

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Abstract

Background: Currently, no pharmacological or device-based intervention has been fully proven to reverse the no-reflow phenomenon.

Objectives: To assess the efficacy and safety of intracoronary (IC) epinephrine in the management of no-reflow phenomenon following percutaneous coronary intervention (PCI), either as first-line treatment or after the failure of conventional agents.

Design: Systematic review.

Data sources and methods: PubMed and Scopus databases were systematically searched up to 28 May 2022, with additional manual search on the Google Scholar and review of the reference lists of the relevant studies to identify all published studies. Cohort studies, case series, and interventional studies written in English which evaluated the efficacy and safety of IC epinephrine in patients with no-flow phenomenon were included in our review.

Results: Six of the 646 articles identified in the initial search met our inclusion criteria. IC epinephrine was used either as a first-line treatment [two randomized clinical trials (RCTs)] or after the failure of conventional agents (two cohort studies and two case series) for restoring the coronary flow, mainly after primary PCI. As first-line therapy, IC epinephrine successfully restored coronary flow in over 90% of patients in both RCTs, which significantly outperformed IC adenosine (78%) but lagged behind combination of verapamil and tirofiban (100%) in this regard. In the refractory no-flow phenomenon, successful reperfusion [thrombolysis in myocardial infarction (TIMI) flow grade = 3] was achieved in three out of four patients after the administration of IC epinephrine based on the results from both case series. Their findings were confirmed by a recent cohort study that further compared IC epinephrine with IC adenosine and found significant differences between them in terms of efficacy [% TIMI flow grade 3: (69.1% *versus* 52.7%, respectively; p value = 0.04)] and 1-year major adverse cardiac event (MACE) outcomes (11.3% *versus* 26.7%, respectively; p value ⩽ 0.01). Overall, malignant ventricular arrhythmias were reported in none of the patients treated with IC epinephrine.

Conclusion: Results from available evidence suggest that IC epinephrine might be an effective and safe agent in managing the no-reflow phenomenon.

Keywords: epinephrine, no-reflow phenomenon, PCI, reperfusion therapy, TIMI

Received: 7 September 2022; revised manuscript accepted: 13 January 2023.

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Introduction

Coronary no-reflow phenomenon, a state of myocardial tissue hypoperfusion despite patent epicardial coronary artery, continues to be a challenging complication encountered by interventionists in percutaneous coronary intervention (PCI).[1,2] No-reflow is thought to be a frequent but underestimated condition after both elective and infarct-related PCI.[3]

If not timely resolved, no-reflow can result in larger infarct area and significant left ventricular (LV) systolic dysfunction, worsening in-hospital and long-term prognosis.[4]

Although several pharmacologic agents and device-based strategies have been proposed to reverse coronary no-reflow, none have received solid approval.[1] In current practice, vasodilators adenosine, nitroprusside, verapamil, and nicardipine are commonly used in managing no-reflow phenomenon.[1] However, they are ineffective in restoring coronary flow in a substantial number of patients (refractory no-reflow phenomenon); furthermore, their use is limited by hypotension, a major consequence of the no-reflow.[5]

Epinephrine can mediate coronary vasodilatation at lower doses and increase inotropic and chronotropic stimulation of the myocardium through activating beta receptors.[6] Hence, previous studies have attempted to identify if intracoronary (IC) epinephrine could be considered as a potential solution to refractory coronary no-reflow during PCI.[7–10]

Also, recent studies have provided evidence for using IC epinephrine as first-line therapy in the no-reflow phenomenon management.[6,11]

We conducted a systematic review of available evidence to assess IC epinephrine's clinical efficacy and safety in treating patients suffering from no-reflow following PCI, as a first-line treatment, or after the failure of current conventional agents.

Method

We followed a standardized methodology and reported the results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. As a systematic review of current literature, our study was exempt from institutional ethics committee approval. We included all eligible studies assessing the efficacy and safety of IC epinephrine in treating the no-reflow phenomenon as first-line therapy or in the case of refractory conditions.

Search

We performed a comprehensive systematic search of online databases, including PubMed and Scopus, on 28 May 2022, using a combination of the key terms in two domains:

(1) Epinephrine and (2) no-reflow phenomenon.

We also manually screened reference lists of relevant articles and the first 100 pages of the Google Scholar survey for any additional eligible citations.

We imported all retrieved articles into EndNote X9 software (version EndNote X9.3.2, Captivate Analytics, CA, USA) and removed duplicates.

Selection criteria

We included all interventional and case series/cohort studies on the efficacy and safety of the IC epinephrine in patients with no-reflow phenomenon after PCI. We included studies that met all following eligibility criteria:

1. Written in English.
2. Included patients with no-reflow phenomenon.
3. IC administration of epinephrine (and comparison agents), as a first-line treatment or after the failure of conventional treatments.
4. Performed on human subjects.

Two independent researchers (P.S. and A.T.) screened the retrieved articles' titles, abstracts, and full texts for these criteria. In addition, a third author's opinion (H.R. or S.Y.) resolved any conflict of opinion.

Data collection

We identified six articles that assessed the efficacy and safety of IC epinephrine in treating the no-reflow phenomenon. Three of our researchers (E.J.A., P.S., and A.T.) collected the following data from the included articles into a 'data extraction form' produced using Microsoft Excel

(version 2016, Microsoft Corp., Redmond, WA, USA) and Microsoft Word (version 2016, Microsoft Corp., Redmond, WA, USA): author's name, year of study, country, % of primary PCI (PPCI), study design, comparison groups and interventions, sample size, patient's age, sex, baseline angiographic findings, culprit coronary vessels, and short- and long-term outcomes.

Risk of bias assessment

Two of our researchers (E.J.A. and A.T.) assessed the quality of included studies independently using the CONSORT appraisal tool adapted for clinical trials studies[12] and the Newcastle–Ottawa scale appraisal tool adapted for observational studies.[13,14] Our third researcher (H.R. or S.Y.) resolved any disagreements. The CONSORT appraisal tool contains 25 items with a total score ranging from 0 to 25, and the Newcastle–Ottawa scale appraisal tool has eight items with a total score ranging from 0 to 9.

Result

Study selection

We identified 646 articles in the initial search. After removal of duplicates ($n = 116$) and excluding ineligible articles (title / abstract: $n = 498$, full-text: $n = 28$) and addition of two citations from the Google Scholar survey, six articles met our inclusion criteria; included studies focused on efficacy and safety of IC epinephrine as a first-line treatment ($n = 2$)[6,11] or after failure of other conventional agents ($n = 4$)[7–10] for the treatment of patients with no-reflow phenomenon. Studies were conducted in Egypt ($n = 2$), Poland ($n = 1$), Pakistan ($n = 1$), the United States ($n = 1$), and Turkey ($n = 1$) (Table 1). The screening and selection process is presented in Figure 1. The quality score of included studies are reported in Supplementary Table 1. Angiographic characteristics of included studies are reported in Supplementary Table 2.

IC epinephrine as a first-line treatment

Two studies were randomized clinical trials (RCTs) with a parallel design but different comparison groups, including verapamil, adenosine, and the current standard treatment (tirofiban, a glycoprotein IIb/IIIa inhibitor) (Tables 1 and 2).

Hafez *et al.*[11] conducted the first study in 2021; they compared the efficacy of IC epinephrine + tirofiban (25 mg/kg) with verapamil + tirofiban (25 mg/kg) and tirofiban alone (25 mg/kg and maintenance dose 0.15 mg/kg/min) in patients with no-reflow following PPCI. Based on their findings, 100% of patients in the comparison groups but 92% of those in the epinephrine group achieved a thrombolysis in myocardial infarction score (TIMI) 3 flow grade (TFG) (p value = 0.016).

A higher proportion of patients in the verapamil group had myocardial blush grade (MBG) 2 and 3 (60%) in comparison with those in tirofiban (46%) and epinephrine groups (38%) (p value = 0.003). In addition, a greater improvement in systolic LV function was observed in the verapamil group [mean (standard deviation (SD) change = 19.6% (29.5)] compared with tirofiban [10.1% (10.7)] and epinephrine groups [9.2% (16.6)] at 3 months follow-up (p value = 0.021).

Khan *et al.*[6] compared the efficacy and safety of IC epinephrine with adenosine for the treatment of the no-reflow phenomenon, mainly after PPCI. They found that patients in the epinephrine group experienced more frequently TFG = 3 (90% *versus* 78%, respectively) and MBG = 3 (55% *versus* 45%, respectively). They also had a lower corrected TIMI frame count (cTFC) [mean (SD) = 24.0 (8.4) *versus* 26.6 (9.2), respectively; p value = 0.036]. Two groups were similar in terms of in-hospital and short-term major adverse cardiac events (MACEs). None of the patients who received epinephrine experienced ventricular fibrillation (VF). At the 30-day follow-up, a lower percentage of patients treated with epinephrine had LVEF < 40% compared with the adenosine group (59% *versus* 77%, respectively; p value = 0.006).

IC epinephrine for the treatment of the refractory no-reflow phenomenon

A total of four studies (including two cohort studies and two case series) retrospectively assessed the short- and long-term efficacy and safety of IC epinephrine in the management of no-reflow phenomenon following PPCI ($N = 3$) or elective PCI ($N = 1$) (Tables 1 and 2). The definition of refractory no-reflow varied among the studies (Supplementary Table 3).

Table 1. Characteristics of the included studies.

ID	Author	Country (year)	Design	PPCI (%)	Main int[a] [dose (µg)]	Other interventions (% of patients)	*N*	Culprit's vessel (%)			Age Mean (SD)	M/F	Baseline angiographic findings	
								LAD	RCA	LCX			TFG 0,1 % (*n*)	MBG 0,1
1	Khan *et al.*[6]	Pakistan (2022)	RCT	~94%[b]	EPI [244 (139)][c]	Nitrate (75%) and GPI (24%)	101	55.4	36.6	5.9	56.8 (11.9)	70/31	59.0%	95%
					ADN [269 (167)][c]	Nitrate (88%) and GPI (20%)	100	62.0	29.0	8.0	57.4 (10.8)	76/24	63.0%	95%
2	Hafez *et al.*[11]	Egypt (2021)	RCT	All[b]	EPI [200]	GPI (L dose,[d] 100%)	50	62.0	28.0	8.0	58.1 (8.3)	38/12	NR	NR
					GPI	GPI (L&M dose,[e] 100%)	50	62.0	26.0	8.0	58.3 (9.7)	40/10	NR	NR
					VRP [200]	GPI (100%)	50	66.0	26.0	8.0	58.8 (9.9)	40/10		
Refractory no-reflow														
3	Navarese *et al.*[9]	Poland (2020)	RC	All[b]	EPI [80–100][f]	Nitrate (79%), ADN (50%), GPI (19%), and TB (57%)	14	50	44.4	14.3	69.9 (8.6)	11/3	92.9%	NR
					No -EPI	Nitrate (69%), ADN (31%), GPI (19%), and TB (38%)	16	56.3	55.6	12.5	68.7 (9.5)	13/3	75.1%	NR
4	Darwish *et al.*[8]	Egypt (2022)	RC	All[b]	EPI [100–400][f]	Nitrate, VRP, and GPI *N* of patients: NR	81	59.3	19.8	21.0	62.0* (9.0)	44/37	NR	NR
					ADN [60–120][f]	Nitrate, VRP, and GPI *N* of patients: NR	75	37.0	32.0	18.7	54.0 (11.0)	46/29	NR	NR
5	Skelding *et al.*[10]	USA (2002)	RC	76%[b]	EPI [139 (189)][c]	Nitrate (21%), VRP (31%), Nitrate + VRP (41%), uPA(3.5%), or Nitrate + VRP + GPI (3.5%)	29	NR	NR	NR	NR	NR	52.0%	NR
6	Aksu *et al.*[7]	Turkey (2015)	RC	All[b]	EPI [333 (123)][c]	Nitrate (50%), VRP (33%), or ADN (17%)	12	33.0	50.0	17.0	62.0 (12.0)	8/4	67.0%	66%

ADN, adenosine; EPI, epinephrine; FM, female; GPI, glycoprotein IIb/IIIa inhibitor; LAD, left anterior descending artery; LCX, left circumflex artery; MBG, myocardial blush grade; *N*, number; NR, not reported; PPCI, primary percutaneous coronary intervention; RC, retrospective cohort; RCA, right coronary artery; RCT, randomized controlled clinical trials; SD, standard deviation; TB, thrombectomy; TFG, thrombolysis in myocardial infarction flow grade; uPA, urokinase plasminogen activator; VRP, verapamil.

[a]Main intervention.

[b]STEMI patients.

[c]Mean, SD.

[d]Loading dose.

[e]Loading and maintenance dose.

[f]Range.

*$p < 0.05$.

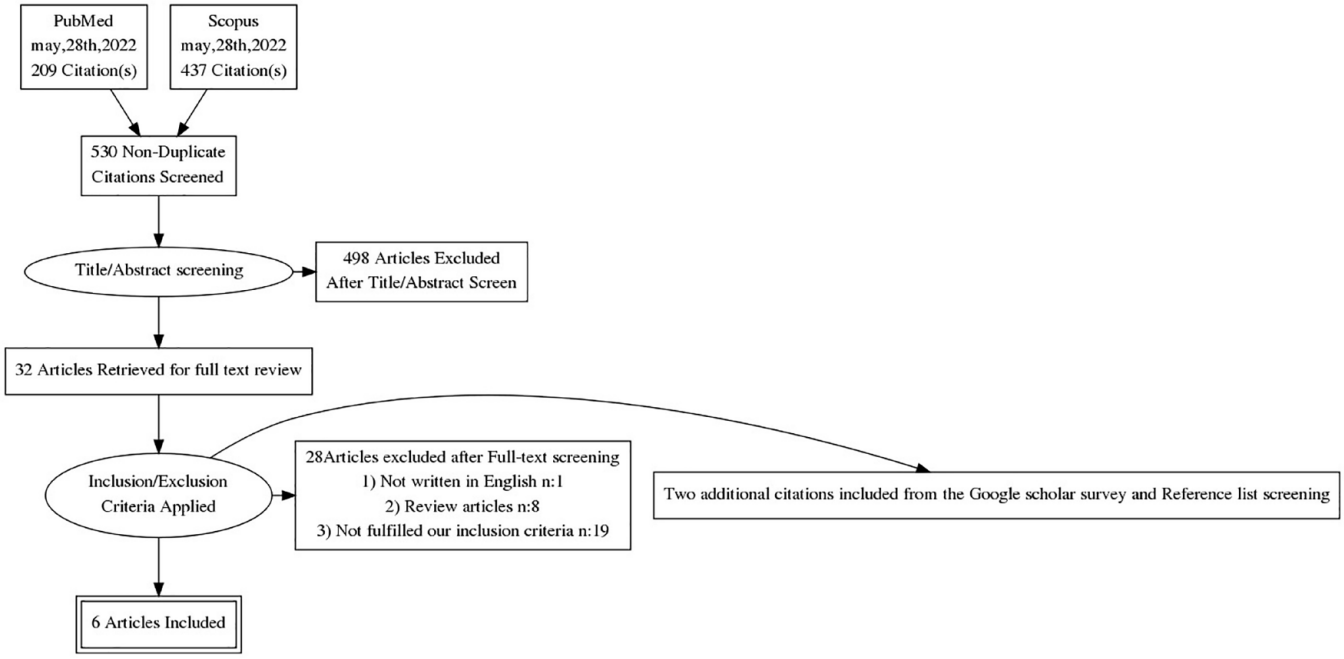

Figure 1. PRISMA flowchart diagram.

The first cohort study was conducted by Navarese *et al.*[9] in 2020; this study compared the safety and efficacy of IC epinephrine with conventional treatments alone (nitrates, thrombectomy, glycoprotein IIb/IIIa inhibitors, and adenosine) in patients with no-reflow after PPCI. The rate of successful reperfusion (TFG 2 and TFG 3) was higher in the IC epinephrine group (TFG 3 = 28.6%, TFG 2 = 64.3%) than in no-epinephrine group (TFG 3 = 18.8%, TFG 2 = 12.5%; p value = 0.004). Patients treated with IC epinephrine experienced a lower rate of 30-day MACE (death and heart failure) in comparison with those in the no-epinephrine group [35.7% (5/14) *versus* 81.3% (13/16), respectively; p value = 0.01]. However, this study lacked information on in-hospital adverse outcomes (Table 2).

Darwish *et al.*[8] conducted the second cohort study in 2022 and found that a higher percentage of patients who were treated with IC epinephrine achieved successful reperfusion (TFG = 3) compared with those with IC adenosine (69.1% *versus* 52.7%, respectively; p value = 0.04). During hospitalization, sustained ventricular tachycardia was observed in one of the patients in the epinephrine group. MACE, including heart failure, stroke, or death, was less frequently observed in epinephrine group compared with adenosine group, in-hospital (7.4% *versus* 10.7%, respectively; p value = 0.477) and at 1-year follow-up (11.3% *versus* 26.7%, respectively; p value < 0.01) (Table 2).

In addition, Skleding *et al.*[10] reported a case series of 29 consecutive patients with refractory no-reflow following elective ($n = 7$) or primary ($n = 22$) PCI who were treated with IC epinephrine. They observed that epinephrine resolved no-reflow (TFG 3) in 69% of cases ($p < 0.001$); mean (SD) TIMI flow increased from 1.0 (1.0) to 2.66 (0.55) ($p < 0.001$). In-hospital death occurred in one patient during the episode of no-reflow phenomenon. However, epinephrine-related dysrhythmia was detected in none of their study population. Similarly, Aksu *et al.*[7] reported a retrospective case series of 12 patients with refractory no-reflow following PPCI who received IC epinephrine. Based on their finding, IC epinephrine successfully restored coronary flow (TFG 3) in 9 of 12 patients. Following administration of IC epinephrine, mean TFG increased from 1.33 (0.49) to 2.66 (0.65) and mean TFC decreased from 56 (10) to 19 (11) (both p values $<$ 0.001). However, in-hospital death occurred in one patient. In terms of safety, sustained ventricular tachycardia following administration of IC epinephrine was observed in none of the cases (Table 2).

Table 2. Main findings of included studies.

	Article	Comparison	Method of administration	Outcomes		Comparison of Outcomes	Qualitative assessment	
							Findings	Conclusion
First-line treatment of no-reflow	Khan *et al.*[6]	EPI *versus* ADN	Intracoronary, 88% proximal *via* guide wire and 12% distal *via* device	In-hospital	TFG = 3	90.1% *versus* 78.0%*	Pos.	• EPI > ADN: • Efficacy ↑ • No case of VF in Epi group
					cTFC	24 ± 8.43 *versus* 26.63 ± 9.22*	Pos.	
					MBG 3	55.4% *versus* 45%	Pos.	
					HF	19.8% *versus* 19.0%	~	
					Death	3.0% *versus* 2.0%	~	
					MACE	38.8% *versus* 41.0%*	Pos.	
				Follow-up 30 days	HF	18.3 *versus* 13.5	Pos.	
					Death	7.1 *versus* 5.2	~	
					MACE	20.3 *versus* 25.9	Pos.	
	Hafez *et al.*[11]	EPI *versus* VRP *versus* GPI	Intracoronary, distal to the lesion using self-made holes in a semi-compliant balloon	In-hospital	TFG = 3	92% *versus* 100% *versus* 100%*	Neg.	• EPI < VRE and GPI: • Efficacy ↑
					MBG 2–3	38% *versus* 60% *versus* 46%*	Neg.	
				Follow-up 3 months	EF [mean% of change (SD)]	9.18 (16.51) *versus* 19.6 (29.4) *versus* 10.11 (10.73)*	Neg.	
Refractory **no-reflow**	Navarese *et al.*[9]	EPI *versus* no-EPI	Intracoronary, proximal using guiding catheter	In-hospital	TFG = 2	64.3% *versus* 12.5%*	Pos.	• EPI → No-EPI: • Efficacy ↑
					TFG = 3	28.6% *versus* 18.8%*	Pos.	
					HF	28.5% *versus* 56.3%	Pos.	
					Death	14.3% *versus* 43.7%	Pos.	
					MACE	35.7% *versus* 81.2%*	Pos.	
				Follow-up 30 days	EF [% mean change]	+20.8% *versus* +6.8%*[a]	Pos.	
	Darwish *et al.*[8]	EPI *versus* ADN	Intracoronary, distal using aspiration catheter or pierced balloon inflated into a culprit lesion	In-hospital	TFG = 3	69.1% *versus* 52.7%*	Pos.	• EPI → ADN: • Efficacy ↑
					cTFC	19.6% *versus* 21.5%	~	
					HF	6.2% *versus* 10.7%	Pos.	

(Continued)

Table 2. (Continued)

	Article	Comparison	Method of administration	Outcomes		Comparison of Outcomes	Qualitative assessment	
							Findings	Conclusion
					Death	1.2% *versus* 0%	Neg.	
					MACE	7.4% *versus* 10.7%	Pos.	
				Follow-up 1 year	HF	6.3% *versus* 19.2%*	Pos.	
					Death	1.2% *versus* 2.7%*	Pos.	
					MACE	11.3% *versus* 26.7%*	Pos.	
	Skelding *et al.*[10]	EPI	Intracoronary, NR	In-hospital	TFG = 3	75.0%*	Pos.	• Efficacy (TIMI 3)in 3/4 of patients • No case of malignant arrhythmia in EPI group
					Death	3.4%		
					cTFC	19.0*	Pos.	
					MBG 3	75.0%*	Pos.	
					EF [mean (SD)]	From 39.3 (6.49) to 42.1 (5.5)*	Pos.	
					Death	8%	-	
				Follow-up 4 years	Death	0%	-	
					MACE	25.0%	-	
Refractory **no-reflow**	Aksu *et al.*[7]	EPI	Intracoronary, through the central lumen of an over-the-wire balloon catheter	In-hospital	TFG = 3	75.0%*	Pos.	• Efficacy (TIMI 3 and MBG 3) in 3/4 of patients • No case of sustained ventricular tachyarrhythmia
					cTFC	19.0*	Pos.	
					MBG 3	75.0%*	Pos.	
					EF [mean % of change (SD)]	39.3 (6.49) to 42.1 (5.5)*	Pos.	
					Death	8%		
				Follow-up 4 years	Death	0%		
					MACE	25.0%		

ADN, adenosine; cTFC, corrected TIMI frame count; EF, ejection fraction; EPI, epinephrine; GPI, glycoprotein IIb/IIIa inhibitor; HF, heart failure; MACE, major adverse cardiac event; MBG, myocardial blush grade; NR, not reported; SD, standard deviation; TFG, TIMI flow grade; TIMI, thrombolysis in myocardial infarction; VF, ventricular fibrillation; VRP, verapamil.
[a]EPI *versus* no-EPI [mean (SD)] 36.9 (13.9) to 44.6 (8.2) *versus* 38.3 (14.7) to 40.9 (34.5).
*Statistically significant difference between groups.

Discussion

Based on limited available evidence, IC epinephrine has shown promising efficacy and safety in managing the no-reflow phenomenon, either as a first-line treatment or after the failure of conventional agents. As a first-line treatment, Khan *et al.*[6] reported that IC epinephrine compared with IC adenosine showed a higher efficacy in resolving the no-reflow phenomenon. However, Hafez *et al.*[11] noted that IC verapamil and the current standard therapy might be better than IC epinephrine to manage the no-reflow phenomenon. Furthermore, observational studies found that IC epinephrine was effective and without serious complications in treating most cases with the refractory no-reflow phenomenon.[7–10]

The main purpose of managing the no-reflow phenomenon is to improve microcirculatory coronary blood flow, resulting in minimized myocardial damage and improved clinical outcomes. IC adenosine, nitroprusside, verapamil, and nicardipine are IC vasodilators commonly used in the treatment of coronary no-reflow. Even though these agents could be therapeutic in many patients, they are not always successful. Furthermore, their use can accelerate hypotension which is induced by the no-reflow phenomenon.

Epinephrine is an adrenergic agonist and can potentially treat the no-reflow phenomenon by stimulating beta receptors; at a lower dose, it predominantly has a beta-2 agonist effect and vasodilates arteries. On the contrary, epinephrine induces inotropic and chronotropic effects on the myocardium through stimulating beta-1 receptors, leading to improved cardiac output.

Skelding *et al.*[10] first described IC epinephrine as a treatment of choice in treating the refractory no-reflows in 2002; they provided evidence of the potential efficacy and safety of IC epinephrine, and later studies supported their findings.

Recently, two RCTs assessed the efficacy and safety of IC epinephrine in treating the no-reflow as a first-line agent. Khan *et al.*[6] found a higher short- and long-term efficacy and safety of IC epinephrine in comparison with IC adenosine. In another study, Hafez *et al.*[11] reported that IC verapamil and tirofiban (glycoprotein IIb/IIIa inhibitor) were superior to IC epinephrine in this regard. However, they failed to provide information on the comparability of groups regarding the baseline angiographic features. In contrast to Hafez *et al.* study, Yassin *et al.*[15] observed that IC epinephrine had higher efficacy than verapamil in preventing no-reflow during PPCI.

One of the main concerns in using epinephrine is its arrhythmogenic effects which may lead to death. Still, none of the included studies reported malignant arrhythmias in patients treated with IC epinephrine.

Limitations

Included studies were inconsistent in terms of design, eligibility criteria, comparison interventions, follow-up periods, and applied definition of outcomes, which all may result in different findings, preventing the pooling of data. In addition, some of the included studies failed to provide information on baseline angiographic examination. Only two RCTs examined the use of IC epinephrine as a first-line treatment for the no-reflow phenomenon. Furthermore, all available studies assessing its efficacy and safety for managing refractory cases were observational studies. Nevertheless, our systematic-review study includes a comprehensive and reproducible search strategy.

Conclusion

Based on the available literature, IC epinephrine might be considered as an effective and safe option to reverse the no-reflow phenomenon, either as a first-line or the failure/contraindications of conventional IC vasodilators. RCTs with a larger sample size are required to confirm the current evidence.

Declarations

Ethics approval and consent to participate

As our work is a systematic review of literature, there is no need for ethical approval.

Consent for publication

Not applicable.

Author contributions

Elmira Jafari Afshar: Conceptualization; Methodology; Software; Validation; Writing – original draft.

Parham Samimisedeh: Methodology; Resources; Validation; Writing – original draft; Writing – review & editing.

Amirhossein Tayebi: Data curation; Software; Validation.

Neda Shafiabadi Hassani: Validation; Writing – review & editing.

Hadith Rastad: Conceptualization; Formal analysis; Project administration; Supervision; Validation.

Shahrooz Yazdani: Conceptualization; Project administration; Supervision; Validation; Visualization.

Acknowledgements

Researchers appreciated the Clinical Research Development Units of Kamali and Rajaee hospital in Alborz University of Medical Sciences.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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