WORKSHEET for Evidence-Based Review of Science for Emergency Cardiac Care

Worksheet author(s)

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Clinical question.

In adult patients with ROSC after cardiac arrest (prehospital or in-hospital) (P), does the use of a specific strategy to manage blood glucose (eg. Target range) (I) as opposed to standard care (C), improve outcome (O) (eg survival)?

Is this question addressing an intervention/therapy, prognosis or diagnosis? Intervention
State if this is a proposed new topic or revision of existing worksheet: Revision of existing worksheet

Conflict of interest specific to this question

Do any of the authors listed above have conflict of interest disclosures relevant to this worksheet? No

Search strategy (including electronic databases searched).

PubMed, Cochrane, EMBase and AHA databases for MeSH keywords:
Cardiac arrest OR cardiopulmonary resuscitation OR heart arrest OR Ventricular Fibrillation
AND
Glucose

I also reviewed the references from the articles selected for review.

- State inclusion and exclusion criteria

excluded studies involving:

1- Animal data
2- Studies lacking outcome data or intervention.
3- Letters to the editor, case reports, reviews of the literature or commentary articles.
4- Non-cardiac arrest studies (generally transplant literature evaluating solutions for organ preservation)
5- Pediatric data

Table of Results by Research Strategy

	CPR and Glucose (N=17)	Heart Arrest and Glucose (N=106)	HA or CPR AND glucose (N=112)	VF and Glucose (N=64)
Relevant	0	2	3	0
Non-human	10	34	32	23
Case report, LTE, Commentary	7	27	31	17
No outcomes/ No intervention		15	9	1
Not arrest		28	37	23

- Number of articles/sources meeting criteria for further review:

299
5 met all criteria from the review
Additional 12 found by review of references in documents.
All 18 are reviewed in this document

Summary of evidence

Evidence Supporting Clinical Question

Good					van den Berghe 2001, p 1359 C
Fair				**Langhelle 2003** **Skrifvars 2003** **Nolan, 2007** **Losert 2008**	
Poor				**Mullner, 1997**	
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Animal studies

Evidence Neutral to Clinical question

Good	**Oksanen, 2007** 				**Van den Berghe, 2006** **Arabi 2008** **Brunkhorst 2008** **Wiener, 2008** **Griesdale, 2009** **Preiser, 2009**
Fair					
Poor				**Steingrub, 1996** **Beiser, 2009**	
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Animal studies

Evidence Opposing Clinical Question

Good					 **NICE SUGAR 2009**
Fair					**Krinsley, 2007** **Arabi, 2009**
Poor					
	1	**2**	**3**	**4**	**5**
Level of evidence					

A = Return of spontaneous circulation
B = Survival of event
C = Survival to hospital discharge
D = Intact neurological survival
E = Other endpoint
Italics = Animal studies

REVIEWER'S FINAL COMMENTS AND ASSESSMENT OF BENEFIT / RISK:

Optimal glucose level or interventional strategy to mange blood glucose during the post-cardiac arrest period has not been defined in the current literature.

Steingrub (1996) observed that an elevated initial blood glucose following either out-of-hospital or in-hospital cardiac arrest was associated with a worse outcome in patients with CPR lasting more than 5 minutes. A worse outcome was defined as a Cerebral Performance Category of 3-5.

Mullner (1997) observed that elevated blood glucose levels both initially and for the first 24 hours following either in or out-of-hospital cardiac arrest were associated with worse outcomes, defined as a Cerebral Performance Category of 3-5. This study was limited to ventricular fibrillation cardiac arrest victims.

Skrifvars (2003) observed that 6 month mortality increased with 72 hour mean blood glucose levels in a group of 98 witnessed ventricular fibrillation arrest victims. (Table)

Mean blood glucose (mmol/L)	Number of patients	Mortality
5.8-6.8	22	9%
6.9-7.9	22	23%
7.9-8.9	22	50%
9.1-27.9	22	64%

The initial survival model demonstrated that age, delay to return of spontaneous circulation, mean blood glucose, serial potassium and use of beta-blocking agents during post-resuscitation care were associated with survival. However, when patients with a do-not-resuscitate order were removed from the model, only mean blood glucose, potassium, and the use of beta-blocking agents were associated with survival. Some of the patients in this study received hypothermia as part of the HACA trial, but their results are not specifically reported.

Langhelle (2003) noted an odds ratio of 2.67 (95% CI 1.17-6.20) for survival in 459 patients with blood glucose levels <10.6 mmol/L. Fever was prevented, but therapeutic hypothermia was not delivered in these patients.

Losert (2007) performed a retrospective analysis from the HACA dataset. As part of the HACA protocol, patients with blood glucose levels >200mg/dL had an insulin infusion initiated as part of their care. The 12 hour blood glucose levels were separated into quartiles. In a multivariate analysis, they demonstrated an odds ratio of 4.55 (95% CI 1.28-16.12) for patients with blood glucose levels between 67-115mg/dL and an odds ratio of 13.02 (95% CI 3.29-49.90) for patients with 12 hour glucose levels of 116-143mg/dL. Glucose levels of 150-175mg/dL had an odds ratio of 1.37 (95% CI 0.38-5.64). The highest quartile of 207-292mg/dL was used as the reference group. The percentage of patients receiving therapeutic hypothermia was not different between these quartiles.

Oksanen (2007) randomized out-of-hospital ventricular fibrillation patients to strict glycemic control (glucose 72-108mg/dL) or moderate glycemic control (108-144mg/dL). Patients received therapeutic hypothermia and insulin infusions were guided by the bed-side ICU nurse. The moderate glycemic control group tended to have glucose levels lower than targeted. Survival was similar in both groups (67% in strict glycemic control; 65% in moderate glycemic control). The study was stopped at the first interim analysis. Hypoglycemic episodes were more common in the strict glycemic group (7 v. 1, $p<0.01$).

The largest trials in the literature on glycemic control in critically ill patients come from van den Berghe and NICE-SUGAR. The work by van den Berghe (2001) in surgical patients suggested a mortality benefit in those patients with tight glucose control at a level of 4.4-6.1 mmol/L. However, subsequent trials by van den Berghe (2006), Arabi (2008), Preiser (2009), and Brunkhorst (2008) failed to demonstrate a survival benefit of strict glucose control compared to norglycemic controls. In fact, the NICE-SUGAR trial found that intensive glucose control increased mortality (OR 1.14; 95% CI 1.02-1.28; p=0.02) when compared to normoglycemia. Many trials have demonstrated that intensive glycemic control has been associated with more frequent episodes of hypoglycemia (van den Berghe, 2001; van den Berghe, 2006; Oksanen, 2007;; Arabi, 2008; Brunkhorst, 2008; NICE-SUGAR 2009; Preiser, 2009). Hypoglycemia (blood glucose <2.2 mmol/L) has been associated with worse outcomes in several trials. (Krinsley, 2007; Arabi, 2009). This risk is not desirable during the post-cardiac arrest period.

Acknowledgements: Maureen Morgan for bibliographic work.

Citation List

1. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359-67.

LOE 5 (not target population, but RCT; no post arrest patients in study)

2. Langhelle, A., S. S. Tyvold, et al. (2003). "In-hospital factors associated with improved outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway." Resuscitation 56(3): 247-263.

LOE 4 (observational). No comment on industry funding.

3. Skrifvars, M. B., V. Pettila, et al. (2003). "A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation." Resuscitation 59(3): 319-328.

LOE 4 (observational). Funded by the Laerdal Foundation for Acute Medicine.

4. Nolan JP, Laver SR, Welch CA, et al. Outcome following admission to UK intensive care units after cardiac arrest: a secondary analysis of the ICNARC Care Mix Programme Database. Anaesthesia 2007;62:1207-16.

LOE 4 (no controls, correct population)

5. **Losert, H., F. Sterz, et al. (2007). "Strict normoglycaemic blood glucose levels in the therapeutic management of patients within 12h after cardiac arrest might not be necessary." Resuscitation.**

LOE 4 (observational). No industry funding.

6. **Mullner, M., F. Sterz, et al. (1997). "Blood glucose concentration after cardiopulmonary resuscitation influences functional neurological recovery in human cardiac arrest survivors." J Cereb Blood Flow Metab 17(4): 430-436.**

LOE 4 (observational). No comment on industry funding.

7. **Oksanen, T., M. B. Skrifvars, et al. (2007). "Strict versus moderate glucose control after resuscitation from ventricular fibrillation." Intensive Care Med.**

LOE 1 (Randomized, controlled trial). Partial funding from Laerdal Foundation for Acute Medicine.

8. **van den Berghe G, Willmer A, Hermans G, et al. Intensive insulin therapy in the Medical ICU. N Engl J Med 2006;354:449-61.**

LOE 5 (not specific to ca patients, RCT, no report on post-ca patients)

9. **Arabi YM, Dabbagh OC, Tamim HM, et al. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. Crit Care Med 2008;36:3190-97.**

LOE 5 (not post-ca patients, RCT)

10. **Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358:125-39.**

LOE 5 (not post-ca patients, RCT)

11. **Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults. A meta-analysis. JAMA 2008;300:933-44.**

LOE 5 (not post-ca patients, analysis of trials)

12. **Griesdale DEG, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009;180:821-7.**

LOE 5 (not post-ca patients, analysis of RCT's)

13. **Preiser J-C, Devos P, Ruiz-Santana P, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med 2009;35:1738-1748.**

LOE 5 (not post-ca patients, RCT)

14. **Steingrub, J. S. and D. J. Mundt (1996). "Blood glucose and neurologic outcome with global brain ischemia." Crit Care Med 1996; 24(5): 802-806.**

LOE 4 (observational). No comment on industry funding.

15. Beiser DG, Carr GE, Edelson DP, et al. Derangements in blood glucose following initial resuscitation from in-hospital cardiac arrest: A report from the national registry of cardiopulmonary resuscitation. Resuscitation 2009;80:624-30.

LOE 4 (post-ca patients, no controls, retrospective, no intervention studied)

16. **NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283-97.**

LOE 5 (No post-ca patients, RCT)

17. **Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: Risk factors and outcomes. Crit Care Med 2007;35:2262-67.**

LOE 5 (not post-ca patients, not randomized controls)

18. **Arabi YM, Tamim HM, Rishu AH. Hypoglycemia with intensive insulin therapy in critically ill patients: Predisposing factors and association with mortality. Crit Care Med 2009;37:2536-44.**

LOE 5 (not post-ca patients, nested cohort of patients)