The Effect of Prehospital Therapeutic Hypothermia on Cardiac Arrest Outcome
Paramedic Mini CAT – Fanshawe College Date of review: 11.03.2021

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Clinical Scenario:
A paramedic crew responds to a 65-year-old male patient who complains of chest pain. Upon initial assessment, the crew suspects ischemic chest pain. A 12-lead ECG reading reveals a lateral STEMI. Appropriate medications are administered, and the patient is prepared for extrication, during which he falls unconscious. The paramedics begin CPR according to their standard level of practice. An advanced care crew arrives on scene and considers initiating prehospital therapeutic hypothermia in an attempt to reduce the patient's chances of neurological damage and increase the likelihood of survival. The crew is hoping that therapeutic hypothermia in the prehospital setting is a superior treatment to standard prehospital practice.

Background
For patients who suffer out-of-hospital cardiac arrest, hospital-initiated therapeutic hypothermia to a temperature range of between 32°C and 34°C for 24 hours has been proven to increase chances of survival and improve neurological outcome. The mechanism behind this effect has not been well established, however, several explanations have been proposed. Hypothermia may reduce oxygen demand in the brain which is beneficial during periods of hypoxia that occur during cardiac arrest. It may also act by slowing down enzymatic reactions in the brain that cause cerebral injury (Mild Therapeutic Hypothermia, 2002). Regardless of the underlying mechanism of action, therapeutic hypothermia has been widely accepted as a treatment option for out-of-hospital cardiac arrest and has been adopted by the American Heart Association (American Heart Association, 2005). It is then logical to assume that initiating therapeutic hypothermia early in the prehospital setting should improve patient outcome further.

Review question (PICO format)
- Patient/problem: Out-of-hospital cardiac arrest.
- Intervention: Paramedic-initiated therapeutic hypothermia during CPR.
- Comparison: Standard paramedic practice.
- Outcome: Patient survivability and neurological outcome.

During out-of-hospital cardiac arrest calls, does paramedic-initiated therapeutic hypothermia during CPR improve patient survivability and neurological outcome in comparison to standard practice.

Search strategy (Basic): Search terms for both databases. For the journal article selection process and database search pictures, refer to *Appendix A.*

- (Paramedic OR EMT OR emergency medical technician OR EMS OR emergency medical services OR prehospital) AND
- (Cardiopulmonary resuscitation OR out-of-hospital OR out-of-hospital cardiac arrest OR CPR OR cardiac arrest) AND
- (Targeted temperature management OR TTM OR cold IV infusion OR therapeutic hypothermia OR cold normal saline OR hypothermia OR prehospital cooling OR cold saline) AND
- (Neurological OR neurological status OR neurological outcome OR neurological injury OR brain injury OR brain damage OR survival)

Limits:

- MEDLINE:
    - Scholarly (Peer Reviewed) Journals
    - January 2010 to January 2021
    - Search mode: Boolean/phrase
- PubMed:
    - Scholarly (Peer Reviewed) Journals
    - Randomized Controlled Trials
    - 2010-2021

Databases searched: MEDLINE and PubMed.

Search results: 289

- MEDLINE: 260
- PubMed: 29

Included for review:

3 out of 289 journal articles were included in this review. They were selected according to the following criteria:

- Relevance: all terms of the PICO question were to be included in the study.
- Design: only multicenter, randomized, controlled trials were included.
- Sample size: studies with the largest sample size were selected over the rest.

Title, author, year	Study design & LOE	Population	Intervention	Outcomes	Results	Weaknesses & Strengths
Effect of Trans-Nasal Evaporative Intra-arrest Cooling on Functional Neurologic Outcome in Out-of-Hospital Cardiac Arrest (Nordberg, et al, 2019) -The PRINCESS Trial	Multicenter, randomized, clinical trial. LOE: 1	-n=677 -Patients with bystander-witnessed out-of-hospital cardiac arrest.	-Intervention group (n=343): received prehospital trans-nasal evaporative cooling. -Control group (n=334): received standard prehospital care.	-Survival with good neurological status based on a Cerebral Performance Category (CPC) of 1-2 after 90 days. -Survival at 90 days. -Time to reach a body core temperature less than 34°C.	- CPC (1-2) at 90 days: (P=0.25) *Intervention group (16.6%). *Control group (13.5%). -Survival at 90 days: (P=0.44) *Intervention group (17.8%). *Control group (15.6%). -Median time to core temperature >34°C: (P<0.001) *Intervention group (105min). *Control group (182min). -**Conclusion**: Trans-nasal evaporative cooling did not improve survival or neurological outcome in a statistically significant way.	**Strengths**: -Multicenter study conducted in 11 emergency medical services. -Researchers and physicians who performed the neurological assessments were blinded to group assignment. -Patients were randomly assigned to treatment groups using sequentially numbered envelopes. -Trans-nasal evaporative cooling does not have side effects that may interfere with the results. **Weaknesses**: -EMS and hospital staff were not blinded to the study.

Induction of Therapeutic Hypothermia During Out-of-Hospital Cardiac Arrest Using a Rapid Infusion of Cold Saline (Bernard, et al, 2016) -The RINSE Trial	Multicenter, randomized, controlled trial. LOE: 1	-n=1198 -Patients in cardiac arrest who received resuscitation efforts by paramedics.	-Intervention group (n=618): received prehospital rapid intravenous infusion of up to 2L of cold saline. -Control group (n=580): received standard prehospital care.	-Survival at hospital discharge. -Rate of return of spontaneous circulation for patients with an initial shockable rhythm.	-Survival at hospital discharge: (P=0.71) *Intervention group (10.2%). *Control group (11.4%). -ROSC: (P=0.03) *Intervention group (41.2%). *Control group (50.6%). **-Conclusion:** Prehospital cold IV infusion does not improve patient outcome at hospital discharge and may decrease the likelihood of ROSC in patients with a shockable initial rhythm.	**Strengths:** -Multicenter study conducted in multiple EMS stations across 3 cities in Australia. -Large test sample. -Patients were grouped randomly by computer. **Weaknesses:** -Paramedics and hospital staff are not blinded to the study. -Cold IV infusion increases total body fluid volume which is a confounding factor. The decreased likelihood of ROSC in the intervention group may be caused by this.

Impact of intra-arrest therapeutic hypothermia in outcomes of prehospital cardiac arrest (Debaty, et al, 2014)	Multicenter, randomized, controlled trial. LOE: 1	-n=245 -Patients in cardiac arrest who received resuscitation efforts by paramedics.	-Intervention group (n=123): received prehospital rapid intravenous infusion of up to 2L of cold saline and surface cooling via four cooling gel pads. -Control group (n=122): received standard prehospital care.	-Inflammatory response markers of neurological injury concentrations: *neuron-specific enolase (NSE) concentration at 24 hours. *Interleukin (IL)-6, -8, and -10 concentrations at 72 hours. -ROSC rate. -Survival at discharge, 30 days and 1 year. -Neurological outcome at discharge and 30 days (CPC).	-NSE median concentrations: (P=0.64) *Intervention group (96.7 μg/L) *Control group (97.6 μg/L). -No significant difference in interleukin levels between the groups. -ROSC rate: (P=0.3) *Intervention group (37.4%). *Control group (31.1%). -Survival (Discharge, 30 days, 1 year): (P=0.73,0.73,0.99) *Intervention group (5.7%, 5.7%, 4.1%). *Control group (4.1%, 4.1%, 4.1%). -No significant difference in neurological outcome between the groups.	**Strengths**: -Multicenter study conducted in 3 EMS stations in France. -The inflammatory markers are accurate predictors of bad neurological outcome after cardiac arrest and act to increase the accuracy of the study. **Weaknesses:** -Small sample size of 245. -The use of IV infusion as a method of therapeutic hypothermia introduces a confounding factor, which is increased body fluid level, similar to the previous study. -Measurement of CPC to determine neurological effect

					-Conclusion: Prehospital therapeutic hypothermia by cold IV infusion did not decrease neurological inflammatory markers when compared with standard practice.	were done on sample sizes of below 10 individuals for each group. Therefore, results have questionable accuracy.

Comments:
The three studies referenced in this review were selected based on the search criteria outlined above. The largest multicenter, randomized, controlled trials were selected to reduce bias and to provide the most accurate answer to the PICO question. Evidence on this topic is consistent throughout the literature and in the studies referenced in this review.

Considerations:
The majority of research on therapeutic hypothermia has been conducted by cold IV infusion. This technique decreases body temperature adequately, however, it increases body fluid levels as well. This may cause hemodynamic instability which may alter the results of the experiments. The RINSE trial found that cold IV infusion was associated with an increase in pulmonary edema as well as a decrease in the rate of ROSC. There is a high probability that these findings are a consequence of the hemodynamic instability caused by cold IV infusion rather than the effect of hypothermia on the body. This confounding variable interferes with the findings of the RINSE trial and the French multicenter study. Researchers in the PRINCESS trial took this into account and selected an alternative method of inducing therapeutic hypothermia. Their trans-nasal evaporative cooling technique had no side effects except for minor epistaxis. This did not change the results, however.

Clinical bottom line:
All three studies showed consistent evidence against the use of therapeutic hypothermia in the prehospital setting. There was no evidence for an increase in survivability or a decrease in neurological damage. Surprisingly, cold IV infusion led to a decrease in the rate of ROSC as a suspected consequence of hemodynamic instability. Trans-nasal evaporative cooling, which is designed to avoid this instability, did not show any benefits in terms of survival or neurological outcome either. More research is needed to determine

why therapeutic hypothermia is not beneficial in the prehospital setting, but beneficial in the hospital setting. Until this is done, the evidence indicates that therapeutic hypothermia should not be used in the prehospital setting.

References

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Nordberg, P., Taccone, F. S., Truhlar, A., Forsberg, S., Hollenberg, J., Jonsson, M., . . . Svensson, L. (2019). Effect of Trans-Nasal Evaporative Intra-arrest Cooling on Functional Neurologic Outcome in Out-of-Hospital Cardiac Arrest; The PRINCESS Randomized Clinical Trial. Jama, 321(17), 1677. doi:10.1001/jama.2019.4149

Appendix A

Journal Article Selection Process		
Search Criteria	Number of Journals Generated	
	MEDLINE	PubMed
Initial search based on search terms and limits	260	29
Filtered for relevance (PICO)	25	6
Filtered for multicenter RCT design	4	4
Duplicates removed	4	0
Filtered for largest sample size (maximum 3 journals)	3	0

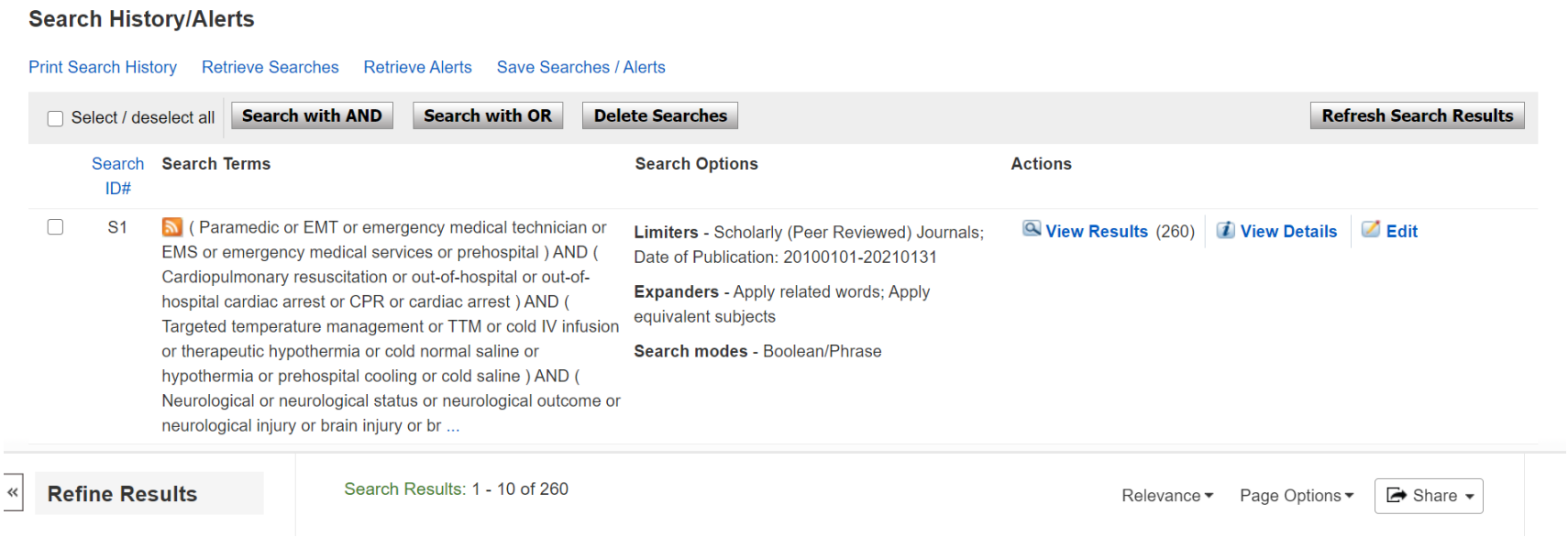

Figure 1 MEDLINE Search Picture

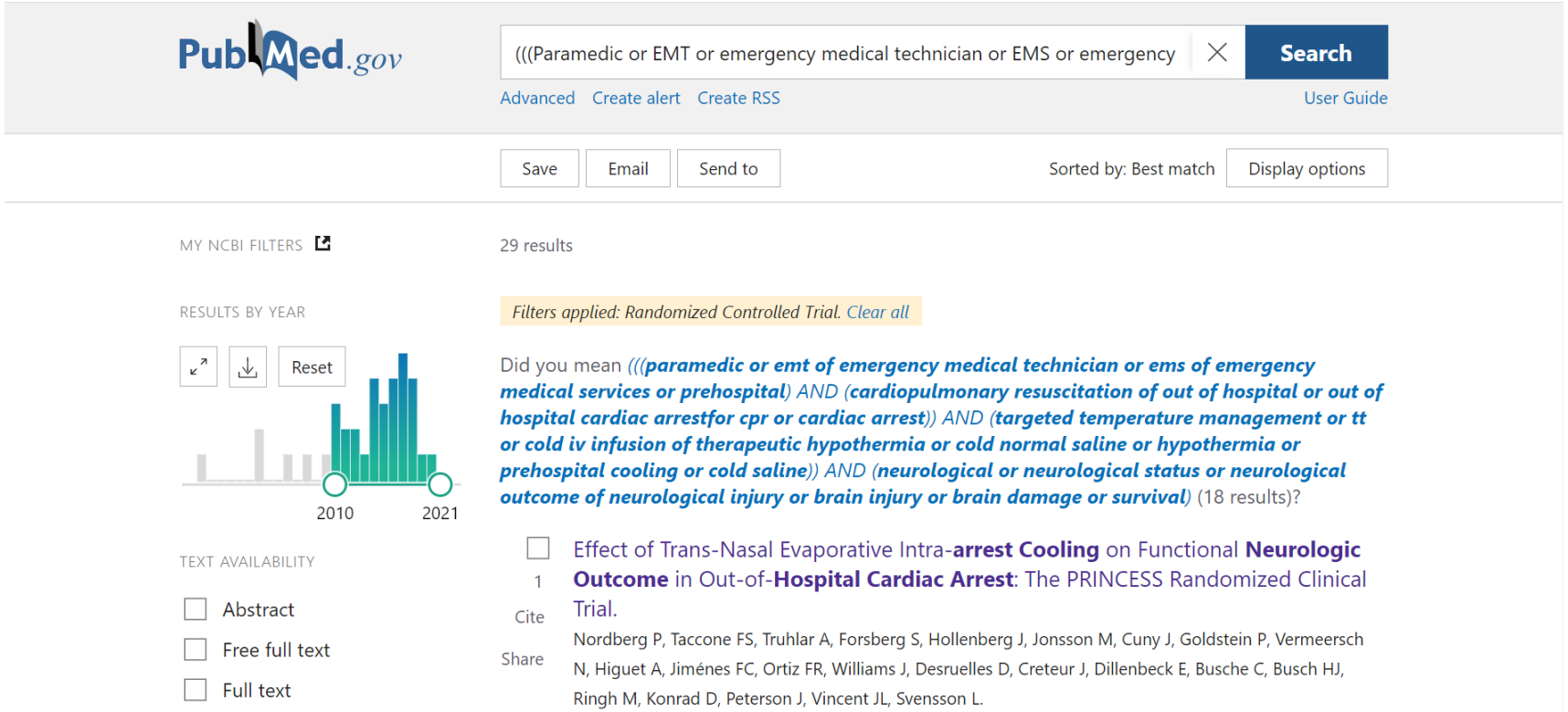

Figure 2 PubMed Search Picture