HHS Public Access

Author manuscript

Anesthesiology. Author manuscript; available in PMC 2016 June 01.

Published in final edited form as:

Anesthesiology. 2015 June ; 122(6): 1214–1223. doi:10.1097/ALN.0000000000000669.

Intraoperative Tight Glucose Control Using Hyperinsulinemic Normoglycemia Increases Delirium After Cardiac Surgery

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Abstract

Background—Postoperative delirium is common in patients recovering from cardiac surgery. Tight glucose control has been shown to reduce mortality and morbidity. We therefore sought to determine the effect of tight intraoperative glucose control using a hyper-insulinemic normoglycemic clamp approach on postoperative delirium in patients undergoing cardiac surgery.

Methods—We enrolled 198 adult patients having cardiac surgery in this randomized, double-blinded single-center trial. Patients were randomly assigned to either tight intraoperative glucose control with a hyperinsulinemic-normoglycemic clamp (target blood glucose: 80–110 mg/dL) or standard therapy (conventional insulin administration with blood glucose target < 150 mg/dL). Delirium was assessed using a comprehensive delirium battery. We considered patients to have experienced postoperative delirium when Confusion Assessment Method testing was positive at any assessment. A positive Confusion Assessment Method test was defined by the presence of features 1 (acute onset and fluctuating course) and 2 (inattention), and either 3 (disorganized thinking) or 4 (altered consciousness).

Results—Patients randomized to tight glucose control were more likely to be diagnosed as being delirious than those assigned to routine glucose control (26/93 vs. 15/105; Relative Risk (RR), 95% CI: 1.89, 1.06–3.37; P = 0.03), after adjusting for preoperative usage of calcium channel blocker and American Society of Anesthesiologist (ASA) physical status. Delirium severity, among patients with delirium, was comparable with each glucose management strategy.

Conclusions—Intraoperative hyperinsulinemic-normoglycemia augments the risk of delirium after cardiac surgery, but not its severity.

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Disclosure

The authors declare no competing interests.

INTRODUCTION

Postoperative delirium is common in patients recovering from cardiac surgery. It is a disturbing complication that is associated with prolonged duration of hospitalization, increased costs, mortality, and long-term neurocognitive impairment.[1–8] The causes of postoperative delirium remain unclear, but are thought to include pain, sleep deprivation, anesthetic and narcotic effects, concomitant medications, surgical stress, and the inflammatory response to surgery.[2,9–19]

Hyperglycemia is both a consequence and a cause of perioperative inflammation. The surgical stress response and concomitant inflammation augment perioperative blood glucose concentrations.[20] Hyperglycemia is thus particularly common in patients having cardiac surgery. “Stress hyperglycemia” is exacerbated by factors specific to cardiopulmonary bypass including heparin administration, hypothermia, and administration of glucose-containing cardioplegic solutions.[21–23] Other factors that worsen hyperglycemia during cardiac surgery include increased renal absorption of glucose, increased substrate availability in the form of lactate, and decreased exogenous insulin activity.[24] Hyperglycemia itself also induces inflammation and expression of proinflammatory cytokines.[25] Consequently, tight perioperative glucose control with intensive insulin therapy decreases perioperative inflammation.[26,27] Insulin *per se* also decreases concentrations of proinflammatory cytokines, adhesion molecules, chemokines, acute phase proteins, and C-reactive protein.[26]

It thus seems likely that tight glucose control and reduced inflammation will also diminish the risk of postoperative delirium. Consistent with this theory, a retrospective analysis suggests an association between hyperglycemia and delirium in patients having abdominal surgery.[28] To the extent that tight glucose control reduces the risk of delirium, using a hyper-insulinemic normoglycemic clamp may be especially helpful since insulin *per se* is anti-inflammatory. We therefore tested the primary hypothesis that tight glucose control using a hyper-insulinemic normoglycemic clamp approach decreases the incidence of postoperative delirium as assessed by the Confusion Assessment Method (CAM) in patients recovering from cardiac surgery. Secondarily, we tested the hypothesis that normoglycemic clamp reduces the severity of delirium as assessed by the Memorial Delirium Assessment Score (MDAS).

MATERIAL AND METHODS

With Cleveland Clinic Institutional Review Board approval, 203 consenting adults having cardiac surgery with cardio-pulmonary bypass between March 2008 and January 2010 were randomly assigned to tight intraoperative glucose control with a hyper-insulinemic normoglycemic clamp or standard therapy. Randomization was based on a computer-generated sequence in random-sized permuted blocks of 4–16 patients. Assignments were stratified by procedure (coronary artery bypass, valve, or both) and history of diabetes (none vs. any of the following: diet-controlled, type I or type II diabetes)). Allocation was concealed until just before surgery by a web-based system. These patients were part of a large multi-center study evaluating the effect of tight glucose control on postoperative

morbidity and mortality in cardiac surgical patients (ClinicalTrials.gov identifier: NCT00524472).

Patients randomized to tight intraoperative glucose control received a hyperinsulinemic-normoglycemic clamp. A constant infusion of insulin (5 mU/kg/min) was given with a concomitant variable infusion of dextrose 20% titrated to maintain blood glucose concentrations 80–110 mg/dL. The standard therapy group received standard insulin infusion as per the Cleveland Clinic insulin treatment protocol, which targets blood glucose concentrations <150 mg/dL.

We recorded blood glucose concentrations preoperatively, prior to anesthetic induction, beginning of cardiopulmonary bypass, end of cardiopulmonary bypass, after weaning from cardiopulmonary bypass, arrival in the Intensive Care Unit (ICU) and 12, 24, and 48 hours after arrival in ICU. In addition, frequent blood glucose concentrations were evaluated during the intraoperative period (every 5–10 minutes in the treatment group; every 30–60 minutes in the control group) and every 30–60 min during the first two hours of ICU stay.

The designated treatment with either hyperinsulinemic-normoglycemic clamp or standard therapy began after induction of anesthesia and continued until sternal closure. Thereafter, the hyperinsulinemic normoglycemic clamp infusion was reduced to 1 mU/kg/min. Upon arrival in the ICU, both groups received standard glucose control therapy as per our ICU protocol which aimed for blood glucose concentrations between 80 and 150 mg/dL on day of surgery, and between 80 and 120 mg/dL on subsequent postoperative days.

We attempted delirium assessments the evening of surgery and then twice daily (morning and evening) for five postoperative days while patients remained hospitalized (a maximum of 11 assessments per patient). Reasons for non-assessments included patient refusal, and when patients were intubated and sedated or ventilated or having a procedure. Delirium was assessed using a comprehensive delirium battery consisting of Richmond Agitation and Sedation Scale (RASS), the Confusion Assessment Method (CAM), Memorial Delirium Assessment Scale and Digit Span. In previous studies utilizing this delirium battery trained research personnel was nearly as accurate in identifying delirium as psychiatrists using DSM-criteria.[29]

Delirium was assessed by trained investigators to who were blinded to intraoperative glucose management. Each investigator underwent a series of mock assessments and required certification before performing assessments on study patients. Monthly meetings and feedback sessions with case discussions ensured quality and consistency of the assessments. We considered patients to have experienced postoperative delirium when CAM testing was positive at any assessment.[30] CAM evaluates four features: 1) acute onset and fluctuating course, 2) inattention, 3) disorganized thinking, and, 4) altered consciousness. A positive CAM test was defined by the presence of features 1 and 2, and either 3 or 4.

Sedation level was evaluated in every patient at the beginning of an assessment using the Richmond Agitation and Sedation Scale (RASS).[31] Patients with a RASS score of −4 or −5 were excluded from further evaluations. The digit span test evaluates working memory and consists of repeating back a series of numbers in the correct order.[32,33] Patients were further

evaluated with the Memorial Delirium Assessment Scale (MDAS), which measures 10 items related to the severity of delirium. Disturbances in arousal, level of consciousness, memory, attention, orientation and disturbances of thinking are rated on a four point scale (0–3).[34,35]

Statistical Analysis

The two randomized groups were compared for balance on demographics and baseline characteristics using standard summary statistics and the absolute standardized difference (ASD), defined as the absolute difference in means or proportions divided by the pooled standard deviation. Any variable with an ASD greater than 0.2 was considered to be imbalanced.

The hyper-insulinemic normoglycemic clamp group and standard therapy group were compared on postoperative delirium using Chi-square test and generalized regression model with log link with adjustment for any imbalanced covariables. The RR was estimated along with the confidence interval. We also conducted a sensitivity analysis to evaluate the treatment effect on postoperative delirium, where we assumed all missing CAM assessments (due to refusal) were assigned to be positive delirium.

Secondly, we evaluated the difference between the two randomized groups on the average digit span score and average and maximum Memorial Delirium Assessment Scores (a total of 3 analyses), using the independent student t test and the Wilcoxon rank-sum test as appropriate. The significance criterion for the three secondary analyses was $P < 0.017$ (i.e., 0.05/3, Bonferroni).

This is a sub study of a prospective, randomized, double-blinded single-center trial. All the available data were used to examine the focused aims and hypotheses. SAS software version 9.3 (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

RESULTS

Among 203 participating patients, 5 patients did not have any postoperative CAM assessments and were excluded; we thus included a total of 198 patients each with at least one postoperative CAM assessment (Fig. 1). On average, patients in each group had 8 ± 2 CAM assessments of the 11 possible measurements. Overall, 19% of the patients had assessments twice daily for 5 days, 28%, 26%, 14%, and 10% patients had assessments twice daily for 4 to 1 day, respectively. Among patients who were available for assessment (in hospital, awake, and unintubated), 94% of the evaluations were completed.

Demographics and baseline variables were well balanced between the hyperinsulinemic normoglycemic clamp and the standard therapy groups (ASD < 0.2, except for preoperative usage of calcium channel blocker and American Society of Anesthesiologist (ASA) physical status, Table 1). Thus, we adjusted for these two variables when we compared the two randomized groups on the postoperative delirium. Intraoperative transfusions, fluids, opioids, medications (except insulin), total clamp and bypass times, and duration of surgery were also similar in each group (Table 2).

The median intraoperative insulin dose was 126 [interquartile range: 94, 184] units for patients in the hyperinsulinemic normoglycemic clamp group and 18 [11, 27] units for patients in the standard therapy group. There were three patients in the standard therapy group who did not require insulin. Time-weighted average intraoperative glucose was 119 ± 18 mg/dl in the hyperinsulinemic-normoglycemic clamp group and 171 ± 29 mg/dl in the standard therapy group (Fig. 2). No glucose assessments showed hypoglycemia (i.e., < 40 mg/dl).

The average RASS was comparable in the clamp (-0.22 ± 0.4) and routine (-0.22 ± 0.5) glucose management groups (P > 0.99). Twenty-one percent (41 / 198) patients screened positive for delirium on at least one assessment. Patients randomized to tight glucose control thus had a higher probability of being diagnosed as delirious than those assigned to standard glucose control. The incidence of delirium was 28% (26 / 93) in hyperinsulinemic-normoglycemic clamp group and 14% (15 / 105) in the standard therapy group (unadjusted RR was 1.96 (95% CI: 1.11–3.46), P = 0.02). After adjusting for preoperative usage of calcium channel blockers and ASA physical status (ASD > 0.20), the estimated RR was 1.89 (95% CI: 1.06–3.37), P = 0.03. Time-weighted average intraoperative glucose concentrations were 138 ± 31 mg/dl in the delirious patients and 149 ± 37 mg/dl in those without delirium (P = 0.14, Fig. 3). For a 10-mg/dl decrease in minimum of intraoperative glucose, the estimated odds ratio of experiencing delirium was 1.15 (0.99, 1.34) (P = 0.06, post-hoc analysis). For information purpose, baseline characteristics were summarized for delirious patients and those without delirium separately (Appendix 1).

Five percent of planned CAM assessments could not be done in the hyperinsulinemic-normoglycemic clamp patients because they refused evaluation; 3% of the assessments in the standard therapy group could not be completed for the same reason (Table 3). Refusal may have been non-random as delirium *per se* often reduces cooperation. We therefore performed a sensitivity analysis in which all missing (due to refusal) CAM assessments were assigned to be positive. Under this assumption, the incidence of delirium in the hyperinsulinemic-normoglycemic clamp group (49%, 46 / 93) was again higher than in the standard therapy groups (32%, 34 / 105). These results were consistent with our original analysis indicating that the hyperinsulinemic-normoglycemic clamp causes delirium (RR, 95% CI: 1.60, 1.13–2.27; P = 0.01), after adjusting for preoperative usage of calcium channel blockers and ASA status.

Additionally we compared the incidence of delirium in patients who refused one or more delirium assessment (34%, 20 / 59) versus patients who never refused any assessment (including patients missed evaluations due to unavailability) (15%, 21 / 139). Patients refusing a delirium assessment were 2.2 times (95% CI: 1.3, 3.8) more likely to develop delirium at a later point in time (P = 0.003, univariably). We found that the average digit span was lower (worse) in hyperinsulinemic-normoglycemic clamp group (4.2 ± 0.7) than in the standard therapy group (4.5 ± 0.6). The estimated mean difference in the average digit span score was −0.32 (98.3% CI: −0.57, −0.08; P = 0.002), after adjusting for usage of calcium channel blocker.

Among the 41 delirious patients, median MDAS scores did not differ significantly in patients assigned to the hyperinsulinemic-normoglycemic clamp (4.9 [2.7, 8.3]) than for patients assigned to standard glucose control [4.1 (3.3, 6.2), P = 0.43]. The estimated median difference in the average MDAS score was 0.6 (98.3% CI: −1.6, 3.4). Likewise, maximum MDAS score was not different in the hyper-insulinemic normoglycemic group [11 (8, 17)] than in the standard therapy group [9 (7, 13)] with an estimated median difference of 2 (98.3% CI: −2, 7), P = 0.29 (Fig. 4).

DISCUSSION

The pathophysiology of delirium is multifactorial and remains poorly understood. However, delirium appears to result from reversible impairment of cerebral oxidative metabolism and multiple neurotransmitter abnormalities. Surgical stress upregulates sympathetic tone and downregulates parasympathetic tone, impairing cholinergic function and thus contributing to delirium. Another theory is that cytokine activation and alteration of growth factors are causes of postoperative delirium.[36]

Hyperglycemia is both a response to inflammation and is itself inflammatory, whereas insulin is anti-inflammatory.[37,38] We thus expected tight glucose control with a hyper-insulinemic strategy to reduce the risk of postoperative delirium. In distinct contrast to our hypothesis, we found that tight intraoperative glucose control using hyperinsulinemic normoglycemic clamp significantly *increased* the incidence of delirium in patients recovering from cardiac surgery.

While tight intraoperative glucose control using a hyperinsulinemic normoglycemic clamp increased the incidence of delirium, it did not alter its severity. (Digit span was significantly reduced in the clamp patients, the difference was not clinically important.) Maximum MDAS scores were elevated in both glucose management groups, but did not differ significantly between the groups, with the maximum scores in the delirious patients being about 10 points. Typically a score of 13 has been associated with delirium diagnosis. Our maximum MDAS scores are slightly lower, but show a great variability. This variability in combination with low overall average MDAS scores (Fig. 4) could indicate the fluctuating nature of delirium or the effects of medical interventions to improve delirium symptoms.

Observational studies report that hyperglycemia worsens delirium risk.[28,39,40] The difficulty with these analyses is that hyperglycemia is a response to inflammation, as well as potentially causing inflammation. Patients with hyperglycemia are thus likely to have baseline inflammatory conditions and have experienced greater surgical stress — both of which likely provoke delirium independent of glycemic status. It is thus difficult to convincingly attribute delirium to hyperglycemia in observational studies because of potential confounding. Randomization eliminates selection bias and confounding, thus providing more reliable results. Our randomized results show just the opposite effect: tight glucose control worsened delirium risk.

Our results are based on controlling glucose with a hyper-insulinemic strategy which we expected to enhance protection since insulin is anti-inflammatory. While it remains possible

that worsened delirium was specific to our hyper-insulinemic strategy, it seems unlikely that insulin *per se* caused delirium. Consistent with this theory, there was no association between insulin concentration and delirium in patients having hip surgery.[41] However, we did not measure insulin concentrations in our patients and therefore cannot directly address this issue.

A consequence of tight glucose control is the occasional episode of severe hypoglycemia (i.e., ≤40 mg/dl), although none was observed in our patients. There is thus little reason to believe that severe hypoglycemia contributed to postoperative delirium. In contrast, it is worth considering that hyperglycemia is the normal physiological response to stress — and cardiac surgery is an enormous stress. In fact, blood glucose concentrations in the routine management group averaged about 170 mg/dl which is consistent with the Society of Thoracic Surgeons recommendation to keep glucose <180 mg/dl adult cardiac surgery.[42] American Diabetes Association[43] and the American Association of Clinical Endocrinologists[44] recommendations are similar. It may be that various organs benefit from generous glucose availability during periods of stress, and that the brain is among them.

A difficulty with delirium assessments is that they are facilitated by a degree of patient cooperation. (Cooperation is more important for hypoactive delirium than for hyperactive delirium which is usually readily apparent.) A small fraction of the patients refused one or more assessments. The concern is that refusal may be non-random in that patients who suspect a cognitive problem may avoid confirmatory testing. Consistent with this theory, patients who refused a delirium assessment were twice as likely to subsequently have a positive CAM test. However, several sensitivity analyses to evaluate attrition bias did not materially alter the results which is unsurprising since attrition was small and comparable in each group (3% in the routine management patients and 5% in the clamp patients).

Our study was restricted to patients recovering from cardiac surgery, a particularly stressful procedure and one that is frequently accompanied by delirium.[45–50] The extent to which our results generalize to other populations remains to be determined. We included both diabetic and non-diabetic patients, but did not attempt a sub-analysis because only about 30 patients in each group were diabetic. A final and important limitation of our study is that it is relatively small. Thus while the incidence of delirium was significantly reduced in patients assigned to hyperinsulinemic-normoglycemic clamp management, this result is fragile and should be confirmed in a much larger trial.

In summary, our present results suggest that delirium incidence is higher in patients treated with intraoperative insulin therapy administered to achieve tight glucose control. These findings provide basis for re-evaluation of beneficial effects of tight intraoperative control in cardiac surgical patients on outcome with specific aim to assess delirium.

Acknowledgments

Funding: This research was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under award number HL093065 (Andra E. Duncan) and the Department of Outcomes Research, Cleveland Clinic, Cleveland, Ohio, USA. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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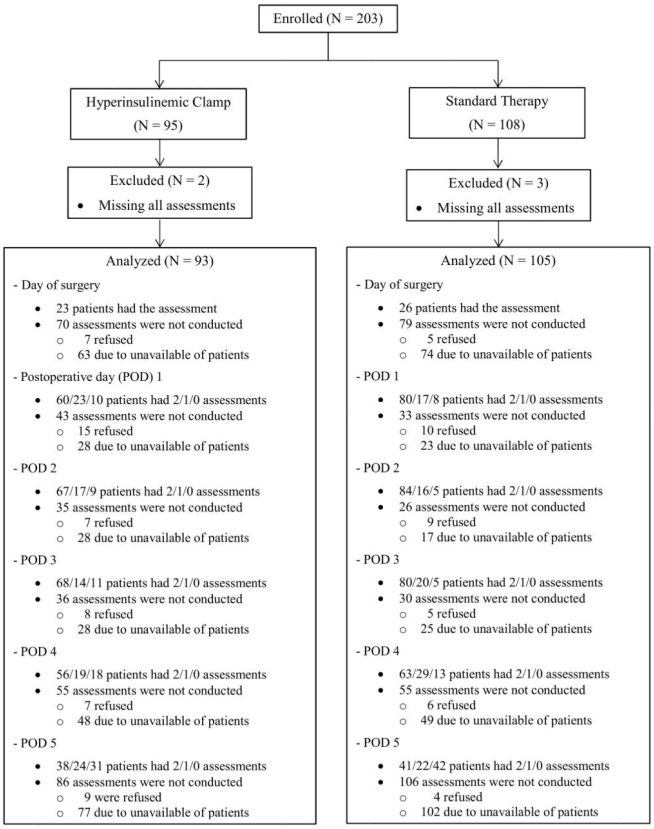

Figure 1.

Trial diagram. Patients missed Confusion Assessment Method (CAM) assessments for the following reasons were considered as missing due to unavailability, including out of the unit, medical reasons (such as, severe pain, shortness of breath, and etc.), asleep, ventilated, intubated, and discharge. POD = postoperative day.

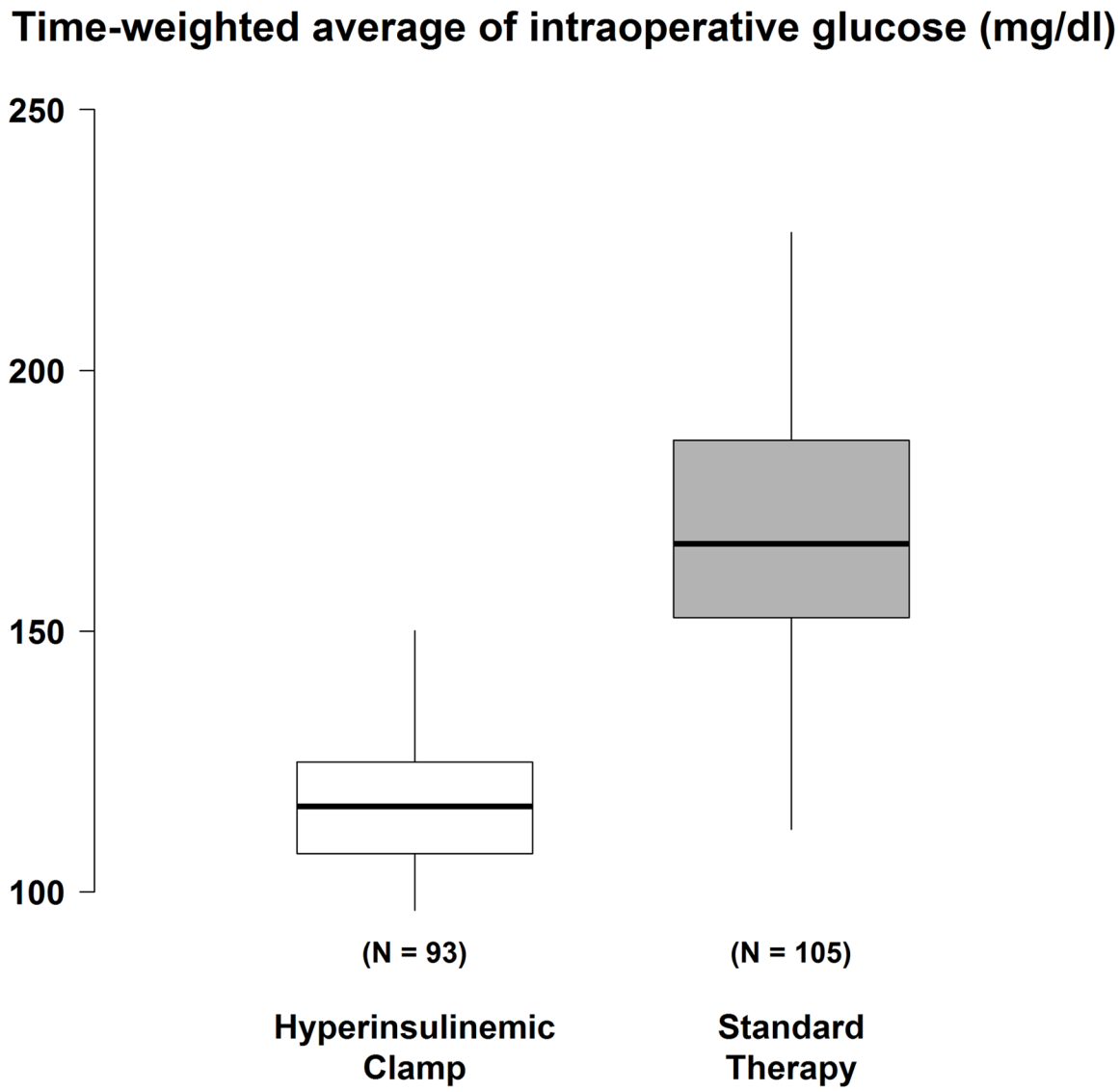

Figure 2.

Time-weighted average (TWA) glucose concentration in patients assigned the hyperinsulinemic-normoglycemic clamp and to routine glucose management. Results presented as boxplots: the first quartile, median, and third quartile comprise the boxes; whiskers extend to the most extreme observations within 1.5 times the interquartile range of the first and third quartiles, respectively.

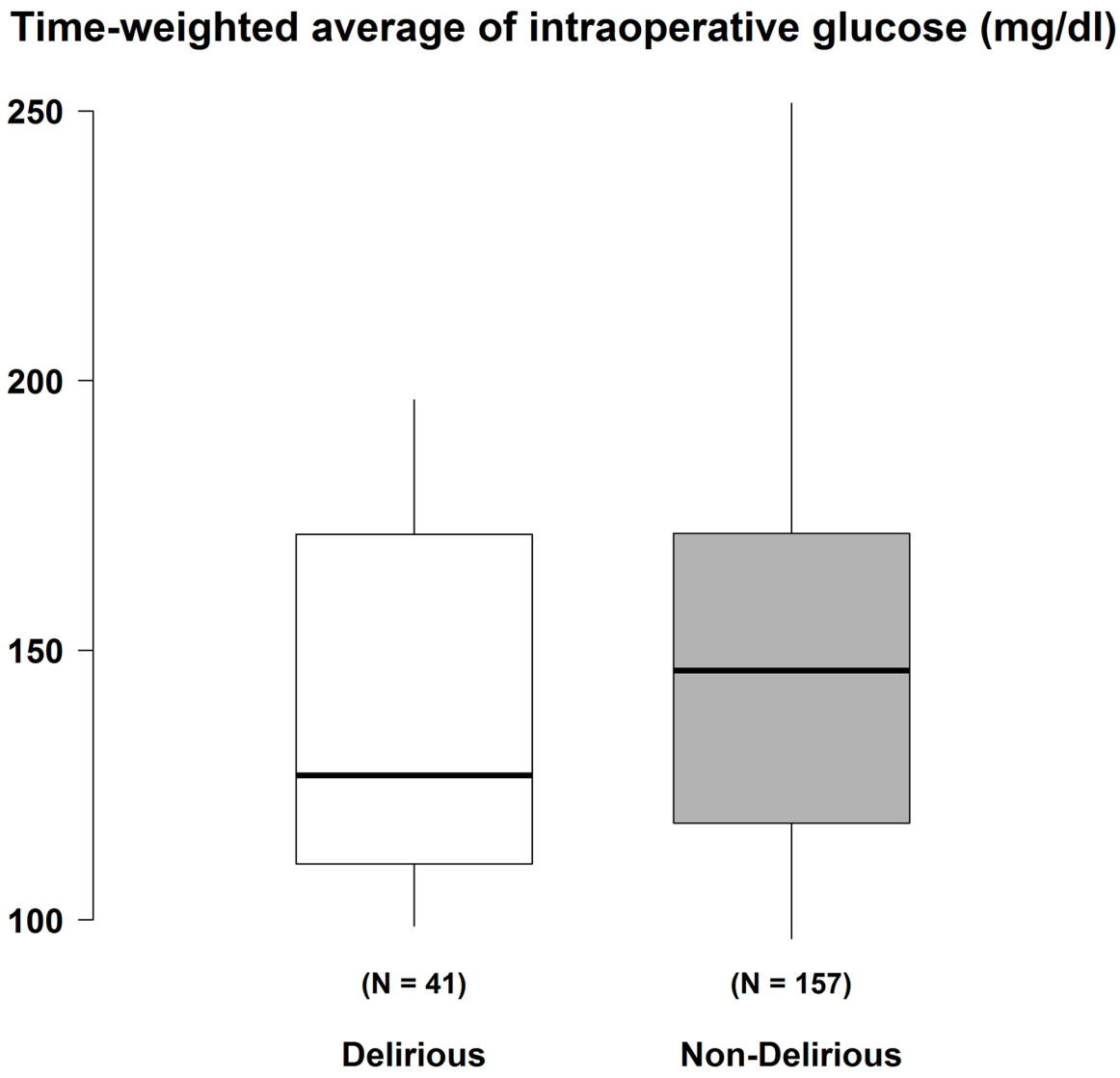

Figure 3.

Time-weighted average (TWA) glucose concentration in delirious (both hyperinsulinemic-normoglycemic clamp and routine glucose management) and non-delirious (both hyperinsulinemic-normoglycemic clamp and routine glucose management) patients. Results presented as boxplots: the first quartile, median, and third quartile comprise the boxes; whiskers extend to the most extreme observations within 1.5 times the interquartile range of the first and third quartiles, respectively.

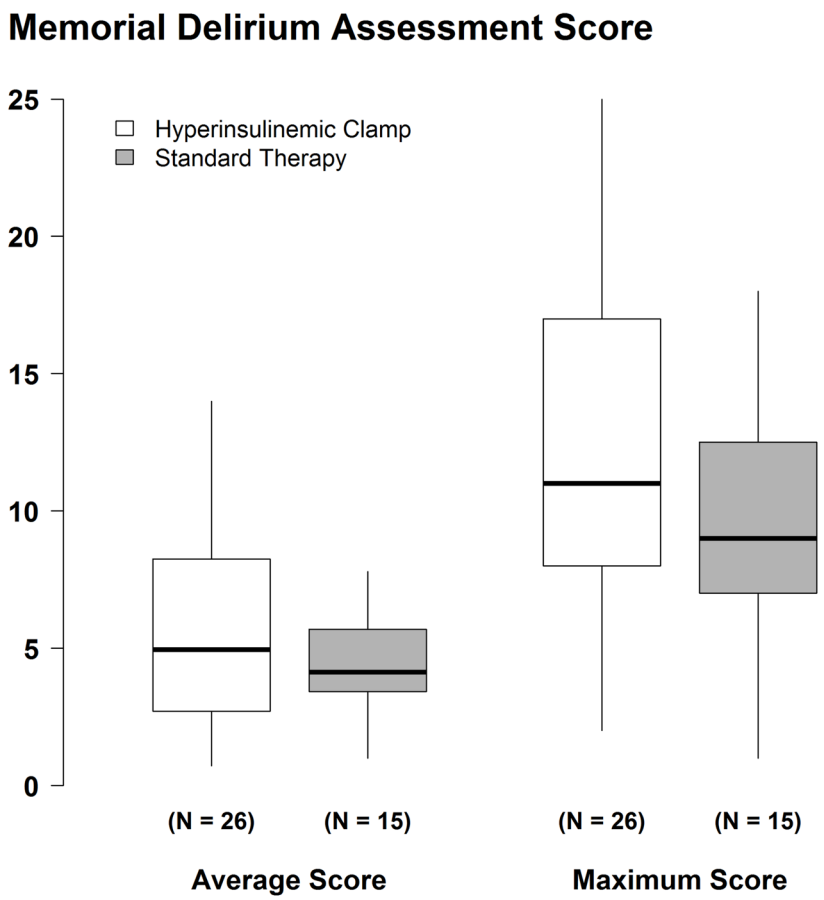

Figure 4.

Average and maximum Memorial Delirium Assessment Score (MDAS) score in all assessments of 26 delirious patients assigned the hyperinsulinemic-normoglucemic clamp and in 15 delirious patients assigned to routine glucose management. Results presented as boxplots: the first quartile, median, and third quartile comprise the boxes; whiskers extend to the most extreme observations within 1.5 times the interquartile range of the first and third quartiles, respectively.

Table 1

Summary of demographics and baselines characteristics (N = 198)

	Hyperinsulinemic Clamp N = 93	Standard Therapy N = 105	ASD *
Variable			
Gender, Male - %	71	73	0.05
Age - yrs	65 ± 15	66 ± 12	0.01
Body mass index - kg/m^2	28 [25, 31]	28 [25, 33]	0.06
Medical History - %			
Chronic obstructive pulmonary disease	19	12	0.19
Pulmonary hypertension	26	33	0.17
Stroke	8	6	0.07
Hypertension	72	71	0.01
Diabetes status			0.10
No diabetes	67	68	
Diet controlled	4	3	
Oral medication controlled	20	19	
Insulin controlled	9	10	
Congestive heart failure	28	30	0.06
Myocardial infraction	22	20	0.04
Dialysis	1	0	0.15
Cardiac surgery	32	26	0.14
Peripheral vascular disease	12	8	0.14
Smoking	56	52	0.07
Atrial fibrillation	25	19	0.14
Ventricular tachycardia	1	1	0.01
Preoperative medication - %			
ACE inhibitor†	30	29	0.03
Antiarrhythmics	10	16	0.19
Beta Blockers	42	46	0.08
Calcium Blockers	12	24	0.32
Cox-2 Inhibitor	3	1	0.16
Statins	47	55	0.16
Steroid	2	6	0.18
Anti-Diabetic Drugs			
Sulfonylureas and Meglitinides	11	9	0.07
Biguanides (metformin)	13	10	0.11
Thiazolidinediones	5	4	0.08
Insulin	13	10	0.11
CCF severity score	5 ± 3	4 ± 3	0.12
ASA physical status - %			0.26
II	1	0	

	Hyperinsulinemic Clamp N = 93	Standard Therapy N = 105	ASD *
III	20	18	
IV	77	82	
V	2	0	
Procedure - %			0.14
CABG (No valve) + other	24	21	
CABG + Valve (and anything else)	28	24	
Valve (No CABG) + other	48	55	

ACE = Angiotensin-converting enzyme; ASA = American Society of Anesthesiologists; ASD = Absolute standardized difference; CABG = Coronary Artery Bypass Graft; CCF = Cleveland Clinic Foundation

Statistics are presented as percentage, mean ± SD or median [inter-quartiles].

*Absolute standardized difference: absolute difference in means or proportions divided by the pooled standard deviation; 0.2, 05, and 0.8 suggest small, medium, and large difference.

†Including angiotensin receptor blockers

Table 2

Summary of intraoperative characteristics (N = 198).

Variable	Hyperinsulinemic Clamp (N = 93)	Standard Therapy (N = 105)	ASD *
Total clamp time, minutes	73 [60, 100]	67 [55, 85]	0.23
Total bypass time, minutes	94 [80, 122]	89 [69, 112]	0.24
Duration of surgery, minutes	376 [319, 449]	342 [303, 412]	0.30
Etomidate, mg	16 [0, 20]	18 [10, 20]	0.29
Fentanyl, mg	1.0 [0.8, 1.0]	1.0 [0.8, 1.0]	0.25
Midazolam, mg	0 [0, 0]	0 [0, 0]	0
Phenylephrine, mg	0.3 [0.1, 0.8]	0.3 [0.1, 0.7]	0.09
Nitroglycerin, mg	1.3 [0.4, 3.8]	2.3 [0.7, 5.9]	0.30
Epinephrine, mg	0 [0, 0.3]	0 [0, 0.1]	0.20
Norepinephrine, mg	0 [0, 0.1]	0 [0, 0]	0.13
Phenylephrine, mg	0.3 [0.1, 0.8]	0.3 [0.1, 0.7]	0.10
Insulin bolus, units	24 [8, 64]	6 [4, 11]	1.04
Insulin infusion, units	94 [68, 116]	11 [7, 17]	3.11
Crystalloid, L	3.0 ± 1.1	3.0 ± 1.0	0.02
Colloid, L	0 [0, 0.5]	0.3 [0, 0.5]	0.09
Red blood cell, units	0 [0, 1]	0 [0, 0]	0.28
Platelets, units	0 [0, 0]	0 [0, 0]	0.17
Fresh frozen plasma, units	0 [0, 0]	0 [0, 0]	0.18

ASD = Absolute standardized difference

*Absolute standardized difference: absolute difference in means or proportions divided by the pooled standard deviation; 0.2, 05, and 0.8 suggest small, medium, and large difference.

Table 3

Summary of CAM assessments (N = 198)

CAM assessment	Hyperinsulinemic Clamp N = 93	Standard Therapy N = 105
Number of planned CAM assessments*	1023	1155
Overall CAM assessment summary – N (%†)		
Evaluated cooperatively	579 (57)	747 (65)
Refused but evaluated	119 (12)	79 (7)
Refused and not evaluated	53 (5)	39 (3)
Not evaluated due to reasons ‡ other than refusing	272 (27)	290 (25)
Within patient CAM assessment summary		
% refused and not evaluated assessments #	7.5 ± 13.4	4.9 ± 10.8
Any refused and not evaluated – N (%)	35 (38)	24 (23)

CAM = Confusion Assessment Method

Statistics are presented as number (percentage) or mean ± SD.

*11 assessments planned per patient

†Out of total number of planned CAM assessments

‡Patients who were non-available for the delirium assessment were due to one of the following reasons: intubation, sleep, ventilation, other procedures, or hospital discharge.

#Within each patient, number of refused and not evaluated assessments out of the total number of assessments in which patient were available to participate.

Appendix 1

Summary of demographics and baselines characteristics by delirium (N = 198)

Variable	Delirium N = 41	No-Delirium N = 157	P-value	ASD *
Age - yrs	73.0 ± 9.5	63.3 ± 13.6	<0.001	0.83
Gender, Male - %	66	74	0.31	0.18
Body mass index - kg/m^2	28.7 [24.7, 31.9]	27.6 [24.8, 31.4]	0.86	0.03
Medical History - %				
Chronic obstructive pulmonary disease	17	15	0.78	0.05
Pulmonary hypertension	39	27	0.15	0.25
Stroke	10	6	0.48	0.15
Hypertension	73	71	0.82	0.04
Diabetes status			0.08	0.49
No diabetes	0	4		
Diet controlled	32	17		
Oral medication controlled	12	9		
Insulin controlled	56	70		
Congestive heart failure	44	25	0.02	0.39
Myocardial infraction	27	19	0.28	0.18
Dialysis	0	1	0.99	-0.11
Cardiac surgery	39	26	0.10	0.28
Peripheral vascular disease	15	8	0.24	0.20
Smoking	56	54	0.77	0.05
Atrial fibrillation	34	18	0.03	0.36
Ventricular tachycardia	0	1	0.99	-0.16
Preoperative medication - %				
ACE inhibitor	34	28	0.44	0.13
Antiarrhythmics	17	12	0.40	0.14
Beta Blockers	44	44	0.99	-0.00
Calcium Blockers	12	20	0.26	-0.21
Cox-2 Inhibitor	5	1	0.19	0.21
Statins	59	50	0.31	0.18
Steroid	10	3	0.06	0.30
Anti-Diabetic Drugs				
Sulfonylureas and Meglitinides	10	10	0.99	0.01
Biguanides (metformin)	12	11	0.78	0.04
Thiazolidinediones	2	5	0.69	-0.14
Insulin	15	10	0.41	0.13
CCF severity score	5.6 ± 3.2	4.3 ± 3.1	0.03	0.40
ASA physical status - %			0.04	0.40
II	0	1		
III	24	17		
IV	71	82		

Variable	Delirium N = 41	No-Delirium N = 157	P-value	ASD *
V	5	0		
Procedure - %			0.13	0.36
CABG (No valve) + other	24	22		
CABG + Valve (and anything else)	39	55		
Valve (No CABG) + other	37	23		

ACE = Angiotensin-converting enzyme; ASA = American Society of Anesthesiologists; ASD = Absolute standardized difference; CABG = Coronary Artery Bypass Graft; CCF = Cleveland Clinic Foundation

Statistics are presented as percentage, mean ± SD or median [inter-quartiles].

P-values were derived from t-test or Wilcoxon rank sum test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. All tests were two-sided.

*Absolute standardized difference: absolute difference in means or proportions divided by the pooled standard deviation; 0.2, 05, and 0.8 suggest small, medium, and large difference.