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Controvèrsies en la hipotèrmia

Contra

Baltasar Sánchez González
Servicio de Medicina Intensiva

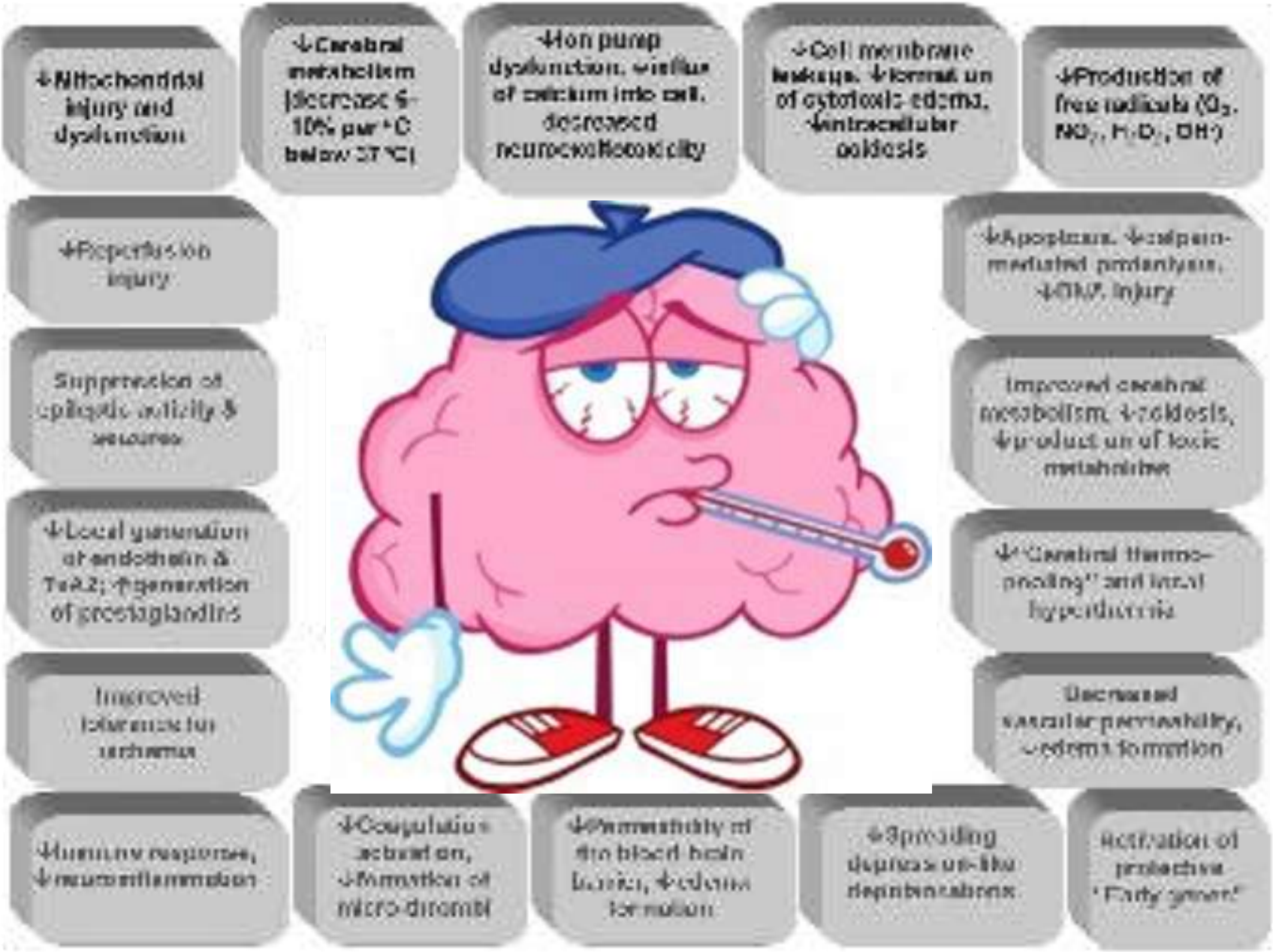

Figure 1. Schematic depiction of the mechanisms underlying the protective effects of mild to moderate hypothermia. *TxA2*, thromboxane A2.

Therapeutic Hypothermia After Cardiac Arrest

An Advisory Statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation

On the basis of the published evidence to date, the ILCOR ALS Task Force has made the following recommendations:

-Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32 C to 34 C for 12 to 24 hours when the initial rhythm was VF.

-Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.

Circulation. 2003;108:118-121.

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Part 9: Post–Cardiac Arrest Care

2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care

-We recommend that comatose (ie, lack of meaningful response to verbal commands) adult patients with ROSC after out-of-hospital VF cardiac arrest should be cooled to 32 C to 34 C (89.6 F to 93.2 F) for 12 to 24 hours (Class I, LOE B).

-Induced hypothermia also may be considered for comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electric activity or asystole (Class IIb, LOE B).

-Active rewarming should be avoided in comatose patients who spontaneously develop a mild degree of hypothermia (32 C [89.6 F]) after resuscitation from cardiac arrest during the first 48 hours after ROSC. (Class III, LOE C).

Circulation. 2010;122[suppl 3]:S768–S786

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Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation (Review)

Authors' conclusions:Conventional cooling methods to induce mild therapeutic hypothermia seem to improve survival and neurologic outcome after cardiac arrest. Our review supports the current best medical practice as recommended by the International Resuscitation Guidelines.

THE COCHRANE COLLABORATION®

Baja tasa de reclutamiento

No cálculo del tamaño muestra

The New England Journal of Medicine

Grupo control sin control de la temperatura

VOLUME 346 FEBRUARY 21, 2002 NUMBER 8

Interrupción prematura del estudio

Nivel de coma no especificado

MILD THERAPEUTIC HYPOTHERMIA TO IMPROVE THE NEUROLOGIC OUTCOME AFTER CARDIAC ARREST

THE HYPOTHERMIA AFTER CARDIAC ARREST STUDY GROUP*

No estandarización de medidas de limitación del esfuerzo tera

No randomización

Diferencias basales entre grupos

TREATMENT OF COMATOSE SURVIVORS OF OUT-OF-HOSPITAL CARDIAC ARREST WITH INDUCED HYPOTHERMIA

No estandarización de medidas de limitación del esfuerzo terapéutico

BRUCE M. JONES, M.B., B.S., WILLIAM SILVESTER, M.B., B.S., GEOFF GUTTERIDGE, M.B., B.S., AND KAREN SMITH, B.SC.

N Engl J Med, Vol. 346, No. 8 · February 21, 2002

Grupos de tratamiento no comparables

No efectos adversos

High-Volume Hemofiltration After Out-of-Hospital Cardiac Arrest

A Randomized Study

Grupo control sin control de la temperatura

JACC Vol. 46, No. 3, 2005

Mild hypothermia induced by a helmet device: a clinical feasibility study

Said Hachimi-Idrissi *, Luc Corne, Guy Ebinger, Yvette Michotte, Luc Huyghens

Causa de la PCR distinta a FV

Resultado no positivo

Resuscitation 51 (2001) 275–281

Hypothermia after cardiac arrest should be further evaluated—A systematic review of randomised trials with meta-analysis and trial sequential analysis

Niklas Nielsen [a,*], Hans Friberg [b], Christian Gluud [c], Johan Herlitz [d], Jørn Wetterslev [c]

	Mori 2000 (abstract)	Hachimi-Idrissi 2001	HACA 2002	Bernard 2002	Laurent 2005
Duration	Not reported	6 months	65 months	33 months	23 months
Participants	OHCA patients with GCS<8	Unconscious OHCA patients, cardiac cause of arrest, initial rhythm asystole or PEA	Unconscious CA patients, cardiac cause of arrest, initial rhythm VF or non-perfusing VT	Unconscious OHCA patients, cardiac cause of arrest, initial rhythm VF or VT	Unconscious OHCA patients, cardiac cause of arrest, initial rhythm VF or asystole
Experimental intervention	MIH to 32–34 °C for 72 h, method of cooling not described, rewarming rate not reported	Helmet cooling to 34 °C. When temperature of 34 °C achieved or more than 4 h elapsed from start of cooling, passive rewarming for 8 h.	Air cooling induced hypothermia to 32–34 °C for 24 h, passive rewarming for 8 h	Ice-pack induced hypothermia to 33 °C for 12 h (started pre-hospitally), active rewarming for 6 h	CVVH to 32–33 °C (CVVH for 8 h and surface cooling for 16 h), passive rewarming
Control intervention	36 °C for 72 h, method of temperature control not described	Standard ICU care, acetaminophen if temperature over 38 °C	Standard ICU care, no temperature control	Standard ICU care, no temperature control	CVVH maintaining 37 °C for 8 h, thereafter no temperature control
Inclusion criteria	OHCA and GCS<8	OHCA of cardiac origin Asystole or PEA as initial rhythm, >18 years, temp >30 °C, GCS<7	Witnessed CA of cardiac origin, VF or non-perfusing VT as initial rhythm, 18–75 years, 5–15 min from arrest to CPR and <60 min to ROSC	OHCA with VF as initial rhythm, persistent coma	OHCA of cardiac origin, VF or asystole, 18–75 years, <10 min to start of CPR, <50 min to ROSC
Exclusion criteria	Not defined	Pregnancy, coagulopathy, CNS depressant medication before CA, cardiogenic shock (MAP<60), GCS≥7	<30 °C, coma because of drugs before CA, pregnancy, response to verbal command, MAP<60 for >30 min, hypoxemia >15 min, terminal illness, factors making follow-up unlikely, coagulopathy, other study, CA after arrival of medical personnel	<18 years for men <50 years for women cardiogenic shock <90 SBP despite epinephrine, other causes of coma than CA, no available ICU bed	Pregnancy, response to verbal command, terminal illness before CA
Follow-up time	1 month	14 days	6 months	Hospital discharge	6 months
Patients screened (n)	Not reported	Not reported	3551	Not reported (84 eligible)	244
Patients included (n)	54	30	275	77	42

Table 3
Description of how risk of bias was evaluated, based on the Cochrane Handbook.

Risk of bias/ Type of bias	Low risk of bias	Uncertain risk of bias	High risk of bias
Sequence generation	If the allocation sequence is generated by a computer or random number table or similar.	If the trial is described as randomised, but the method used for the allocation sequence generation was not described.	If a system involving dates, names, or admittance numbers are used for the allocation of patients (quasi-randomised).
Allocation concealment	If the allocation of patients involves a central independent unit, on-site locked computer, or consecutively numbered, sealed envelopes.	If the trial is described as randomised, but the method used to conceal the allocation is not described.	If the allocation sequence is known to the investigators who assigned participants or if the study is quasi-randomised.
Blinding	If the outcome assessors are blinded and the method of blinding is described.	If the outcome assessors are blinded and the method of blinding is not described.	If the outcome assessors are not blinded.
Incomplete data outcomes	If there are no post-randomization drop-outs or withdrawals.	If it is not clear whether there are any drop-outs or withdrawals or if the reasons for these drop-outs are not clear.	If the reasons for missing data are likely to be related to true outcomes, 'as-treated' analysis is performed, potential for patients with missing outcomes to induce clinically relevant bias in effect estimate or effect size.
Selective outcome reporting	If all the important outcomes are reported or if the trial's protocol is available and all of the trial's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way.	If there is insufficient information to assess whether the risk of selective outcome reporting is present.	If not all the pre-specified outcomes are reported, or if the primary outcomes are changed, or if some of the important outcomes are incompletely reported.
Baseline imbalance	If there was no baseline imbalance in important characteristics.	If the baseline characteristics were not reported.	If there was a baseline imbalance due to chance or due to imbalanced exclusion after randomization.
Early stopping	If sample-size calculation is reported and the trial is not stopped or the trial is stopped early by an adequate stopping rule.	If sample size calculations are not reported and it is not clear whether the trial is not stopped early.	If the trial is stopped early without formal stopping rules.
Sponsor bias	If the trial is without specific funding, or is not funded by an instrument, equipment, or drug manufacturer.	If the source of funding is not clear.	If the trial is funded by an instrument, equipment, or drug manufacturer.
Academic bias	If the author of the trial has not conducted previous trials addressing the same interventions.	If it is not clear if the author has conducted previous trials addressing the same interventions.	If the author of the trial has conducted previous trials addressing the same interventions.

Table 4
Components of risk of bias for the individual randomised clinical trials.

Trial/ Type of bias	Mori 2000	Hachimi-Idrissi 2001	HACA 2002	Bernard 2002	Laurent 2005
Sequence generation	Not described U	Not described U	Adequate L	Odd- and even days H	Adequate L
Allocation concealment	Not described U	Not described U	Sealed envelopes L	Quasi-randomised H	Sealed envelopes L
Blinding	Not described U	Not described U	Assessors blinded, procedure not described U	Assessors blinded, procedure described L	Not described U
Incomplete data outcomes	Not described U	No lost to follow-up L	One lost to follow-up in each allocation group. Intention to treat analysis performed. L	No lost to follow-up H	Not described U
Selective outcome reporting	Only neurological outcome reported H	All important outcomes reported L	All important outcomes reported L	All important outcomes reported L	All important outcomes reported L
Baseline imbalance	Important baseline characteristics not described. U	Important baseline characteristics not described. U	Imbalance in baseline characteristics H	Imbalance in baseline characteristics. Comorbidities not reported H	Important baseline characteristics not described. U
Sample size, power calculations, interim analysis and early stopping	No sample size reported U	No sample size reported U	Trial stopped early without formal stopping rules H	Interim analysis without adequate correction of significance H	Trial stopped early without formal stopping rules H
Sponsor bias	Not described U	No funding with conflicts of interest L	No funding with conflicts of interest L	No funding with conflicts of interest L	No funding with conflicts of interest L
Academic bias	No previous trials on hypothermia L	No previous trials on hypothermia L	No previous trials on hypothermia L	No previous trials on hypothermia L	No previous trials on hypothermia L

Table 5
Forest plot of the effect of mild induced hypothermia on mortality suggested by the randomised and quasi-randomised clinical trials (424 patients).

Study or subgroup	MIH		Control			Risk ratio	Risk ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.1.1 Trials with least risk of bias							
HACA 2002	56	137	76	138	36.0%	0.74 [0.58, 0.95]	
Laurent 2005	15	22	11	20	12.6%	1.24 [0.76, 2.02]	
Subtotal (95% CI)		159		158	48.6%	0.92 [0.56, 1.51]	
Total events	71		87				
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 3.39$, df = 1 (P = 0.07); $I^2 = 70\%$							
Test for overall effect: Z = 0.34 (P = 0.74)							
1.1.2 Trials with high risk of bias							
Hachimi-Idrissi 2001	13	16	13	14	31.6%	0.88 [0.66, 1.15]	
Subtotal (95% CI)		16		14	31.6%	0.88 [0.66, 1.15]	
Total events	13		13				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.95 (P = 0.34)							
1.1.3 Quasi-randomised trials							
Bernard 2002	22	43	23	34	19.9%	0.76 [0.52, 1.10]	
Subtotal (95% CI)		43		34	19.9%	0.76 [0.52, 1.10]	
Total events	22		23				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.47 (P = 0.14)							
Total (95% CI)		218		206	100.0%	0.84 [0.70, 1.01]	
Total events	106		123				
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.86$, df = 3 (P = 0.28); $I^2 = 22\%$							
Test for overall effect: Z = 1.90 (P = 0.06)							
Test for subgroup differences: Not applicable							

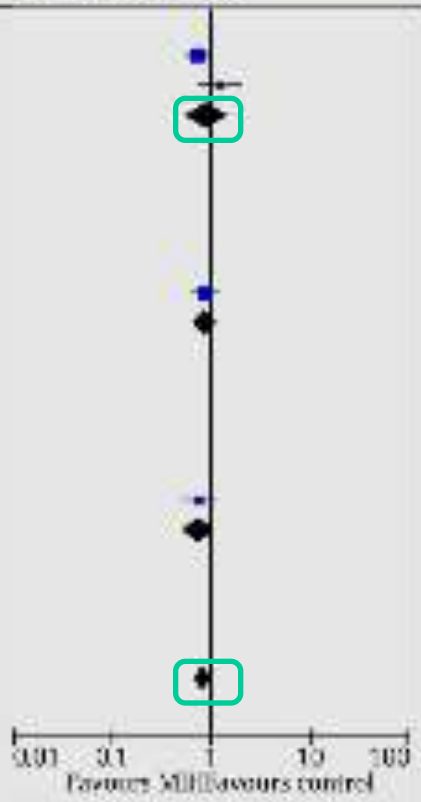

Table 6
Forest plot of the effect of mild induced hypothermia on neurological function suggested by the randomised and quasi-randomised clinical trials (478 patients).

Study or subgroup	MIH		Control			Risk ratio	Risk ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.2.1 Trials with least risk of bias							
HACA 2002	62	37	84	138	26.2%	0.74 [0.59, 0.93]	
Laurent 2005	15	22	11	20	11.9%	1.24 [0.76, 2.02]	
Subtotal (95% CI)		159		158	38.1%	0.92 [0.56, 1.50]	
Total events	77		95				
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 3.47$, df = 1 (P = 0.06); $I^2 = 71\%$							
Test for overall effect: Z = 0.35 (P = 0.73)							
1.2.2 Trials with high risk of bias							
Hachimi-Idrissi 2001	14	16	14	14	26.9%	0.88 [0.71, 1.10]	
Mori 2001	18	36	16	18	17.2%	0.56 [0.39, 0.81]	
Subtotal (95% CI)		52		32	44.1%	0.72 [0.43, 1.20]	
Total events	32		30				
Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 5.81$, df = 1 (P = 0.02); $I^2 = 83\%$							
Test for overall effect: Z = 1.27 (P = 0.20)							
1.2.3 Quasi-randomised trials							
Bernard 2002	22	43	25	34	17.7%	0.70 [0.49, 0.99]	
Subtotal (95% CI)		43		34	17.7%	0.70 [0.49, 0.99]	
Total events	22		25				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.00 (P = 0.05)							
Total (95% CI)		254		224	100.0%	0.78 [0.64, 0.95]	
Total events	131		150				
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 8.52$, df = 4 (P = 0.07); $I^2 = 53\%$							
Test for overall effect: Z = 2.42 (P = 0.02)							
Test for subgroup differences: Not applicable							

Table 7
GRADE profile for assessing quality of evidence for mild induced hypothermia after out-of-hospital cardiac arrest.

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Mild induced hypothermia	Control	Relative (95% CI)	Absolute		
Mortality (follow-up 180 days[a])												
4	Randomised trials	Serious[b]	No serious inconsistency	Serious[c]	No serious imprecision[d]	None	106/218 (48.6%)	123/206 (59.7%)	RR 0.84 (0.7 to 1.01)	96 fewer per 1000 (from 179 fewer to 6 more)	⊕⊕◯◯ LOW	CRITICAL
Neurological function (follow-up 180 days[a]; Cerebral performance category[e])												
5	Randomised trials	Serious[b]	No serious inconsistency	Serious[c]	No serious imprecision	None	131/254 (51.6%)	150/224 (67%)	RR 0.78 (0.64 to 0.95)	147 fewer per 1000 (from 33 fewer to 241 fewer)	⊕⊕◯◯ LOW	CRITICAL

Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia*

Table 3. Number and frequency of adverse events with corresponding univariate and adjusted odds ratios for mortality

Adverse Event and Concomitant Treatment	Total, n (%)	Alive, n (%)	Dead, n (%)	Univariate Odds Ratio (Lower Confidence Limit—Upper Confidence Limit)	p	Adjusted Odds Ratio (Lower Confidence Limit—Upper Confidence Limit)	p
	754 (100)	363 (48)	391 (52)				
Bleeding requiring transfusion	43 (6)	20 (6)	23 (6)	1.1 (0.57–2.2)	.76	1.0 (0.43–2.5)	.94
Pneumonia	361 (48)	208 (56)	153 (39)	0.48 (0.36–0.65)	<.001	0.88 (0.57–1.37)	.58
Sepsis	31 (4)	21 (6)	10 (3)	0.43 (0.18–0.97)	.028	0.59 (0.20–1.8)	.47
Antibiotic prophylaxis	207 (27)	94 (26)	113 (29)	1.2 (0.83–1.6)	.37	1.3 (0.80–2.0)	.31
Antibiotic therapy	414 (55)	242 (67)	172 (44)	0.39 (0.29–0.53)	<.001	.62 (0.40–0.98)	.04
Bradycardia <40 bpm	108 (14)	61 (17)	47 (12)	0.68 (0.44–1)	.062	.79 (0.42–1.5)	.47
Tachycardia >130 bpm	50 (7)	21 (6)	29 (7)	1.3 (0.70–2.5)	.38	1.7 (0.74–4.0)	.21
Atrial fibrillation	70 (9)	37 (10)	33 (8)	0.81 (0.48–1.4)	.45	1.1 (0.56–2.1)	.82
Ventricular tachycardia	76 (10)	36 (10)	40 (10)	1 (0.63–1.7)	.90	1.7 (0.87–3.3)	.12
Ventricular fibrillation	58 (8)	26 (7)	32 (8)	1.2 (0.65–2.1)	.68	2.0 (0.88–4.6)	.09
Hypoglycemia <3.0 mmol/L	40 (5)	12 (3)	28 (7)	2.3 (1.1–4.9)	.022	1.3 (0.47–3.7)	.6
Hyperglycemia >8 mmol/L >4 hrs	277 (37)	95 (26)	182 (46)	2.5 (1.8–3.4)	<.001	2.6 (1.6–4.1)	<.001
Hypokalemia <3.0 mmol/L	134 (18)	54 (15)	80 (20)	1.5 (1.0–2.2)	.046	1.3 (0.76–2.4)	.31
Hypomagnesemia <0.7 mmol/L	128 (17)	61 (17)	67 (17)	1 (0.69–1.5)	.92	1.2 (0.73–2.1)	.41
Hypophosphatemia <0.7 mmol/L	141 (19)	74 (20)	67 (17)	0.81 (0.55–1.2)	.26	0.68 (0.40–1.1)	.15
Seizures	182 (24)	44 (12)	138 (35)	4 (2.7–5.9)	<.001	1.1 (0.5–2.4)	.78
Anticonvulsants	154 (20)	32 (9)	122 (31)	4.7 (3–7.4)	<.001	5.4 (3.2–9.3)	<.001
Renal replacement therapy	32 (4)	13 (4)	19 (5)	1.4 (0.63–3.1)	.47	3.6 (1.1–12)	.04

Effect of Prehospital Induction of Mild Hypothermia on Survival and Neurological Status Among Adults With Cardiac Arrest

A Randomized Clinical Trial

CONCLUSION AND RELEVANCE Although use of prehospital cooling reduced core temperature by hospital arrival and reduced the time to reach a temperature of 34°C, it did not improve survival or neurological status among patients resuscitated from prehospital VF or those without VF.

JAMA. 2014;311(1):45-52. doi:10.1001/jama.2013.282173
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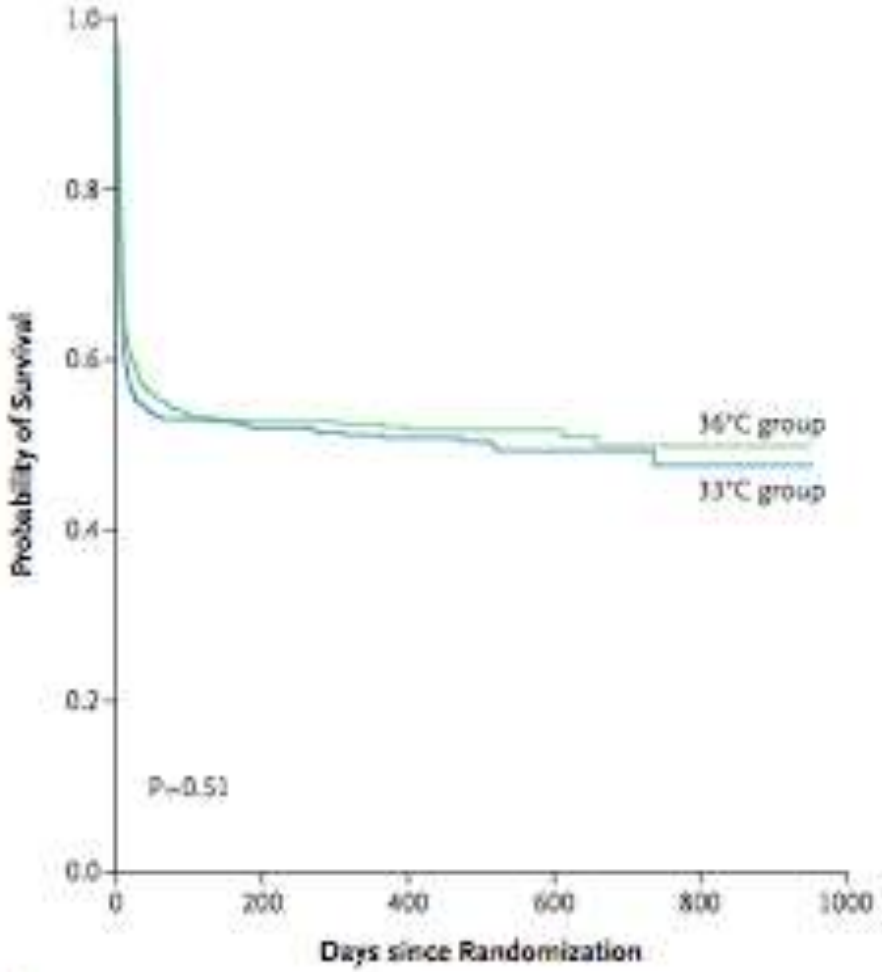

Figure 2. Probability of Survival through the End of the Trial.

Shown are Kaplan–Meier estimates of the probability of survival for patients assigned to a target temperature of either 33°C or 36°C and the number of patients at risk at each time point. The P value was calculated by means of Cox regression, with the effect of the intervention adjusted for the stratification variable of study site.

Table 3. Neurologic Scores.*

Variable	33°C Group	36°C Group
CPC at follow-up†		
Total no. of patients	469	464
Category — no. (%)		
1	195 (42)	183 (39)
2	23 (5)	39 (8)
3	17 (4)	20 (4)
4	6 (1)	2 (0.5)
5	228 (49)	220 (47)
P value for trend	0.85	

AHA nuevas guías

- We recommend targeted temperature management as opposed to no targeted temperature management for adults with OHCA with an initial shockable rhythm who remain unresponsive after ROSC

- We suggest targeted temperature management as opposed to no targeted temperature management for adults with OHCA with an initial nonshockable rhythm who remain unresponsive after ROSC.

- We suggest targeted temperature management as opposed to no targeted temperature management for adults with IHCA with any initial rhythm who remain unresponsive after ROSC.
We recommend selecting and maintaining a constant, target temperature between 32 C and 36 C for those patients in whom temperature control is used (strong recommendation, moderate-quality evidence).

- Whether certain subpopulations of cardiac arrest patients may benefit from lower (32-34oC) or higher (36oC) temperatures remains unknown, and further research may help elucidate this.

Conclusiones

¿Hemos hecho mal en aplicar estas recomendaciones y re

- La hipertermia después de la reanimación de una PCR se ha demostrado que se asocia con malos resultados y un aumento de la mortalidad.

- Tal vez el mensaje más importante es que los cuidados modernos y agresivos, que incluyen una temperatura objetivo post-PCR de 36ºC y con un estricto control de la temperatura, hacen que la supervivencia sea más probable que la muerte cuando un paciente es hospitalizado después de la RCP.

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¿Sería razonable aplicar esta temperatura objetivo de 36ºC y un estricto control de la temperatura a cualquier paciente con sospecha de daño cerebral por anoxia, sea cual sea la causa?

MútuaTerrassa

Gracias por su atención