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REVIEW ARTICLE

Efficacy and Safety of Pressure-controlled Intermittent Coronary Sinus Occlusion in STEMI: A Systematic Review and Meta-analysis

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Abstract

This systematic review will provide a comprehensive assessment of the evidence on PICSO in STEMI patients, and it will help to determine the role of this novel technique in the management of STEMI. The review searched for the relevant articles in the PubMed, Embase, Cochrane Library, and Web of Science databases regarding PC-ICSO. Four cohort studies were eligible to be included in the quantitative analysis. In the pooled analysis, the use of PICSO was associated with a significant reduction in infarct size (SMD = −0.44, 95% CI = −0.76,-0.13, p = 0.004). PICSO administration was associated with a reduced risk of developing microvascular resistance (RR = 0.75, 95% CI = 0.62,0.92, p = 0.0051). The post-procedural Index of Microvascular Occlusion (MVO) was lower in the PICSO treated compared to the control group and this result was homogenous and statistically significant (SMD = −0.35, 95% CI = −0.68-0.01, p = 0.03, I_2 = 0%). Compared to matched controls, the use of PICSO was associated with higher Left Ventricular Ejection Fraction (LVEF) at the longest follow-up (SMD = 0.328, 95% CI = 0.03, 0.06, p = 0.03, I_2 = 0%). This review suggested that PICSO can be used during PPCI in STEMI with improved outcomes of infarct size, LVEF, and microvascular perfusion.

Keywords: Ischemia, Ischemic heart disease, Microvascular obstruction

1. Introduction

Acute ST-elevation myocardial infarction (STEMI) is a life-threatening condition that requires prompt treatment to minimize cardiac damage.[1] Percutaneous coronary intervention (PCI) is the standard of care for STEMI, but it is associated with some limitations, including distal embolization, no-reflow phenomenon, and microvascular dysfunction.[2] Pressure-controlled intermittent coronary sinus occlusion (PICSO) is a novel technique that aims to reduce infarct size and improve microvascular perfusion by temporarily interrupting blood flow to the infarcted area.[3] The efficacy and safety of PICSO in STEMI patients have been evaluated in several small studies, but the results have been inconsistent.[4-7] A systematic review of the literature is needed to provide a comprehensive assessment of the evidence. The objective of this systematic review is to evaluate the safety and efficacy of PICSO in STEMI patients by analyzing the available studies. This systematic review will provide a comprehensive assessment of the evidence on PICSO in STEMI patients, and it will help to determine the role of this novel technique in the management of STEMI. The results of this review

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will interest cardiologists, interventionists, and other healthcare professionals involved in the care of STEMI patients. Moreover, this review will help in planning future studies to further evaluate the use of PICSO in STEMI. PICSO is a novel technology designed to mitigate microvascular dysfunction in the setting of STEMI.

2. Methods

2.1. Search strategy and selection criteria

The search strategy for this review was guided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8] The review searched for the relevant articles in the PubMed, Embase, Cochrane Library, and Web of Science databases. The review used the following keywords and Medical Subject Heading (MeSH) terms: "pressure-controlled intermittent coronary sinus occlusion" OR "PC-ICSO" OR "PiCSO" AND "STEMI" OR "myocardial infarction" OR "infarct size" OR "microvascular perfusion" OR "left ventricular function" AND "major adverse cardiovascular events" OR "myocardial blush grade" OR "TIMI flow grade" OR "ST-segment resolution". The review searched for articles with no time filters and language restrictions. Two reviewers screened the riddles and abstracts of the articles identified by the search strategy, and selected studies that met the inclusion criteria. The full text of the selected studies was then reviewed to confirm eligibility.

The review included randomized controlled trials (RCTs) and observational studies that evaluated the efficacy and safety of PC-ICSO, including adult patients with confirmed diagnoses of STEMI who underwent PC-ICSO. The primary outcomes of interest were infarct size, microvascular perfusion, left ventricular (LV) function, and major adverse cardiac events (MACE). Secondary outcomes were myocardial blush grade, TIMI flow grade, and ST-segment resolution. The final search ended on January 29, 2023. The review excluded case reports, case series, reviews, editorials, letters to the editor, and studies that did not report any of the primary or secondary outcomes of interest.

2.2. Data extraction and quality of evidence

The data from each included study were extracted by 2 independent reviewers (M.F. and J.M.), and any discrepancies were resolved through consensus. The following were extracted: study design, patient characteristics, intervention details, primary and secondary outcomes, and results.

The quality of evidence in each included study was assessed using the Newcastle–Ottawa Scale. The domains evaluated were study design, risk of bias, consistency, directness, precision, and publication bias. The quality of included studies is presented in Supplementary Fig. S1 (https://scholarlycommons.gbmc.org/cgi/editor.cgi).

3. Results

3.1. Study characteristics

The detailed baseline characteristics of the included studies are presented in Table 1. All 4 studies included in this review were non-randomized. The year of publication ranged between 2015 and 2020. In terms of geographical region, most (n = 3) of the studies were conducted in the UK, while one took place in four different countries in Central Europe including Germany, the Netherlands, Switzerland, and Austria. The sample sizes of the studies ranged from 30 to 108 representing a total population of 288 study participants. PRISMA flow chart is shown in Fig. 1.

Table 1. Study characteristics.

Study	Publishing year	Country	Study Design	Single centre/multi centre	Study duration	Sample size	Inclusion & exclusion criteria	Intervention	Primary outcome	Secondary outcome	Follow up duration	Limitations
De Maria (4)	2018	UK	prospective, non randomized	single-centre	Aug 2015-Sept 2017	105	Main inclusion criteria were clinical presentation for PCI with stenting for anterior STEMI and left anterior descending artery as the clear culprit vessel. Main exclusion criteria were previous STEMI, previous coronary artery bypass grafting, and presentation with cardiogenic shock.	IMR guided treatment with PICSO	IMR-guided therapy with PICSO improved coronary microvascular function and reduced infarct size in patients with ST-elevation myocardial infarction (STEMI).	The study also found that the IMR-guided therapy with PICSO was safe and feasible, with no major adverse events related to the procedure.	6 months	single-centre study, non-random sampling, small sample size, short follow up, The study protocol allowed for additional interventions, such as thrombus aspiration or percutaneous coronary intervention (PCI), which may have affected the outcomes.
Scarsini (5)	2020	UK	non-randomized	single-centre	Aug 2015-Jan 2020	108	Main inclusion criteria were clinical presentation for PCI with stenting for anterior or inferior STEMI in the left anterior descending artery or dominant right coronary artery as the clear culprit vessel, respectively.	PICSO assisted primary percutaneous intervention (PPCI)	PICSO treatment enhances the microvascular vasodilatory capacity of patients with both anterior and inferior STEMI as demonstrated by a significantly higher IMR values post-PICSO treatment.	The study found that microvascular obstructionand infarct size, as measured by cardiac MRI at 2-7 days after the intervention, was significantly smaller in the PICSO group compared to the standard care group. No significant difference in LVEF between the two groups at 6 months after the intervention. The incidence of MACE, including death, recurrent myocardial infarction, and heart failure, was lower in the PICSO group compared to the standard care group	6 months	small sample size, non-blinded study design
Egred (6)	2020	UK	prospective, parallel-cohort, non-randomized	multi-centre	Jan 2015-Oct 2017	45	first occurrence of STEMI; culprit lesion in the left anterior descending artery; and age 25 years. Patients were excluded for any of the following: complicated pPCI (i.e. angioplasty followed by stent placement or direct stenting with adverse event(s) that would preclude the use of PICSO, including major bleeding, perforation, hypotension, pulmonary edema, or clinical instability; symptom onset time > 12 h; previous coronary artery bypass graft surgery; history of stroke, transient ischemic attack, or reversible ischemic neuro-logical disease within the past 6 months; hospitalization with a primary diagnosis of acute myocardial infarction previously or evidence of previous Q-wave infarct; known contraindication for cardiac magnetic resonance imaging (CMR); active or treated malignancies in the previous 12 months; pregnancy; non-cardiac comorbidities and life expectancy <1 year; and use of warfarin.	pPCI plus PICSO	The infarct size was consistently lower in the PICSO vs. parallel control group at 5 days	pressure-controlled intermittent coronary sinus occlusion was associated with a significant improvement in LVEF in patients with anterior STEMI. Although the mean microvascular obstruction among all patients was similar, numerically fewer patients in the PICSO group had microvascular obstruction when compared to the parallel control group.	6 months	small sample size, short follow up duration, study used a composite primary endpoint of infarct size and LV function, which has not been validated in previous studies.
Van de hoef (7)	2015	4 (The Netherlands, Germany, Switzerland, Austria)	prospective, non randomized	multi-centre	2012-2014	30	Patients aged ≥18 years with a first STEMI, defined by symptoms consistent with STEMI >30 minutes duration but <12 hours, and ≥1 mm of ST-segment elevation in two or more contiguous leads in V1-V4, who underwent uncomplicated pPCI of a single-vessel left anterior descending coronary artery (LAD) culprit lesion were eligible for enrolment. Exclusion criteria included: the presence of a left main coronary artery culprit lesion; previous coronary artery bypass graft surgery; known contraindication to CMR; known creatinine clearance less than 30 mL/min/1.73 m2 or dialysis; haemoglobin level less than 10 g/dL, platelet count less than 100,000 cells/mm3, known coagulopathy or bleeding diathesis; history of stroke, transient ischaemic attack or reversible ischaemic neurological disease within the previous six months; the presence of any lead in the coronary sinus; cardiogenic shock or cardiopulmonary resuscitation; and any comorbid condition likely to interfere with protocol compliance or associated with less than one-year survival	PCI with PICSO	At 30 days after the procedure, there were no cases of MACE reported, indicating that PICSO was safe in this patient population.	PICSO was feasible in this patient population, with successful device implantation and activation in all patients. Additionally, the study found a significant improvement in myocardial perfusion and microvascular function, as assessed by cardiac magnetic resonance imaging (MRI) and the index of microcirculatory resistance (IMR), respectively.	4 months	small sample size, lack of control group

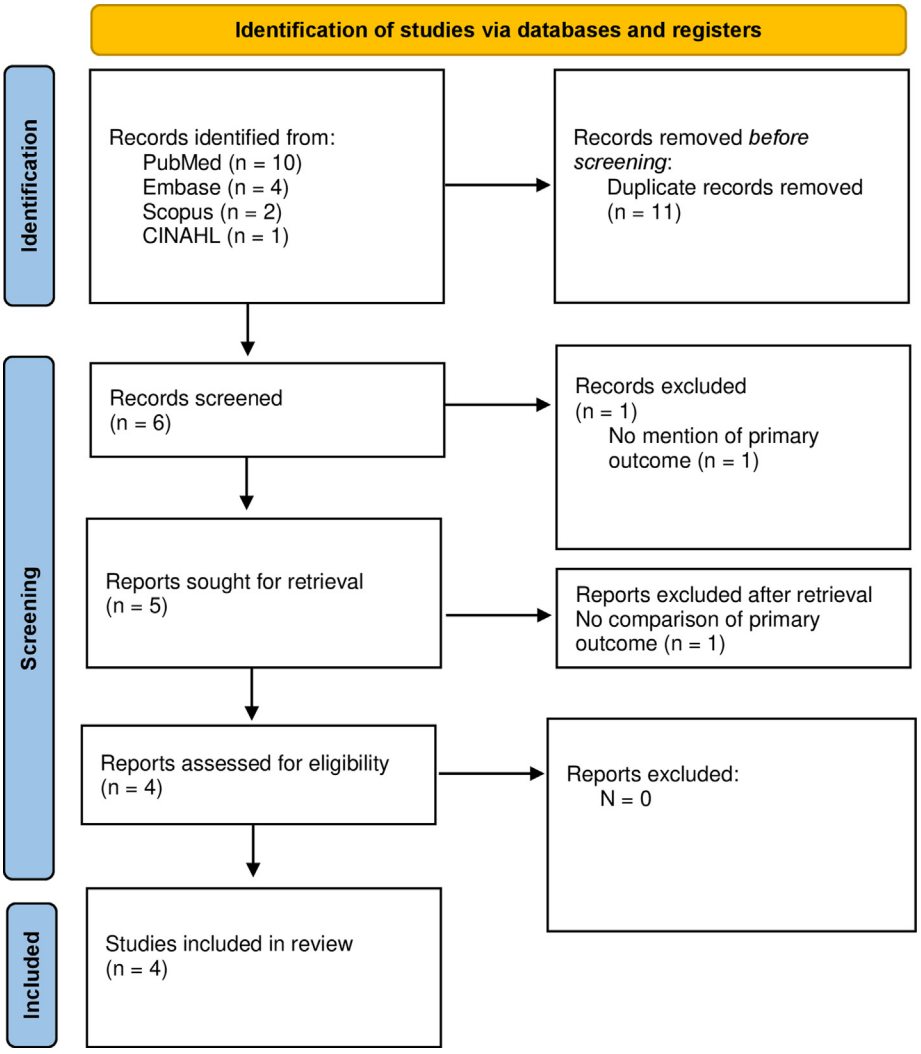

Fig. 1. PRISMA flowchart.

Three studies used PCI with PICSO as the intervention whereas, one used IMR-guided treatment with PICSO. All studies reported a reduction in the infarct size and improvement in the coronary microvasculature function in patients with STEMI following PICSO treatment. The incidence of MACE, including death, recurrent myocardial infarction, and heart failure, was lower in patients who underwent PICSO showing that it is safe and feasible, with no significant adverse effects related to the procedure. It was also observed to significantly improve the left ventricular ejection fractions in patients with STEMI.

3.2. Statistical analysis

All categorical data were presented as frequency and percentages while continuous data were documented as mean and standard deviation (SD). In the case of segregated data for Anterior and Inferior STEMI, data were obtained for anterior STEMI. The medians and Inter quartile ranges were converted to mean with Standard Deviations where applicable using the formula proposed by Lau et all and Wan et all.[9,10] In cases where outcome data were reported for more than one follow-up, the Longest follow-up was considered. The variables were pooled using the StatsDirect statistical software version 3.3.5. Estimates of relative risk for dichotomous variables and Standardized Mean Difference (SMD) for continuous variables were pooled using the Random effects model with the DerSimonian-Laird method. The I_2 statistic was used to assess heterogeneity across studies.

4. Outcomes

Four cohort studies were eligible to be included in the quantitative analysis. In the pooled analysis, the use of PICSO was associated with a significant

reduction in infarct size (SMD = −0.44, 95% CI = −0.76-0.13, p = 0.004). There was no heterogeneity (I_2 = 0%). PICSO administration was associated with a reduced risk of developing microvascular resistance (RR = 0.75, 95% CI = 0.62,0.92, p = 0.0051). The heterogeneity across three studies which reported this outcome was zero (I_2 = 0%). The post-procedural Index of Microvascular Occlusion (MVO) was lower in the PICSO treated compared to the control group and this result was homogenous and statistically significant (SMD = −0.35, 95% CI = −0.68-0.01, p = 0.03, I_2 = 0%). Compared to matched controls, the use of PICSO was associated with higher Left Ventricular Ejection Fraction (LVEF) at the longest follow-up (SMD = 0.328, 95% CI = 0.03, 0.06, p = 0.03, I_2 = 0%). There was no significant difference between the two groups in End Diastolic Volume (EDV) at the longest available follow-up (SMD = 0.010, 95% CI = −0.28,0.30, p = 0.80). Moreover, the results suffered from high heterogeneity (I_2 = 53.9%). End Systolic Volume (ESV) was also comparable between the two groups and suffered from mild heterogeneity (SMD = −0.15, 95% CI = −0.47, 0.16, p = 0.34, I_2 = 13.7%). The pooled relative risk for Major Adverse Cardiovascular Events (MACE) from three studies indicated a 17% higher chance of PICSO-treated patients experiencing a MACE at follow-up. Still, the results were statistically insignificant and highly heterogenous (RR = 1.17, 95% CI = 0.20, 7.01, p = 0.86, I_2 = 64.4%). This is demonstrated in **Supplementary Files S2** (https://scholarlycommons.gbmc.org/cgi/editor.cgi).

5. Discussion

This meta-analysis showed that PICSO administration was associated with reduced infarct size post-STEMI, reduced risk of developing microvascular resistance, and lower incidence of post-procedural microvascular occlusion. PICSO leads to an increased LVEF and EDVs among patients with STEMI. However, there was a 17% higher risk of MACE in patients with PICSO, although the results were highly heterogeneous and nonsignificant.

Infarct size assessment post-STEMI has been widely used as an efficacy endpoint in clinical studies of reperfusion therapy as it is associated with all-cause mortality and heart failure hospitalizations.[7] In this review, the pooled data suggest that STEMI patients treated with PICSO in adjunct to PCI had a favorable outcome in terms of infarct size, microvascular resistance, and LVEF. As myocardial salvage is the main objective of PCI, STEMI mortality should be lessened due to optimized workstreams, and advanced reperfusion techniques. However, the mortality rate is still increasing, mainly because of incomplete recovery after PCI. The underlying pathophysiology behind this might be the clinical consequence of microcirculatory obstruction and reperfusion.[4,5]

Intermittent occlusion of the CS with a PICSO balloon increases the venous pressure by 70 mmHg, leading to the more homogeneous distribution of coronary flow to the border zone of the infarct area of the myocardium with collateral recruitment from the venous outflow of coronaries.[11] This leads to improved myocardial perfusion and vasodilates the small coronary collaterals. After the pressure plateaus, there is a sudden deflation of the balloon which causes clearance of inflammatory and vasoconstrictive mediators and microthrombi.[12]

In one meta-analysis of 7 experimental studies, PICSO reduced infarct size by 29% compared with the control.[13] In our meta-analysis, the use of PICSO was associated with a significant reduction in infarct size (SMD = −0.44, 95% CI = −0.76,-0.13, p = 0.004) in human participants as well. The first-in-human PICSO treatment was done in 2012.[14] Fifteen patients with elective PCI of LAD underwent PICSO. Treatment with PICSO augmented CS pressure, causing an increased LAD wedge pressure. PICSO was later studied in STEMI patients as a support device for high-risk elective PCI, and in patients with heart failure.[7] PICSO is unique as the only adjunctive therapy utilizing venous circulation and a retrograde approach to microcirculation.[15] PICSO has been shown to reduce microvascular resistance in this meta-analysis (RR = 0.75, 95% CI = 0.62,0.92, p = 0.0051) immediately followed by PCI. Microvascular perfusion should be adequate for prompt recovery of the peri-infarcted myocardium. It also facilitates the removal of micro-thrombi and microvascular debris from the circulatory system, leading to prompt myocardial recovery.[4] No major complications have been noted with PICSO in any of the included studies, and this treatment is initiated after reperfusion of the culprit artery, therefore; there is no delay in door-to-balloon time.

6. Limitations

To the best of our knowledge, the present study is the first to systematically review the published literature on PICSO and STEMI. Most studies were limited to the Northern Hemisphere and did not include a long-term follow-up; thus, the durability of the benefits observed with PICSO is unclear. In addition, these studies did not assess the cost-effectiveness of PICSO compared to standard care.

All studies stated the precise aim or issue to be addressed and showed promising results; however, the small sample size and possible publication bias imposed another limitation on the devised substantiation. The PISCO procedure requires specialized equipment and training which may limit its reproducibility in other hospitals or countries. Further studies are needed to confirm the safety and efficacy of PICSO in a larger and more diverse patient population.

7. Conclusion

In conclusion, PICSO is a novel technology designed to mitigate microvascular dysfunction in the setting of STEMI. Uncontrolled and non-randomized trials have suggested that PICSO can be used during PPCI in STEMI with improved outcomes of infarct size, LVEF, and microvascular perfusion. Ongoing and planned prospective trials will determine the efficacy and safety of this treatment in the future.

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Conflict of interest

The authors declare no competing interests.

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