

Should Glucocorticoid-Induced Hyperglycemia Be Treated in Patients With Septic Shock?

~ JAMA, January 27, 2010; 303(4):365-366
 ~ Editorial, Greet Van den Berghe, MD, PhD
 ~ Corticosteroid Treatment and Intensive Insulin Therapy for Septic Shock in Adults: A Randomized Controlled Trial
 The COITSS Study Investigators, JAMA. Jan 27, 2010;303(4):341-348

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Preface

- Corticosteroids was used for reversal of fluid- and vasopressor-resistant septic shock which induces insulin resistance and hyperglycemia
- Glucocorticoid-induced hyperglycemia
 - should be treated in noncritically ill patients
 - be treated in patients with septic shock in the ICU ? and to what blood glucose level ?

History

- Hyperglycemia
 - an appropriate stress response
 - probably a potentially beneficial adaptation to critical illness
- Hyperglycemia was not treated unless glycemia exceeded the renal threshold (200~215 mg/dL, with glucosuria and hypovolemia)
- Conventional glucose control with insulin infusion
 - started only if the blood glucose > 215 mg/dL
 - adjusted to maintain the level at 180 ~200 mg/dL

Evolution

- Greet Van den Berghe et al. NEJM 2001;345(19)
 - In predominantly cardiac surgical ICU patient in Leuven
 - Intensive insulin therapy with insulin infusion
 - Started if the blood glucose > 110 mg/dL
 - adjusted to maintain the level at 80 ~110 mg/dL
 - ↓ mortality by an absolute 3% and reduced morbidity by prevention of secondary complications
- 2004 Surviving Sepsis Campaign (SSC) guidelines
 - targeting a blood glucose level to <150 mg/dL in the patient with sepsis (2c)
 - Post hoc data analysis
 - best results at the group of 80~110 mg/dL
 - improved outcome at the group of <150 mg/dL

COITSS study

- Corticosteroids and Intensive Insulin Therapy for Septic Shock (COITSS) study, JAMA. 2010;303(4)
 - 11 participating intensive care units in France, randomized, 2X2 factorial, open-label trial
 - 509 patients was randomized to
 - Intensive insulin therapy / hydrocortisol 50mg q6h
 - Intensive insulin therapy / add fludrocortisone 50ug qd
 - Usual care / hydrocortisol 50mg q6h
 - Usual care / add fludrocortisone 50ug qd
 - In-hospital death, overall survival, # of days vesopressin-free, cumulative incidence of SOFA <8 at 7th day (Sequential Organ Failure Assessment), length of stay at ICU

Variables	Intensive Insulin Therapy (n = 255)		Conventional Glucose Control (n = 254)		P Value		Hydrocortisone + Fludrocortisone (n = 245)		P Value		
	Unadjusted	Adjusted ^a	Unadjusted	Adjusted ^a	Unadjusted	Adjusted ^a	Unadjusted	Adjusted ^a	Unadjusted	Adjusted ^a	
In-hospital death, No./Total (%)	117/255 (45.9)	109/254 (42.9)	50	37	105 (42.9)	121 (49.8)	50	91			
Overall survival	122 (47.9)	118 (46.5)			112 (45.7)	126 (48.5)					
Kaplan-Meier estimate of survival rates, HR (95% CI), d	1.04 (0.80-1.34)		1		.78	.39	0.94 (0.73-1.21)		.61		.67
28	62.2 (65.4-68.5)	61.1 (65.3-67.5)			62.5 (66.6-68.9)	60.9 (65.2-67.1)					
90	51.8 (45.0-58.4)	54.8 (48.9-61.4)			54.2 (48.2-61.0)	52.4 (46.6-58.0)					
180	50.9 (45.0-57.6)	52.1 (46.2-58.8)			52.9 (46.9-59.7)	50.2 (44.4-56.8)					
No. of patients who died	103	82			105	121					
Causes of death, No. (%)											
Multiple organ failure	60 (78.4)	66 (80.8)			76 (71.4)	83 (88.6)					
Cardiovascular	9 (8.7)	7 (8.5)			7 (6.5)	9 (17.6)					
Stroke	1 (1.0)	2 (2.4)			3 (2.8)	0					
Brain hemorrhage	0	2 (2.4)			0	2 (4.1)			.67 ^b	.74 ^b	
Pulmonary hypoxia	1 (1.0)	2 (2.4)			2 (1.9)	1 (0.8)					
Unknown	0	3 (3.7)			3 (2.8)	0					
No. of days, median (IQR)											
Vasopressor-free within the first 7 days	4 (1.6)	4 (2.5)	58	60	4 (2.5)	4 (1.5)	82	61			
Mechanical ventilation-free within 28 days	10 (2.2)	13 (2.2)	51	20	12 (2.2)	12 (2.2)	50	81			
Cumulative incidence of SOFA <8 at day 7 (95% CI)	64.3 (58.6-70.1)	60.6 (54.7-66.6)	.38	.76	63.3 (57.3-69.2)	61.7 (56.0-67.5)	.76	.76			
Length of stay, median (IQR), d											
ICU											
All patients	9 (4-15)	9 (4-15)	.70	.39	9 (4-16)	9 (4-17.5)	.86	.35			
Survivors	10 (5-19)	9 (5-15)	.68	.46	10 (5-16)	9 (5-17)	.52	.10			
Hospital											
All patients	16 (5-34)	15 (7-30)	.87	.94	14 (6-29)	18 (7-34)	.15	.07			
Survivors	24 (12-43)	22 (11-39)	.87	.57	19 (5-40)	25 (14-42)	.09	.13			

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.
^aAdjusted on baseline prognostic variables, namely age, time in hospital prior to ICU admission, time in ICU prior to randomization, Simplified Acute Physiology Score II, SOFA score, lactate level and mechanical ventilation, and a random center effect.
^bComparison of multiple organ failure vs other causes.

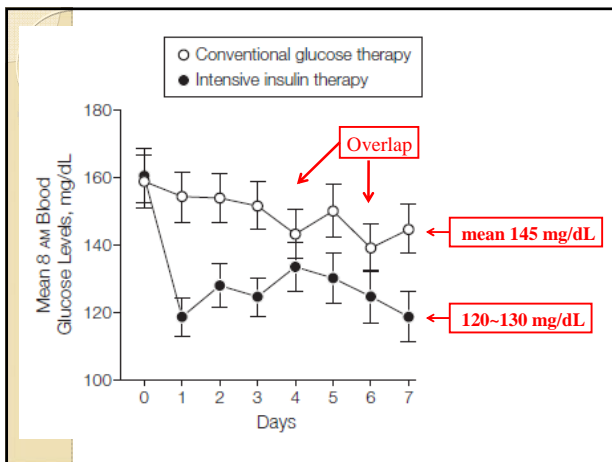
Table 3. Serious Adverse Events

Variables	Intensive Insulin Therapy (n = 255)	Conventional Glucose Control (n = 254)	P Value	Hydrocortisone + Hydrocortisone (n = 248)	Hydrocortisone Alone (n = 254)	P Value
Supernitricion, No. of patients/episodes						
Total	47/106	43/132	.66	52/144	27/94	.02
Lung	36/59	29/94	.49	26/62	29/71	.18
Peritoneal	4/10	1/1	.27	4/10	1/1	.28
Urinary tract	7/8	13/16	.18	15/17	5/7	.02
Central nervous system	0/0	1/1	.80	1/1	0/0	.48
Blood	9/10	4/5	.26	8/9	5/6	.40
Others	14/19	8/15	.28	15/26	7/9	.06
In-hospital death among patients with supernitricion, No./total (%)	26/47 (55.3)	21/43 (48.8)	.87	27/52 (50.9)	20/27 (74.1)	.33
Hypoglycemia, glucose <40 mg/dL						
No. of measures per patient, median (IQR)	77 (43-110)	44 (22-56)	<.001	51 (21-79)	53 (26-81)	.36
No. of patients/episodes	42/72	20/44	.003	32/51	30/53	.59
No. of episodes						
0	211	234		212	223	
1	26	13		19	20	
2	9	3	.002	8	4	.54
3	5	1		3	2	
4	1	2		2	2	
≥4	1	1		1	1	
Episodes, mean (SD)	0.280 (0.50)	0.139 (0.56)	.003	0.236 (0.66)	0.198 (0.68)	.63
In-hospital death among patients with hypoglycemia, No./total (%)	19/42 (45.2)	10/20 (50.0)	.79	14/32 (43.8)	15/30 (50.0)	.80
MORF day 28						
1	3	11		5	9	
2	3	3		4	2	
3	3	1	.06	2	2	.10
4	9	3		1	1	
5	5	3		8	6	

Abbreviations: IQR, interquartile range; MORF, muscular disability rating score.
 † Conversion factor: To convert blood glucose levels from mg/dL to mmol/L, multiply by 0.055.

Conclusion

- **No difference** between Intensive insulin therapy targeting normoglycemia (range of 80 to 110 mg/dL) compared with usual care (<150mg/dL) among patients with hydrocortisone-treated septic shock
- Increased hypoglycemia episodes in the group of intensive insulin therapy
- The addition of fludrocortisone did not improve in-hospital mortality compared with use of hydrocortisone alone



- Normoglycemia (80~110mg/dL) was difficult to achieve in a multicenter setting
- The actual blood glucose levels were not different between two groups (intensive insulin therapy vs SSC guidelines)
- Clinicians caring for patients with septic shock treated with hydrocortisone will still be left with uncertainty as to whether insulin should be given and to what level the blood glucose should be lowered, adding to the uncertainty of whether to treat with hydrocortisone in the first place

- Thank you for your attention

Table 1. Grading system

Grading of recommendations

- Supported by at least two level I investigations
- Supported by one level I investigation
- Supported by level II investigations only
- Supported by at least one level III investigation
- Supported by level IV or V evidence

Grading of evidence

- Large, randomized trials with clear-cut results; low risk of false-positive (alpha) error or false-negative (beta) error
- Small, randomized trials with uncertain results; moderate-to-high risk of false-positive(alpha) and/or false-negative (beta) error
- Nonrandomized, contemporaneous controls
- Nonrandomized, historical controls and expert opinion
- Case series, uncontrolled studies, and expert opinion

SOFA score	0	1	2	3	4
Respiratory PaO ₂ /FIO ₂ (mm Hg) SaO ₂ /FIO ₂	>400	<400 221–301	<300 142–220	<200 67–141	<100 <67
Coagulation Platelets 10 ³ /mm ³	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular hypotension	No hypotension	MAP <70	Dopamine <=5 or dobutamine (any)	Dopamine >5 or norepinephrine <=0.1	Dopamine >15 or norepinephrine >0.1
CNS Glasgow Coma Scale	15	13–14	10–12	6–9	<6
Renal Creatinine (mg/dL) or urine output (mL/d)	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200