

QUESTION

Should endovascular cooling vs. surface cooling be used for cardiac arrest?	
POPULATION:	Adults in any setting (in-hospital or out-of-hospital) with cardiac arrest
INTERVENTION:	endovascular cooling
COMPARISON:	surface cooling
MAIN OUTCOMES:	Survival to hospital discharge/28 days ; Favorable neurological outcome at hospital discharge/28 days;
SETTING:	
PERSPECTIVE:	
BACKGROUND:	
CONFLICT OF INTERESTS:	<p>Soar J, Nolan JP, Andersen LW, Granfeldt A, Holmberg MJ. None of the SR authors have any financial conflicts of interests and none of the authors have academic conflicts related to ongoing or planned trials. Lars W. Andersen was compensated in his role as a systematic reviewer by the American Heart Association on behalf of ILCOR for his work related to this systematic review.</p> <p>Soar J, Nolan JP, Andersen LW, Böttiger BW, Couper K, Deakin CD, Drennan I, Hirsch KG, Hsu CH, Nicholson TC, O'Neil BJ, Paiva EF, Parr MJ, Reynolds JC, Sandroni C, Wang TL, Callaway CW, Donnino MW, Granfeldt A, Holmberg MJ, Lavonas EJ, Morrison LJ, Nation K, Neumar RW, Nikolaou, Skrifvars MB, Welsford M, Morley PT, Berg KM</p> <p>CHH, JCR, KGH, RWN, CWC declared intellectual conflicts on going trials. BWB, MBS and BO'N declared speaker fees.</p>

ASSESSMENT

Problem																	
Is the problem a priority?																	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS															
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	Seven trials compared different methods of TTM but the majority were small feasibility or pilot trials. Three trials compared endovascular with surface cooling and were included in a meta-analysis (Pittl 2013; Deye 2015; Look 2018)																
Desirable Effects																	
How substantial are the desirable anticipated effects?																	
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS															
<input type="radio"/> Trivial <input type="radio"/> Small <input checked="" type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know	<p>Ultimately, the desirable effect is improved neurological outcome. The ideal cooling technique would be easily implementable, would achieve target temperature rapidly and enable tight temperature control without complications</p> <table border="1"> <thead> <tr> <th>Outcomes</th> <th>With surface cooling</th> <th>With endovascular cooling</th> <th>Difference</th> <th>Relative effect (95% CI)</th> </tr> </thead> <tbody> <tr> <td>Survival to hospital discharge/28 days</td> <td>399 per 1,000</td> <td>455 per 1,000 (371 to 551)</td> <td>56 more per 1,000 (28 fewer to 152 more)</td> <td>RR 1.14 (0.93 to 1.38)</td> </tr> <tr> <td>Favorable neurological outcome at hospital discharge/28 days</td> <td>291 per 1,000</td> <td>355 per 1,000 (276 to 453)</td> <td>64 more per 1,000 (15 fewer to 163 more)</td> <td>RR 1.22 (0.95 to 1.56)</td> </tr> </tbody> </table>	Outcomes	With surface cooling	With endovascular cooling	Difference	Relative effect (95% CI)	Survival to hospital discharge/28 days	399 per 1,000	455 per 1,000 (371 to 551)	56 more per 1,000 (28 fewer to 152 more)	RR 1.14 (0.93 to 1.38)	Favorable neurological outcome at hospital discharge/28 days	291 per 1,000	355 per 1,000 (276 to 453)	64 more per 1,000 (15 fewer to 163 more)	RR 1.22 (0.95 to 1.56)	The desirable effects assume that TTM is beneficial. In addition there is an assumption that a stable constant temperature during TTM is best and there is no evidence that this is the case.
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Undesirable Effects																	

How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know 	Complications associated with intravascular cooling include bleeding and venous thromboembolism	Thrombosis associated with intravascular cooling catheters (Andreumont 2018 1; Maze 2014 1354)

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																														
<ul style="list-style-type: none"> ○ Very low ● Low ○ Moderate ○ High ○ No included studies 	<p>The overall certainty in the evidence for endovascular vs. surface cooling was assessed as low for both survival to hospital discharge and survival to hospital discharge with a favourable neurologic outcome.</p> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th rowspan="2">Outcomes</th> <th rowspan="2">Relative effect (95% CI)</th> <th colspan="3">Anticipated absolute effects* (95% CI)</th> <th rowspan="2">Certainty of the evidence (GRADE)</th> <th rowspan="2">What happens</th> </tr> <tr> <th>Without endovascular cooling</th> <th>With endovascular cooling</th> <th>Difference</th> </tr> </thead> <tbody> <tr> <td rowspan="2">Survival to hospital discharge/28 days No of participants: 523 (3 RCTs)</td> <td rowspan="2">RR 1.14 (0.93 to 1.38)</td> <td colspan="3">Study population</td> <td rowspan="2">⊕⊕○○ LOW^{a,b}</td> <td rowspan="2"></td> </tr> <tr> <td>39.9%</td> <td>45.5% (37.1 to 55.1)</td> <td>5.6% more (2.8 fewer to 15.2 more)</td> </tr> <tr> <td rowspan="2">Favorable neurological outcome at hospital discharge/28 days No of participants: 523 (3 RCTs)</td> <td rowspan="2">RR 1.22 (0.95 to 1.56)</td> <td colspan="3">Study population</td> <td rowspan="2">⊕⊕○○ LOW^{a,b}</td> <td rowspan="2"></td> </tr> <tr> <td>29.1%</td> <td>35.5% (27.6 to 45.3)</td> <td>6.4% more (1.5 fewer to 16.3 more)</td> </tr> </tbody> </table> <p style="margin-left: 20px;">a. The 95%CI includes both no effect and clinically relevant benefit b. All included trials were assessed as having an intermediate risk of bias</p>	Outcomes	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)			Certainty of the evidence (GRADE)	What happens	Without endovascular cooling	With endovascular cooling	Difference	Survival to hospital discharge/28 days No of participants: 523 (3 RCTs)	RR 1.14 (0.93 to 1.38)	Study population			⊕⊕○○ LOW ^{a,b}		39.9%	45.5% (37.1 to 55.1)	5.6% more (2.8 fewer to 15.2 more)	Favorable neurological outcome at hospital discharge/28 days No of participants: 523 (3 RCTs)	RR 1.22 (0.95 to 1.56)	Study population			⊕⊕○○ LOW ^{a,b}		29.1%	35.5% (27.6 to 45.3)	6.4% more (1.5 fewer to 16.3 more)	
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Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important 	People generally value good functional outcome over survival. They are likely to favour a cooling technique that resulted in better functional outcome.	

uncertainty or variability ● No important uncertainty or variability		
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Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input checked="" type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know	There are no significant differences in the outcome between intravascular and other methods of cooling	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Large costs <input checked="" type="radio"/> Moderate costs <input type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know	Intravascular cooling and external cooling with a feedback system are more expensive than simple surface cooling with wet towels and ice pack.	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies	No included studies	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
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<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input checked="" type="radio"/> No included studies 	No cost-effectiveness studies in our SR	
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Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Reduced <input checked="" type="radio"/> Probably reduced <input type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know 	The more expensive cooling methods, such as intravascular cooling, are unlikely to be available in low-income countries	

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	There is wide variation in the use of different cooling methods but they are generally accepted by stakeholders	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know 	Most of these cooling methods have been widely implemented.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			

JUDGEMENT

BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention ○	Conditional recommendation against the intervention ○	Conditional recommendation for either the intervention or the comparison ●	Conditional recommendation for the intervention ○	Strong recommendation for the intervention ○
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CONCLUSIONS

Recommendation

We suggest surface or endovascular temperature control techniques when temperature control is used in comatose patients after ROSC (weak recommendation, low certainty of evidence).

When a cooling device is used, we suggest using a temperature control device that includes a feedback system based on continuous temperature monitoring to maintain the target temperature (good practice statement).

Justification

Cooling devices

- Task Force members agreed that based on our SR either surface or endovascular cooling should be suggested.
- There is no consensus on whether a feedback surface cooling device should be routinely used so this was added as a good practice statement as there is no evidence this approach improves outcomes. There was consensus that temperature should be continually monitored by the cooling device in order to maintain a stable temperature.

There was a comment that endovascular cooling is superior – there are two recent SRs with conflicting conclusions: Bartlett ES (Resuscitation 2020 82) showed intravascular cooling is associated with improved neurological outcome, and Kim JG (Resuscitation 2020 14) found no associated with survival or neurological outcomes.

Research priorities

Is temperature control using a cooling device with feedback more effective?