

# **Therapeutic Hypothermia as Effective Therapy For ROSC Patients With Cardiac Arrest: A Systematic Review**

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## **ABSTRACT**

Prehospital cardiac arrest is a relevant cause of death worldwide. The patients who can reach the ROSC (Return of Spontaneous Circulation) phase after experiencing cardiac arrest, only about 10% can experience improvement and are discharged from the hospital, in addition, only a small proportion can go home with neurological conditions back well. However, there are no studies that reveal when is the right time to implement therapeutic hypothermia, and whether therapeutic hypothermia measures are safe and effective for ROSC patients in cardiac arrest.

This systematic review aimed to identify therapeutic hypothermia as a safe and effective action in post cardiac arrest patients and the appropriate time and temperature for the procedure. This research was taken from the electronic database PubMed, Science Direct, EBSCO, and Google Scholar, through database scanning, and article screening was carried out independently by researchers. Researchers followed the requirements in fulfilling the inclusion criteria. We used all electronic search strategies for each electronic database according to inclusion data, with search strings: therapeutic hypothermia, prehospital, out-of-hospital Cardiac Arrest, randomized controlled trials.

Therapeutic hypothermia is safe and effective for use in ROSC patients with cardiac arrest and the right time to perform this action is at the pre-hospital time with the use of a temperature of 34-36 ° C.

Therapeutic hypothermia can be performed pre-hospital with intravenous fluids at a temperature of 34-36 ° C after the patient is resuscitated or during resuscitation, thereby reducing neurological failure due to cardiac arrest.

**Keywords:** Therapeutic Hypothermia, Prehospital, Cardiac Arrest, A Randomized Controlled Trials

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**BACKGROUND**

Prehospital cardiac arrest is a relevant cause of death worldwide. According to the American Heart Disease and Stroke Statistics, the survival rate for discharge from hospital after a heart attack is 10%. Furthermore, only a small proportion of patients can go home with neurological conditions back to normal from the hospital. (Mahmoud *et al.*, 2016)

Hypothermia is a state of core body temperature (core)  $\leq 35^{\circ}\text{C}$  as a result of the body's inability to retain heat and exposure to cold environments. Hypothermia is associated with physiological changes in all organ systems and has a negative impact if it is not treated quickly and effectively. The body's self-warming mechanism becomes ineffective so that the heart rate and blood pressure are very weak which results in decreased circulation and peripheral pulse, in this case dysrhythmias can occur and other disorders such as hypoxemia and acidosis (Smeltzer, 2014) (Song & Lyden, 2012)

Based on research, therapeutic hypothermia is a potential life-saving treatment in cardiac arrest patients. Therapeutic hypothermia (33-35 °C) is induced after the return of spontaneous circulation (ROSC) (Kamarainen *et al.*, 2009). Clinical trials in the therapeutic application of hypothermia for 12-24 hours significantly improve survival and neurological outcomes in patients after cardiac resuscitation (Scales *et al.*, 2017). Cardiac arrest patients who remain comatose after ROSC will exhibit ventricular fibrillation (VF) or ventricular tachycardia as the initial heart rhythm. The effects of therapeutic hypothermia include a reduction in cerebral metabolism and the production of oxygen free radicals, a weakening of the immune response during reperfusion and brain edema, but it can also inhibit the release of amino acids. However, what is still unknown is when the right time to treat hypothermia is and how safe and effective it is. (Kuhnke *et al.*, 2019)

In 2011, the National Health Service (NHS) for the National Institute for Health and Care Excellence (NICE) was published in support of the use of therapeutic hypothermia for hypoxic ischemic encephalopathy. NICE also describes guidelines for the use of therapeutic hypothermia in cardiac arrest and has been published in the United States (Nielsen *et al.*, 2013) The American Heart Association recommends hypothermia as the standard of care for patients with ROSC because of insufficient evidence to demonstrate an improvement in patient outcomes from therapeutic hypothermia (Bernard *et al.*, 2012)

**METHODS**

This study used a design review analysis method: Systematic Review and in accordance with specific inclusion indicators in document selection through a comprehensive search system (Comprehensive literature search).

Eligibility Criteria in this study was carried out based on inclusion criteria to eliminate and select data. Types of studies using the Randomized Control Trial on the effect of therapeutic hypothermia as a safe and effective action in post cardiac arrest patients. The language used is English, the journal publication year is 2009-2019. Respondents were cardiac arrest patients. The type of intervention was the provision of therapeutic hypothermia in cardiac arrest patients.

**1. Data Search**

Researchers conducted literature searches from electronic databases search, namely PubMed, Science, Direct, EBSCO, and Google Scholar. Researchers used a search string: therapeutic hypothermia, prehospital, out-of-hospital cardiac arrest, randomized controlled trials. Researchers followed the requirements in fulfilling the inclusion criteria.

## 2. Data Collection Process

Researchers identified data using extraction sheets through the PICO approach (Population, Intervention, Compare, and Outcome). Researchers extracted and checked data. Researchers performed a Critical Appraisal.

## 3. Data Items

The extracted data information includes; 1) Characteristics of respondents including post cardiac arrest patients, 2) Underwent therapeutic hypothermia, 3) At the prehospital location of Out-of-hospital 4) Using the RCT (Randomized Controlled Trials) method. 5) The type of Outcome measured included time and temperature of therapeutic hypothermia.

## 4. Data Extraction

The researchers conducted an independent review of the title including the abstract and full text of the article to extract data according to the inclusion criteria. Data extraction was designed such as publication year, language, study design, characteristics of study population, cooling procedure, time of hypothermic therapy, measurement of outcome.

## 5. Risk of Bias

The researchers validated the literature by extracting data. The researchers identified the research has been carried out according to the procedure or not. Researchers explored the variability in the results of the study (heterogeneity), before conducting the analysis. Researchers identified therapeutic hypothermia according to the research methodology used. Bias Possibility in this study was the difference in the way of action in therapeutic hypothermia in each study.

## 6. Study Outcome Definition

The primary outcome was survival with a good neurologic outcome until the patient was discharged from the hospital or referred for therapy temperature rehabilitation on admission. The outcome measured was the appropriate temperature and timing of hypothermic therapy.

## 7. Summary Measures

The impact of giving hypothermic therapy is to improve the improvement of the condition after ROSC patients. Researchers reviewed 7 articles with the Critical Appraisal Skill Program (CASP), after which data extraction was carried out using the PICO approach to identify the indicators in the article. This Systematic Review was to analyze the effects of a therapeutic hypothermia intervention. Researchers also analyzed the follow-up measures of hypothermic therapy.

## C. RESULT

### 1. Study Selection

The researcher obtained a total of 7 research articles according to the inclusion criteria. 7 research studies that match the criteria include Kamarainen (2009), Bernard, (2010), Bernard (2012), Nielsen, (2013), Kim, (2017), Mahmoud, (2016) and Scales et al., (2017). Researchers conducted a literature search strategy for NCBI's PubMed, Science Direct and Google Scholar. Total data were obtained using a search string. Initial results obtained 32 data. These data were identified the possibility of duplication and an abstract

review was carried out whether they matched the research criteria. After the identification of the data, it was obtained 18 suitable data, after that Eligibility was carried out and obtained 12 literatures. The researchers made an in-depth identification of 7 articles and articles that could be used (include).

## 2. Characteristics of Included Studies

It has characteristics, namely based on the research of Bernard, (2010) with the number of respondents 234 pre-hospital adults with cardiac arrest, consisting of 116 people in the control group and 118 people. Risk ratio 0.90, 95% confidence interval 0.70 to 1.17, (P = 0.43). The results of Bernard's (2012) study with 1198 respondents with cardiac arrest at prehospital. 618 patients under hypothermic therapy and 580 patients with standard prehospital care. Spontaneous circulation in patients receiving cold saline was compared with standard care (41.2% compared with 50.6%, P = 0.03).

Kamairan (2009) study of 125 patients underwent cooling and conventional treatment. In the large volume ice cold fluid (LVICH) treatment group, the volume remained 2 liters.

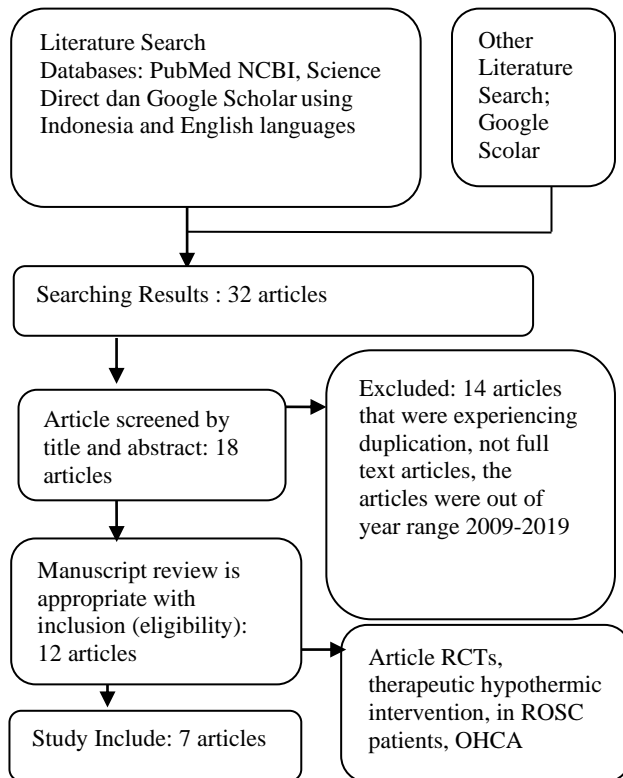
Cooling Method: Infusion of 4 °C, Ringer's solution of 100 ml / min in the treatment group versus the control (p <0.0001).

In Nielsen, (2013) the number of respondents was 473 patients were given cooling with a temperature of 33° C and 466 patients were given cooling with a temperature of 36° C. Group analysis of temperature was 33° C, 1.06; 95% confidence interval [CI], 0.89 to 1.28; P= 0.51). Results of analysis for the temperature group 36° C (risk ratio, 1.02; 95% CI, 0.88 to 1.16; P = 0.78). In this case hypothermic therapy is more effective at 36° C.

In Kim's study, (2017) with 125 patients, 63 patients received cooling, 62 patients did not get cooling. Infusion of up to 2 L of 4 ° C normal saline in the field is feasible, safe, and effective in lowering temperature, neurological impact, and ventricular fibrillation rhythm after cardiac arrest.

Based on the results of Mahmoud's research, (2016) with 1391 respondents consisting of groups with a temperature of 32-34° C and groups with control of core body temperature. In the intervention group, the cooling temperature was 32-34° C and the group with core body temperature control. These results suggested that only mild hypothermia could improve outcomes among patients who had cardiac arrest at prehospital.

According to Scales (2017) in his research on 585 respondents. Consisting of a group with a temperature of 32-34° C were 279 respondents and a group with core body temperature control of 306 respondents. Prehospital hypothermia therapy started 5 minutes after ROSC did not lead to improvement of the target temperature of 32-34° C in 6 hours, but was safe, and increased the application of TTM (targeted temperature management) in the hospital.



Picture 1. PRISMA flowchart for literature identification

### 3. Synthesis of Result

The results of the synthesis forest plot showed that of the 7 research studies using RCTs, all of them consisted of an intervention group and a control group in respondents with cardiac arrest

Table 1. Data Extraction using the PICO Approach

Authors & year	Level JBI	Purpose	Method (design)	Sample	Intervention	Data Analysis	Major Findings
Kamarainen, (2009)	III b	Evaluating recent clinical studies on hypothermia induction after cardiac arrest. (about cooling level, safety and the feasibility of different methods)	RCT	N = 125 patients with cooling and conventional care	125 patients Randomized cooling and conventional treatment. In the large volume ice cold fluid (LVICH) treatment group, the volume remained 2 liters. Cooling Method: Infusion of 4 °C Ringer's solution 100ml/mentit	The oesophageal temperature decreased 1.24 ° C (SD ± 1.09, n = 54) was observed in the treatment group compared to the treatment group 0.10 ° C (SD ± 0.94, n = 36) increased in the control group (p <0.0001).	Effective drop at temperature regardless of the cooling method
Bernard, (2010)	III b	Comparing which one was more effective in doing therapeutic hypothermia after resuscitation at the pre-hospital with the time at the hospital in cardiac arrest patients	RCT	N = 234 pre-hospital adult patients with cardiac arrest	Of the 118 patients allocated to paramedic cooling, 57 (48%) received 2000 mL, 11 received 1500-2000 mL, 37 received 1000-1500 mL, 5 received 500-1000 mL considering the length of transport and 8 did not receive ice cold liquid reasons for administration. Of the 116 patients allocated to hospital refrigeration, 1 received 2000 mL of ice-cold liquid. Cooling method: Infusion of 2 L of ice-cold lactated Ringer's solution	Risk ratio 0.90, 95% confidence interval 0.70 to 1.17, (P = 0.43).	In adults who experienced cardiac arrest who have been resuscitated in pre-hospital with the initial heart rhythm of ventricular fibrillation, cooling with cold / ice intravenous fluids could reduce heart rhythm.
Bernard (2012)	III b	Compared which ones most influence CPR on the incidence of spontaneous circulation in cardiac arrest patients between hypothermia therapy	RCT	N = 1198 with cardiac arrest at pre hospital. 618	All patients underwent initial resuscitation care including defibrillation, intravenous cannulation, administration of an initial dose of epinephrine and 100% oxygen O2 ventilation. The	Spontaneous circulation in patients receiving cold saline was compared with standard care (41.2% compared with 50.6%, P = 0.03). Overall 10.2% of patients were allocated to therapeutic hypothermia while CPR was alive	In adults with cardiac arrest at pre-hospital, induction with hypothermic therapy using a fast-high volume infusion, as long as CPR could reduce the rate of

Authors & year	Level JBI	Purpose	Method (design)	Sample	Intervention	Data Analysis	Major Findings
		using rapid high-volume infusions, and the provision of standard prehospital care		patients under hypothermic therapy and 580 patients with standard prehospital care	patient then received an infusion of 30 mL / kg rapidly and coldly at a temperature of 33 ° (maximum 2 L) via the intravenous cannula. Cooling method: Infusion of ice-cold Ringer's solution	in hospital compared to 11.4% who received standard care (P = 0.71).	return Spontaneous circulation in a patient with an initial nerve rhythm
Nielsen, (2013)	III b	Compared the effectiveness of 33° C and 36° C to determine the target temperature management for cooling therapy after cardiac arrest	RCT	N = 939 was cooled with a temperature of 33° C and 36° C	473 patients were given cooling with a temperature of 33 ° C and 466 patients were given cooling with a temperature of 36 ° C	Analysis of temperature groups 33° C, 1.06; 95% confidence interval [CI], 0.89 to 1.28; P = 0.51). Analysis results Temperature group 36 ° C (risk ratio, 1.02; 95% CI, 0.88 to 1.16; P = 0.78).	In an unconscious person with a heart attack outside the hospital, it was more effective to give cooling / cooling at a temperature of 36 ° C than a temperature of 33 ° C which did not provide significant benefits for the progress of the patient's condition.
Kim, (2017)	III b	Assessed the feasibility, safety, and effectiveness of prehospital cooling of 4° C Normal Saline Rapid Infusion.	RCT	N = 125 patients, 63 patients received cooling, 62 patients did not get cooling	Randomly, 125 patients received standard care without intravenous cooling. Of the 63 randomized patients received cooling 33 ° C Cooling Method: Infusion up to 2 L of ice-cold 0.9% saline solution	After cooling, the temperature increase was ± 0.10 - 0.94 ° C (P = 0.0001)	Infusion of up to 2 L of 4 ° C normal saline in the field was feasible, safe, and effective in lowering temperature, neurological impact, and ventricular fibrillation rhythm after cardiac arrest.
Mahmoud, (2016)	III b	Compared between the targeted temperatures management (core	RCT	N = 1391 consisted of a group	Respondents consisted of 2 groups with cooling temperature 32-34 ° C and groups with core	Insignificant mortality rate (relative risk [RR] 0.90; 95% confidence interval [CI], 0.77-1.04; P ¼, 15, 12 ¼ 34%), surprising	These results suggest that only mild hypothermia may be required

Authors & year	Level JBI	Purpose	Method (design)	Sample	Intervention	Data Analysis	Major Findings
		body temperature 32-34 ° C) with control (core body temperature 36 ° C) in heart failure patients. The primary outcome assessed was all-cause death and poor neurologic outcome.		with a temperature of 32-34° C and a group with control of core body temperature.	body temperature control.	rhythm (RR 0.89 ; 95% CI, 0.74-1.08, P ¼, 25, I2 ¼ 46%). All hypothermia was mild in the control group (RR 0.83; 95% CI, 0.71-0.96; P ¼, 01, I2 ¼ 0%). There was a nonsignificant reduction in poor neurologic outcome with targeted temperature management compared with controls (RR 0.87; 95% CI, 0.74-1.03, P ¼, 10, I2 ¼ 54%), rhythm shock (RR 0.87; 95% CI, 0.70-1.07, P ¼, 19, I2 ¼ 63%)	improved outcomes among patients who had heart attacks in pre-hospital.
Scales (2017)	III b	Determine whether pre-hospital cooling by paramedics led to higher 'TTM success' rates, defined as attainment of a target temperature of 32-34 °C within 6 hours of hospital arrival	RCT	N = 585 Consist of the group with the temperature of 32-34 ° C was 279 and the group with control of core body temperature was 306	Respondents consisted of 2 groups with cooling temperature 32-34° C and groups with core body temperature control. 585 patients were randomized to receive hypothermic therapy at prehospital (n=279), control (n=306). Hypothermic therapy did not increase TTM levels (Pre-hospital cooling started 5 minutes after ROSC did not lead to improvement in target temperature 32-34°C within 6 hours after hospital admission after OHCA	TTM / targeted temperature management in the hospital) was successful (30% vs 25%; RR, 1.17; 95% confidence interval [CI] 0.91–1.52; p = 0.22), but improved adoption rate. TTM in hospital (68% vs 56%; RR, 1.21; 95% CI 1.07–1.37; p = 0.003). Survival with good neurologic outcome (29% vs 26%; RR, 1.13, 95% CI 0.87-1.47; p = 0.37) was similar. Pre-hospital chilling was not associated with refinement during transport (7.5% vs 8.2%; RR, 0.94; 95% CI 0.54–1.63; p = 0.83) but was associated with a reduced incidence of pulmonary edema in the emergency department (12% vs 18%; RR, 0.66; 95% CI 0.44-0.99; p = 0.04).	Pre-hospital hypothermia therapy started 5 minutes after ROSC did not lead to improvement of the target temperature of 32-34° C in 6 hours, but was safe, and increased the application of TTM (targeted temperature management) in the hospital.



**DISCUSSION**

In recent years, therapeutic hypothermia is an increasingly used temperature management in the post-resuscitation care of patients with cardiac arrest. TTM / Targeted Temperature Management or hypothermic therapy has been shown to improve survival with good neurological outcomes and is recommended for resuscitated patients. (Scales *et al.*, 2017) Unconscious patients admitted to the critical care unit after prehospital heart attack are at high risk for death, and neurologic deficits are frequent among those who survive. Therapeutic hypothermia (also called target temperature management) is now recommended in international resuscitation guidelines. (Bernard *et al.*, 2012)

The American Heart Association, International Liaison Committee on Resuscitation, and other international agencies now highly recommend TTM for eligible patients following resuscitation from a heart attack. Despite these recommendations, TTM was administered inconsistently, incompletely, and often with delay. The reasons are due to awareness of recommended practices, perceptions of poor prognosis, limited time and resources, and lack of manpower. (Scales *et al.*, 2017)

Out of hospital heart attack (OHCA) after return of spontaneous circulation (ROSC). Whereas the mechanism is not fully understood, a decrease in core body temperature might reduce the inflammatory response that occurs after reperfusion ischemic injury, directly reduce cellular injury, and increase brain neuronal healing and oxygen demand by reducing intracranial pressure. (Song & Lyden, 2012)

Pre-hospital cooling interventions by emergency medical service providers (EMS) (paramedics) can act as a catalyst to drive more timely application of TTM by hospital doctors, and pre-cooling can also improve clinical outcomes (Bernard *et al.*, 2010). Randomized controlled trials (RCTs) with cold intravenous saline, and other applications have been shown to be more helpful to victims than no prehospital cooling.

Many treatments provide benefits for therapeutic hypothermia after heart failure. This mechanism is thought to affect all Level 3 injuries after cardiac arrest: ischemic injury, direct reperfusion injury, and delayed reperfusion injury.

The study characteristics of the 7 studies that were obtained all examined the use of the cooling method in cardiac arrest patients undergoing ROSC. Before cooling (cooling), the patient must first be resuscitated. The research management site was homogeneous, namely the pre-hospital cooling action (OHCA). All studies used the RCTs (Randomized Control Trial) design. There are 4 studies comparing the effectiveness of management in patients after cardiac arrest using cooling with conventional measures, namely the management of standard pre-hospital cardiac arrest treatments such as drug administration, CPR and so on in patients. There are 2 studies comparing the use of cooling with a temperature range of 32-34° C with a core body temperature of 36° C. The infusions used include Infusion of ice-cold Ringer's solution, Infusion of 4° Ringer's acetate, and Infusion of 4° normal saline. All studies conducted blinded respondents. The timing of therapeutic hypothermic management was at the time of prehospital CPR.

Bernard *et al.* (2012) cooled all patients undergoing initial resuscitation treatment including defibrillation, intravenous cannulation, administration of an initial dose of epinephrine and O2 ventilation of 100% oxygen. The patient then received an infusion of 30 mL / kg rapidly and coldly at a temperature of 33° (maximum 2 L) through an intravenous cannula: Infusion of ice-cold Ringer's solution, and the other group had only pre-hospital cardiac arrest management according to standard without cooling treatment. From the results, it was found that cardiac arrest experienced in adults, after induction with hypothermic therapy during CPR, can trigger a return of spontaneous circulation and

restore the patient's heart rhythm back to a normal rhythm. The timing of therapeutic hypothermia management is during pre-hospital resuscitation.

Based on research by Bernard *et al.*, (2010) by comparing which one was more effective in doing therapeutic hypothermia after resuscitation while in pre-hospital with when in hospital in cardiac arrest patients. Of the 118 patients 57 (48%) received 2000 mL, 11 received 1500-2000 mL, 37 received 1000-1500 mL, 5 received 500-1000 mL, the amount of fluid was influenced by the length of transportation from the scene to the hospital. Meanwhile, 116 patients were cooled down in the hospital. From this study, what distinguishes was the management time of giving hypothermia therapy, namely at the pre-hospital and at the hospital. The results obtained that giving resuscitation and hypothermic therapy were more effective at reducing heart rhythm in the state of ventricular fibrillation compared to tuning at the hospital. The timing of therapeutic hypothermia management was during prehospital resuscitation.

The results of a study conducted by Kim *et al.* (2017) examined the feasibility, safety, and benefits of prehospital care for hypothermia. OHCA patients with cardiac arrest were randomized to rapid prehospital cooling to an infusion of 4 °C normal saline. The hospital temperatures differed significantly ( $p < 0.0001$ ). This study presented survival outcomes based on the VF and non-VF heart rhythm groups. This cooling method is not associated with side effects in terms of hemodynamic instability, nor with other clinical measures such as pulmonary edema assessed by chest X-ray or arrest. Although these results indicated that this cooling method was safe to perform in patients after resuscitation. The timing of therapeutic hypothermia management was during prehospital resuscitation.

Another study by Nielsen *et al.*, (2013) compared the effectiveness of cooling with a temperature of 33° C and 36° C to determine the target temperature management for cooling therapy after cardiac arrest. Of the 473 patients who were given cooling with a temperature of 33° C and 466 patients were given cooling at a temperature of 36° C, the results showed that people who were unconscious with a heart attack in situations outside the hospital were more effective at cooling at 36° C than at 33° C. The temperature that tended to be lower did not provide a significant benefit for the progress of the patient's condition. The timing of therapeutic hypothermia management was during pre-hospital resuscitation.

Research by Nielsen *et al.*, (2013) is also supported by research conducted by Mahmoud *et al.*, (2016). The study compared cooling with a temperature of 32-34 ° C with cooling (core body temperature of 36 ° C) in patients with heart failure.

The primary outcome assessed among these was cause of death and poor neurological outcome. The results obtained from mild hypothermia were necessary and may improve outcomes among pre-hospital heart attack patients. So that cooling with a mild temperature of 36° C showed more impact on neurological, ROSC patients. The timing of therapeutic hypothermia management was during pre-hospital resuscitation.

Characteristics of included studies that were the characteristics of the 7 eligible studies were summarized in research published between 2009 and 2019, and all of them were RCTs. Of the six studies, 2 were conducted in Europe, 2 in North America and the USA, 23 and 1 in Finland and 1 in Australia. All studies were published in English. Heart rhythms in three studies were ventricular fibrillation (VF) and non-VF, one was VF, and the last was non-VF. In one study, therapeutic hypothermia was initiated before ROSC, and in another, after ROSC. Two studies induced therapeutic hypothermia by infusing NSI 4° C23 solution or Ringer's acetate solution, two studies with cold Ringer's solution.

All studies used blink of respondents, both patients and health workers who performed therapeutic hypothermia, so as to reduce bias. All respondents in the study had a large enough sample to reduce bias in the study.

Safety of intravenous cold fluids infusion to induce therapeutic hypothermia at pre-hospital (Kim *et al.*, 2017) The results of respondents randomized / randomized treatment with therapeutic hypothermia, patients discharged from the hospital after experiencing cardiac arrest, will be more effective because it is minimal in neurological impact, compared to conventional management, namely CPR, pharmacodynamic resuscitation measures.

The quality of research in this systematic review is good, it is shown that all studies report the criteria desired by researchers, besides that the number of respondents is large. After searching the literature, all data met the requirements, the patient data were treated with therapeutic hypothermia at the pre-hospital, temperature, fluids used and the mean 95% CI results were converted to mean  $\pm$  SD by the formula method. All studies reported similar results on hospital admissions and patient survival after pre-hospital to hospital.

There were no significant differences regarding safety outcomes or secondary outcomes such as neurologic outcomes and mortality in patients with ROSC. There are also those who do not. The results of the study of Kamarainen *et al.* (2009) showed statistically significant with respect to survival for hospital discharge and favorable outcome at hospital. A drawback in this study was an unobserved rearrest rate of increase, further related to the side effects of hemodynamic instability in ROSC patients.

Based on the results of the seven studies, it shows that the effective time to do pre-hospitalization is when resuscitation helps in cardiac arrest, and does not have to wait for ROSC patients. Therapeutic hypothermic action is safe and effective based on the results of existing research, so this action can be recommended for emergency management of patients with cardiac arrest, this action is also effective because it does not require a lot of money so that it can reduce the financial burden borne by the patient

## CONCLUSION

Therapeutic hypothermia is safe and effective for use in ROSC patients with cardiac arrest and the right time to perform this action is during pre-hospital resuscitation. Therapeutic hypothermia measures can be done during resuscitation, not having to wait for successful resuscitation actions / ROSC. Therapeutic hypothermia can be performed pre-hospital with intravenous fluids at a temperature of 34°- 36° C so as to reduce neurological failure due to cardiac arrest.

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