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The Intraoperative Glycemic Response to Intravenous Insulin during Non-cardiac Surgery: A Sub-analysis of the DeLiT Randomized Trial

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Summary

Patient characteristics may affect patients' response to insulin. We examined the impact of body weight, and presence of diabetes on the response to insulin during non-cardiac surgery. We studied 202 patients who were enrolled in the DeLiT Trial and received intraoperative intravenous insulin. Univariable and multivariable analyses (Bonferroni-corrected) assessed the relationship between patient's response to the initial intraoperative bolus of regular insulin and the factors of interest. Blood glucose concentrations decreased 8.3 ± 10 mg dl-1 (0.46 ± 0.56 mmol litre-1) per unit of insulin in 30 minutes. The response to insulin was similar in patients with or without diabetes [adjusted mean difference (97.5% CI): 0.2 (-3.9, 4.2) mg dl-1, 0.01 (-0.22, 0.24) mmol litre-1, $P = 0.93$]. No relationship was found between insulin response and body weight.

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Our results suggest that adjustment for body weight and the presence of diabetes may not improve intraoperative insulin treatment algorithms.

Keywords

blood-glucose; diabetes; hormones-insulin; surgery

Hyperglycaemia is associated with increased risk for morbidity and mortality following major surgery.[1,2] Thus, there is considerable interest in some degree of perioperative glucose control especially since intraoperative glucose control in noncardiac surgery patients with intravenous insulin infusion techniques may provide beneficial effects on postoperative outcomes.[3] The recommended target for glucose control has experienced significant change over the past few years. However, regardless of the target glucose concentration, insulin infusion algorithms vary widely in terms of time required to achieve target concentration and ability to maintain glucose at target concentration, with many taking surprisingly long to reach stable concentrations.[9-14] Furthermore, all present at least some risk of hypoglycaemia. Some algorithms include patient-related factors such as weight,[8] and diabetic status,[13,15] while others do not.[4-6] There is no consensus about which baseline factors should be included, although insulin sensitivity has been related to various factors in non-operative settings.

Insulin sensitivity can vary according to diabetic status. For example, diabetics, have either absolute insulin deficiency (type I) or relative insulin deficiency with insulin resistance (type II).[16] As might be expected, the presence of diabetes, high baseline blood glucose concentrations, and increased body mass index are all important determinants of daily insulin requirements in critically ill patients.[17] Others have found that obesity,[18] elevated C-reactive Protein (CRP) levels (a sensitive marker of inflammation),[19] and metabolic syndrome[20] also correlate with insulin sensitivity.

The intraoperative period is unique due to the hyperglycemic surgical stress response resulting from the release of stress hormones such as growth hormone, glucagon, catecholamines, and glucocorticoids[21] — all of which contribute to insulin resistance in the liver and in skeletal muscle by modifying signaling properties of insulin receptor substrates.[22] The extent to which patient-related factors determine the response to intraoperative insulin administration during non-cardiac surgery remains unknown. Consequently, it remains unknown whether insulin treatment algorithms might be improved by including individual factors that might influence insulin sensitivity.

Our primary goal was thus to assess the association between the hypoglycemic effect of intraoperative regular insulin and the following two primary factors of interest: presence of diabetes mellitus and body weight. Furthermore, we also conducted a secondary analysis to explore the association between the hypoglycemic effect of intraoperative regular insulin and presence of metabolic syndrome, pre-insulin treatment glucose concentration, and serum concentration of high sensitivity C-reactive protein (hsCRP).

Methods

The study protocol was approved by the Institutional Review Board, and written consent was obtained from every patient. This is a substudy of the **Dexamethasone, Light Anaesthesia and Tight Glucose control Randomized Controlled Trial (DeLiT Trial)** (Clinical trials.gov identifier: NCT00433251), details of which have been reported elsewhere.[23] Briefly, DeLiT was a single center trial which tested the primary hypotheses that major perioperative morbidity is reduced by: 1) low-dose I.V. dexamethasone (8 mg 1-2 hours pre-incision, 4 mg POD 1, and 2 mg POD 2 vs. placebo; 2) intensive intra-operative glucose control [80-110 mg dl⁻¹ (4.4-6.1 mmol litre⁻¹, intensive control) vs. 180-200 mg dl⁻¹ (10-11.1 mmol litre⁻¹, conventional control)]; and, 3) light vs. deep anaesthesia (55 vs 35 of target BIS).

Metabolic syndrome was defined according to the modified criteria based on the International Diabetes Federation 2006, which included body mass index (BMI) greater than 30 kg/m² and two of the following three factors: 1) treatment of hypercholesterolemia or hypertriglyceridemia; 2) history of hypertension or treatment of hypertension; and, 3) raised fasting glucose (≥ 100 mg dl⁻¹, 5.6 mmol litre⁻¹) or previously diagnosed type 2 diabetes.

In most patients, whole arterial blood was used for the blood glucose determination with Accu-Chek Inform system (Roche Diagnostics, Indianapolis, IN) monitors. Whole blood samples had less chance of having an erroneous reading compared to the capillary blood samples (7 versus 15% respectively).[24] Each Accu-Chek was checked in three dimensions [linearity, inter-method (lab vs. meter), and meter-meter] and used only when acceptable results on all three metrics were found. Additionally, calibrations with low and high controls were performed daily to ensure continued high performance.

The DeLiT trial was stopped after the second interim analysis with 381 patients because all three interventions crossed the futility boundary for the primary outcome.

[23] Anesthetic management was standardized, as previously described. [23] Patients were randomly assigned to blood-glucose concentration ranges of either 80-110 mg dl⁻¹ (4.4-6.1 mmol litre⁻¹, intensive control) or 180-200 mg dl⁻¹ (10-11.1 mmol litre⁻¹, conventional control) using pre-determined algorithms (Appendix 1). Among them, 202 (53%) received insulin during the intraoperative period. All patients who received intravenous insulin during surgery, irrespective of randomization, and regardless of the stage of surgery at which this intervention is implemented were included in this analysis. Per protocol, glucose measurements were to be taken approximately 30 minutes after any insulin bolus.

Insulin therapy was started with a single bolus of intravenous regular insulin and a continuous IV insulin infusion. Per protocol, 50 ml of the insulin infusion solution was discarded to saturate the plastic tubing with insulin before the initiation of the insulin treatment, and the infusion tubing was attached to the distal hub of an intravenous line. Details of the intraoperative insulin infusion protocol are described elsewhere. [25] Our primary outcome was a patient's response to insulin ("insulin response"). This was defined as the decrease in blood glucose concentration per unit initial bolus of insulin, using the

single initial intravenous bolus of regular insulin and the corresponding before-after glucose measurements:

$$\text{Insulin response} = \frac{\text{Glucose}_{\text{before initial bolus of insulin}} - \text{Glucose}_{\text{after initial bolus of insulin}}}{\# \text{ of units in the initial bolus of insulin}}$$

We also calculated total units of the insulin infusion received between the initial bolus and next glucose concentration measurement and adjusted for this variable in the multivariable analyses.

Statistical methods

Univariable and multivariable analyses were used to assess the relationship between the primary outcome of insulin response (i.e., decrease in glucose per unit initial bolus of regular insulin) and variables of interest (body weight, pre-treatment glucose concentration, preoperative hsCRP, diabetes diagnosis status, and metabolic syndrome).

The univariable association between insulin response and continuous factors was assessed using Pearson's correlation coefficient analyses, and categorical factors using the *t*-test. In the multivariable analysis we adjusted for the following covariates: gender, age, ASA physical status, surgical type, dexamethasone administration, pre-operative use of statin, the duration between the initial bolus and the following glucose concentration measurement, and the total units of the insulin infusion.

A single multivariable linear regression model was used to simultaneously assess the relationship between insulin response and the above factors of interest. Pre-specified interactions between pre-treatment glucose concentration and the other four factors, and between diabetic status and weight, were tested and considered significant if $P < 0.15$. We also checked for collinearity among the five factors using the variance inflation factor.

We assessed the dose-response relationship between decrease in glucose concentration and the number of units in the initial intraoperative bolus of intravenous regular insulin using scatterplots as well as unadjusted and covariable-adjusted Pearson's correlation coefficients. The latter analysis adjusted for diabetic status, weight, metabolic syndrome, pre-treatment glucose, preoperative hsCRP, gender, age, ASA physical status, surgical type, dexamethasone administration, pre-operative use of statin, the duration between the initial bolus and next glucose concentration measurement, and the total units of the insulin infusion. We also performed sensitivity analyses to assess the association between the insulin response and factors of interest as well as the dose-response relationship using patients who were randomized to the tight glucose control group.

We used a Bonferroni correction to control type I error for testing two primary factors of interest, with P values < 0.025 considered as statistically significant to maintain the overall significant level of 0.05. Similarly, P values less than 0.017 (i.e., $\alpha = 0.05/3$) were considered statistically significant when assessing three secondary factors of interest.

Power Analysis—For the first primary factor of interest, body weight: A small-to-moderate correlation ($r = 0.25$ or more) between insulin response and weight was considered clinically meaningful. With the sample size of $N = 202$ in this study we had 90% power at the 0.025 significance level to detect a Pearson correlation coefficient of 0.25 versus no correlation ($r = 0$).

For the other primary factor of interest, diabetes history status: we considered that history of diabetes would be clinically important if patients without that history were to experience double the glucose lowering effect for a given insulin dose (i.e. ratio of the mean of 2), compared with those diagnosed with diabetes. With 68 patients with and 134 without diabetes we had 90% power at the 0.025 significance level to detect a ratio of means in the insulin response (without vs. with diabetes) as small as 1.6, using the observed coefficient of variation of 1 in the group with diabetes from this study since it was larger than the coefficient of variation in the group without diabetes.

Data are presented as means $\pm$ SDs or medians [interquartile ranges]. SAS 9.3 statistical software, (Cary, NC), was used for all analyses.

Results

Two hundred and two patients who were given insulin during surgery were included (Figure 1). Patient characteristics, co-morbidities, and surgical procedures are shown in Table 1. Among these, 176 (82%) were randomized to tight glucose control. The mean initial bolus of intravenous regular insulin was 2.3 ± 0.8 units (SD), with the mean insulin infusion of 1.5 ± 0.8 units received between the initial bolus and following glucose concentration measurement. The overall decrease in blood glucose concentration per unit initial bolus of insulin for all patients was 8.3 ± 10 mg dl⁻¹ (0.46 ± 0.57 mmol litre⁻¹).

Univariable Association

There was no statistically significant difference in the insulin response between patients with and without diabetes: 10 ± 10 vs. 7 ± 10 mg dl⁻¹, (0.56 ± 0.56 vs. 0.39 ± 0.56 mmol litre⁻¹), $P = 0.038$, which exceeded our significance criteria of 0.025, Table 2 and Figure 2. The insulin response did not correlate with body weight ($r = -0.08$, 97.5%CI = -0.23 to 0.08 , $P = 0.26$), Figure 3.

Among the three secondary factors of interest, the primary outcome of insulin response correlated with logarithm-transformed pre-treatment glucose concentration ($r = 0.30$, 98.3%CI = 0.13 to 0.44 , $P < 0.001$) but not with logarithm-transformed preoperative hsCRP ($r = 0.02$; 98.3%CI = -0.15 to 0.19 ; $P = 0.79$). No difference on the insulin response was found between patients with or without metabolic syndrome: 7 ± 9 vs. 9 ± 10 mg dl⁻¹, (0.39 ± 0.50 vs. 0.5 ± 0.56 mmol litre⁻¹), $P = 0.47$.

Multivariable Association

Our two priori - defined primary factors (diabetes history and body weight) were not significantly associated with the outcome in the multivariable analysis after adjusting for potentially confounding variables (i.e., all $P > 0.025$, Table 3).

The mean difference (97.5% CI) between patients with diabetes receiving insulin and patients without diabetes on the hypoglycemic effect per insulin unit was -0.1 (-6.6 , 6.4) mg dl^{-1} , 0.01 (-0.37 , 0.36) mmol litre^{-1} , $P = 0.97$, $^{-1}$. On the other hand, the difference between patients with diabetes who are not receiving insulin and patients without diabetes was 0.2 (-4.0 , 4.5) mg dl^{-1} , 0.01 (-0.22 , 0.25) mmol litre , $P = 0.90$.

The estimated slope (SE) of body weight was 0.4 (0.5) mg dl^{-1} , 0.02 (0.028) mmol litre^{-1} , meaning that with each 10 kg increase in body weight, the decrease in glucose concentration per unit initial bolus of insulin was 0.4 mg dl^{-1} , 0.02 mmol litre^{-1} less than expected, $P = 0.38$.

None of the *three secondary factors of interest* (metabolic syndrome, pre-treatment glucose concentration, or preoperative hsCRP) were significantly associated with the outcome (i.e., all P values were > 0.017) after Bonferroni correction (Table 2).

None of the pre-specified interactions between pretreatment glucose concentration and weight ($P = 0.48$), preoperative CRP ($P = 0.45$), diabetes ($P = 0.32$) or metabolic syndrome ($P = 0.75$) or between diabetes and weight ($P = 0.12$) was significant. No collinearity was found since all variance inflation factors (VIF) of predictors were less than 2, with a VIF of 5 considered as a collinearity problem.

There was a positive correlation between initial dose of insulin and decrease in blood glucose concentrations; the corresponding unadjusted and covariable-adjusted Pearson's correlations were estimated at 0.51 (95% CI: 0.40 , 0.61), $P < 0.001$ and 0.28 (0.14 , 0.40), $P < 0.001$, respectively, Figure 4.

Results of sensitivity analyses using only patients who were randomized to tight glucose control group ($N = 176$) also gave the same conclusions when we assessed the association between the insulin response and factors of interest as well as the dose-response relationship.

Discussion

The ability to estimate patient's response to insulin would help guide insulin therapy and possibly improve intraoperative glycemic management, decrease glycemic variability, and reduce the risk of hypoglycemia. However, we found that commonly used clinical determinants of insulin dose were poor predictors of the clinical response to insulin intraoperatively in patients undergoing major non-cardiac surgery. The response to insulin, measured by the decrease in blood glucose concentration, was unrelated to pre-treatment glucose concentration or other patient characteristics associated with insulin resistance, including a diagnosis of diabetes mellitus, metabolic syndrome, obesity, or elevated concentrations of hsCRP. In fact, the only significant predictor of an increased response was a higher dose of insulin. Intraoperative dosing regimens are thus unlikely to be improved by adjustment for these baseline factors. Type II diabetes mellitus is characterized by insulin resistance, and therefore patients with this disease would be expected to require more insulin than patients without diabetes. However, our investigation did not find evidence supporting a higher initial insulin dose requirement in patients with diabetes nor there was a higher

hypoglycemic response to insulin in patients without diabetes or with diabetes and no prior insulin therapy. Our results thus do not support the common belief that patients without diabetes and with diabetes who have not previously received insulin are especially sensitive to insulin and thus at special risk of hypoglycemia.[26] Such a common belief may result in reluctance on behalf of the clinicians to treat patients who are not diagnosed with diabetes albeit hyperglycemic intraoperatively using insulin. Nonetheless, this is the population that might benefit the most from such intervention as emerging evidence suggests that benefits from glycemic control strategies can only be illustrated in hyperglycemic patients without diabetes compared to those with diabetes.[27-29] Of note, there were no episodes of severe hypoglycaemia, defined by a plasma glucose concentration of $< 2.2 \text{ mmol litre}^{-1}$ (40 mg dl^{-1}), in our patients. Additional detail on the performance of our insulin infusion algorithm has been previously described. [25]

Obese patients are often insulin resistant,[18] possibly due to chronic inflammation and elevated serum concentrations of tumor necrosis factor- α and interleukin-6.[30,31] Nonetheless, obesity was not associated with insulin resistance in our patients. Thus we did not find any evidence to support dosing insulin intraoperatively based on patient body size as it is the common practice in other settings.[8] In fact, the lack of association between body weight and the hypoglycemic response to insulin suggests that giving more insulin to patients with higher body weight might well provoke undesirable hypoglycemia. We chose to analyze the association between insulin dose and body weight, rather than BMI, since the use of body weight (kg) to adjust drug dosages is more common. Moreover BMI is already included within the metabolic syndrome definition that we have investigated.

We also evaluated the association between the response to insulin and the presence of metabolic syndrome or elevated hsCRP. Insulin resistance is the major underlying pathophysiologic factor of metabolic syndrome which is characterized by metabolic abnormalities including obesity, hypertension, decreased high-density lipoprotein, and elevated serum triglycerides.[20] Elevated CRP concentrations are also a sensitive marker of inflammation with a strong association with insulin resistance.[19] Nonetheless, neither the presence of the metabolic syndrome nor elevated hsCRP concentrations affected the clinical response to a bolus of intravenous insulin intraoperatively. It thus seems unlikely that adjusting for either factor will improve intraoperative insulin delivery algorithms.

Collectively, baseline conditions associated with insulin resistance in other clinical settings did not influence intraoperative insulin requirement. A plausible explanation is that patient response to insulin was masked by the hypermetabolic stress response to surgical tissue injury. Patients undergoing major non-cardiac surgery typically develop a profound perioperative stress response,[32] a reaction that is substantial, but highly variable. This systemic stress response which is associated with an increase in hepatic glucose production and worsened peripheral insulin resistance[33,34] may have exacerbated severe hyperglycemia and insulin unresponsiveness. The impact of this hypermetabolic stress response may have been sufficiently severe to obscure patients' underlying insulin sensitivity (clinically defined as how many mg dl^{-1} (mmol liter^{-1}) of glucose each unit of insulin lowers the patient's blood glucose[35]). In support of this theory is the substantial difference noted between our estimated intraoperative insulin sensitivity (approximately 10

mg dl⁻¹ /unit, 0.56 mmol litre⁻¹ / unit) and that under other circumstances. The estimated insulin sensitivity in hospitalized patients with diabetes is approximately 25 mg dl⁻¹ /unit, 1.4 mmol litre⁻¹ / unit of regular insulin,[35] while this ratio can be as high as 50 or even 60 mg dl⁻¹ /unit, 3.36 mmol litre⁻¹ / unit of insulin in outpatients with diabetes.[36]

Van den Berghe and colleagues reported that body mass index, history of diabetes, and hyperglycemia on presentation were important determinants of insulin dose requirements to maintain normoglycemia in critically ill patients.[17] In contrast, our analysis found no relationship between these factors and the response to insulin. Thus it might be prudent to assume that insulin infusion protocols which proved successful in critically ill patients may not perform as well intraoperatively. Such a differential response to insulin in these two populations could be due to different degrees of physiological stress between the intraoperative period when the surgical insult takes place and the postoperative (early recovery) phase.

Unexpectedly, a few patients had an increase in glucose concentrations following insulin administration. This increase may have been associated with the endocrine and inflammatory response to surgical stimulation. Presumably, the increases in blood glucose concentrations would have been greater had they had not received insulin.

This is a subanalysis of the DeLiT Trial, [23] in which the insulin treatment algorithm did not adjust for the studied factors in this analysis. [25]. However we have designed and utilized a dynamic insulin infusion algorithm that would have accounted for such a variability in response to insulin based on these factors has there been one. [25] Yet we decided to perform this analysis to ascertain whether such association exists between the studied factors, and insulin response to help clinicians with intraoperative insulin dosing decisions should they choose to build or utilize a different algorithm.

This investigation is limited by the fact that in addition to the initial bolus, patients received a low-dose insulin infusion which may have contributed, in part, to the change in blood glucose concentrations. To mitigate this effect, we adjusted for the total insulin dose of administered infusion between the initial bolus and the approximately 30-minute glucose measurement. Moreover, patients were randomized to two different glucose concentration triggers to start the insulin treatment as per the randomization strategy. However, the majority (176/202) were randomized to the tight control strategy and results were similar in this sub-group sensitivity analysis. The hypoglycemic response to insulin bolus was unrelated to pre-treatment glucose concentration. These data suggest that an algorithm based on our results can be used independent of patients' initial glycemic state.[36]

The generalizability of the results of our study may be limited since the majority of our patients were generally at high baseline risk, with American Society of Anesthesiologists physical status scores of 3 and 4. Furthermore, all patients had major surgery that resulted in a sizable stress response, thus these results may not apply to patients undergoing smaller surgical procedures. Since our study is a substudy of the DeLiT trial it carries some of the inherent bias of such study type. That said, the prospective nature of the study has contributed to the accuracy, and completeness of data. Furthermore the availability of

complete set of data, and the use of statistical models adjusting for the study interventions, and any other potential confounders have minimized such bias. In summary, clinical factors such as diabetes mellitus, metabolic syndrome, the degree of baseline hyperglycemia, obesity, and hsCRP concentration were not associated with the responsiveness to insulin during the intraoperative period of major non-cardiac surgery. Only a higher dose of insulin was associated with a greater decrease in blood glucose concentrations. Our results thus suggest that intraoperative insulin treatment algorithms will not be much improved by adjusting for body weight or the presence of diabetes or metabolic syndrome — probably because the stress response to surgery and other factors dominate. The observed intraoperative insulin sensitivity in our study is considerably less than that observed historically in non-surgical inpatient, and outpatient settings so that extrapolation from these two groups to perioperative patients may not be valid. Additional trials are needed to confirm these findings.

Acknowledgments

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Appendix 1: Intensive Glucose Control

Initiation of insulin infusion

Blood Glucose (mg.dL ⁻¹)	Intravenous Bolus	Start Infusion At
110-130	2 units	2 units/hour, recheck in 1/2 hour
131-150	2 units	3 units/hour, recheck in 1/2 hour
151-200	3 units	3 units/hour, recheck in 1/2 hour
201-250	5 units	4 units/hour, recheck in 1/2 hour
251-300	5 units	6 units/hour, recheck in 1/2 hour
>300	7 units	8 units/hour, recheck in 1/2 hour

Infusion adjustment

Blood Glucose (mg/dL)	Decreasing Blood Glucose (↓ by more than 20 mg.dL ⁻¹)	Stable Blood Glucose (No more than 20 mg/dL ↓ or ↑)	Increasing Blood Glucose (↑ by more than 20 mg.dL ⁻¹)	Re-check in
< 60	Hold infusion, give 10-50ml dextrose 50%. Notify staff anesthesiologist	Hold infusion, give 10-50ml dextrose 50%. Notify staff anesthesiologist	Hold infusion, give 10-50ml dextrose 50%. Notify staff anesthesiologist	immediately
61-80	Stop infusion	Stop infusion	Continue same rate	½ hour
81-110	Decrease rate by 50%	Continue same rate	Increase rate by 25%*Max. increase = 10 units/hr	½ hour
111-130	Decrease rate by 25%	Bolus 2 units I.V. and maintain the current rate	Bolus 2 units I.V. and increase rate by 25%*Max. increase = 10 units/hr *	½ hour
131-150	Decrease rate by 25%	Bolus 2 units I.V. and increase rate by	Bolus 2 units I.V. and increase rate by	½ hour

Blood Glucose (mg/dL)	Decreasing Blood Glucose (↓ by more than 20 mg.dL ⁻¹)	Stable Blood Glucose (No more than 20 mg/dL ↓ or ↑)	Increasing Blood Glucose (↑ by more than 20 mg.dL ⁻¹)	Re-check in
		50%*Max. increase = 10 units/hr	50%*Max. increase = 10 units/hr	
151- 200	Continue same rate	Bolus 3 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	Bolus 3 units I.V. and increase rate by 50%*New rate = current rate × 2*Max. increase = 10 units/hr	½ hour
201-250	Bolus 3 units I.V. and continue same rate	Bolus 3 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	Bolus 4 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	½ hour
251-300	Bolus 4 units I.V. and continue same rate	Bolus 4 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	Bolus 5 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	½ hour
301-350	Bolus 5 units I.V. and continue same rate	Bolus 5 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	Bolus 7 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	½ hour
351-400	Bolus 7 units I.V. and continue same rate	Bolus 7units I.V. and increase rate by 50%*Max. increase = 10 units/hr	Bolus 7 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	½ hour
>400	Bolus 8 units I.V. and continue same rate Notify staff anesthesiologist	Bolus 8 units I.V. and increase rate by 50%*Max. increase = 10 units/hr Notify staff anesthesiologist	Bolus 10 units I.V. and increase rate by 50%*Max. increase = 10 units/hr Notify staff anesthesiologist	½ hour

¹ Blood glucose may be checked via ABG or bedside glucose monitor

² The above are guidelines only. Insulin infusions may need modification for certain individuals based on clinical judgement and different clinical situations.

³ Round infusion rates to nearest 0.5 mL/hour

Conventional Glucose Control

Initiation of insulin infusion

Blood Glucose (mg.dL ⁻¹)	Intravenous Bolus	Start Infusion At
215-250	2 units	2 units/hour, recheck in 1/2 hour
251-300	3 units	3 units/hour, recheck in 1/2 hour
301-350	4 units	4 units/hour, recheck in 1/2 hour
351-400	6 units	6 units/hour, recheck in 1/2 hour
>400	7 units	8 units/hour, recheck in 1/2 hour

Infusion adjustment

Blood Glucose (mg.dL ⁻¹)	Decreasing Blood Glucose (↓ by more than 30 mg.dL ⁻¹)	Stable Blood Glucose (No more than 30 mg/dL ↓ or ↑)	Increasing Blood Glucose (↑ by more than 30 mg.dL ⁻¹)	Re-check in
< 60	Hold infusion, give 10-50ml dextrose	Hold infusion, give 10-50ml dextrose 50%.	Hold infusion, give 10-50ml dextrose 50%.	immediately

Blood Glucose (mg.dL ⁻¹)	Decreasing Blood Glucose (↓ by more than 30 mg.dL ⁻¹)	Stable Blood Glucose (No more than 30 mg/dL ↓ or ↑)	Increasing Blood Glucose (↑ by more than 30 mg.dL ⁻¹)	Re-check in
	50%. Notify staff anesthesiologist	Notify staff anesthesiologist	Notify staff anesthesiologist	
61-150	Stop infusion	Stop infusion	Stop infusion	½ hour
151-180	Stop infusion	Decrease infusion by 50%	Continue same rate	½ hour
181-215	Stop infusion	<i>Continue same rate</i>	increase rate by 25%*Max. increase = 10 units/hr	½ hour
216-230	Decrease rate by 25%	Bolus 2 units I.V. and increase rate by 25%*Max. increase = 10 units/hr	Bolus 2 units I.V. and increase rate by 25%*Max. increase = 10 units/hr	½ hour
231- 250	Continue same rate	Bolus 3 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	Bolus 3 units I.V. and increase rate by 50%*New rate = current rate × 2*Max. increase = 10units/hr	½ hour
251-300	Bolus 3 units I.V. and continue same rate	Bolus 3 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	Bolus 4 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	½ hour
301-350	Bolus 4 units I.V. and continue same rate	Bolus 4 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	Bolus 5units I.V. and increase rate by 50%*Max. increase = 10 units/hr	½ hour
351-400	Bolus 5 units I.V. and continue same rate	Bolus 5 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	Bolus 7 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	½ hour
401-450	Bolus 7 units I.V. and continue same rate	Bolus 7units I.V. and increase rate by 50%*Max. increase = 10 units/hr	Bolus 7 units I.V. and increase rate by 50%*Max. increase = 10 units/hr	½ hour
>450	Bolus 8 units I.V. and continue same rate Notify staff anesthesiologist	Bolus 8 units I.V. and increase rate by 50%*Max. increase = 10 units/hr Notify staff anesthesiologist	Bolus 10 units I.V. and increase rate by 50%*Max. increase = 10 units/hr Notify staff anesthesiologist	½ hour

¹ Blood glucose may be checked via ABG or bedside glucose monitor

² The above are guidelines only. Insulin infusions may need modification for certain individuals based on clinical judgement and different clinical situations.

³ Round infusion rates to nearest 0.5 mL/hour

References

1. Furnary AP, Wu YX, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: The Portland diabetic project. *Endocr Pract.* 2004; 10(Suppl 2):21–33. [PubMed: 15251637]
2. Krinsley JS. Glycemic control, diabetic status, and mortality in a heterogeneous population of critically ill patients before and during the era of intensive glycemic management: six and one-half years experience at a university-affiliated community hospital. *Seminars in Thoracic & Cardiovascular Surgery.* 2006; 18:317–25. [PubMed: 17395028]
3. Subramaniam B, Panzica PJ, Novack V, et al. Continuous perioperative insulin infusion decreases major cardiovascular events in patients undergoing vascular surgery: a prospective, randomized trial. *Anesthesiology.* 2009; 110:970–7. [PubMed: 19387173]

4. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *New England Journal of Medicine*. 2008; 358:125–39. [PubMed: 18184958]
5. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *New England Journal of Medicine*. 2009; 360:1283–97. [PubMed: 19318384]
6. Preiser JC, Devos P, Ruiz-Santana S, 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 Medicine*. 2009; 35:1738–48. [PubMed: 19636533]
7. Moghissi ES, Korytkowski MT, DiNardo M, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Endocrine Practice*. 2009; 15:353–69. [PubMed: 19454396]
8. Umpierrez GE, Hellman R, Korytkowski MT, et al. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*. 2012; 97:16–38. [PubMed: 22223765]
9. Saager L, Collins GL, Burnside B, et al. A randomized study in diabetic patients undergoing cardiac surgery comparing computer-guided glucose management with a standard sliding scale protocol. *Journal of Cardiothoracic and Vascular Anesthesia*. 2008; 22:377–82. [PubMed: 18503924]
10. Blaha J, Kopecky P, Matias M, et al. Comparison of three protocols for tight glycemic control in cardiac surgery patients. *Diabetes Care*. 2009; 32:757–61. [PubMed: 19196894]
11. Kremen J, Blaha J, Kopecky P, et al. The treatment of hyperglycaemia in critically ill patients: comparison of standard protocol and computer algorithm. *Vnitřní lékařství*. 2007; 53:1269–73. [PubMed: 18357861]
12. Amrein K, Ellmerer M, Hovorka R, et al. Hospital glucose control: safe and reliable glycemic control using enhanced model predictive control algorithm in medical intensive care unit patients. *Diabetes Technology and Therapeutics*. 2010; 12:405–12. [PubMed: 20388051]
13. Zimmerman CR, Mlynarek ME, Jordan JA, Rajda CA, Horst HM. An insulin infusion protocol in critically ill cardiothoracic surgery patients. *Annals of Pharmacotherapy*. 2004; 38:1123–9. [PubMed: 15150382]
14. Tamaki M, Shimizu T, Kanazawa A, et al. Efficacy and safety of modified Yale insulin infusion protocol in Japanese diabetic patients after open-heart surgery. *Diabetes Research and Clinical Practice*. 2008; 81:296–302. [PubMed: 18556085]
15. Furnary AP, Cheek DB, Holmes SC, Howell WL, Kelly SP. Achieving tight glycemic control in the operating room: lessons learned from 12 years in the trenches of a paradigm shift in anesthetic care. *Seminars in Thoracic and Cardiovascular Surgery*. 2006; 18:339–45. [PubMed: 17395031]
16. Association AD. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 2011; 34:S62–S9. [PubMed: 21193628]
17. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. *Critical Care Medicine*. 2003; 31:359–66. [PubMed: 12576937]
18. Pieracci F, Hydo L, Eachempati S, Pomp A, Shou J, Barie PS. Higher body mass index predicts need for insulin but not hyperglycemia, nosocomial infection, or death in critically ill surgical patients. *Surgical Infections*. 2008; 9:121–30. [PubMed: 18426344]
19. McLaughlin T, Abbasi F, Lamendola C, et al. Differentiation Between Obesity and Insulin Resistance in the Association With C-Reactive Protein. *Circulation*. 2002; 106:2908–12. [PubMed: 12460870]
20. McCullough AJ. Epidemiology of the metabolic syndrome in the USA. *Journal of Digestive Disease*. 2011; 12:333–40.
21. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. *Critical Care Clinics*. 2001; 17:107–24. [PubMed: 11219223]
22. Hotamisligil GS, Spiegelman BM. Tumor necrosis factor alpha: a key component of the obesity-diabetes link. *Diabetes*. 1994; 43:1271–8. [PubMed: 7926300]
23. Abdelmalak B, Maheshwari A, Mascha E, et al. Design and Organization of the Dexamethasone, Light Anesthesia and Tight Glucose Control (DeLiT) Trial: a factorial trial evaluating the effects of corticosteroids, glucose control, and depth-of-anesthesia on perioperative inflammation and

- morbidity from major non-cardiac surgery. *BMC Anesthesiology*. 2010; 10:11. [PubMed: 20591163]
24. Desachy A, Vuagnat AC, Ghazali AD, et al. Accuracy of bedside glucometry in critically ill patients: influence of clinical characteristics and perfusion index. *Mayo Clinic Proceedings*. 2008; 83:400–5. [PubMed: 18380985]
25. Abdelmalak B, Maheshwari A, Kovaci B, et al. Validation of the DeLiT Trial intravenous insulin infusion algorithm for intraoperative glucose control in noncardiac surgery: a randomized controlled trial. *Canadian Journal of Anaesthesia*. 2011; 58:606–16. [PubMed: 21598057]
26. Furnary AP, Cheek DB, Holmes SC, Howel WL, Kelly SP. Achieving tight glycemic control in the operating room: Lessons learned from 12 years in the trenches of a paradigm shift in anesthetic care. *Seminars in Thoracic and Cardiovascular Surgery*. 2006; 18:339–45. [PubMed: 17395031]
27. Van den Berghe G, Wilmer A, Milants I, et al. Intensive insulin therapy in mixed medical/surgical intensive care units: benefit versus harm. *Diabetes*. 2006; 55:3151–9. [PubMed: 17065355]
28. Krinsley JS. Glycemic control, diabetic status, and mortality in a heterogeneous population of critically ill patients before and during the era of intensive glycemic management: six and one-half years experience at a university-affiliated community hospital. *Seminars in Thoracic and Cardiovascular Surgery*. 2006; 18:317–25. [PubMed: 17395028]
29. Abdelmalak B, I M. IM Revisiting Tight Glycemic Control in Perioperative and Critically Ill Patients: When One Size Might Not Fit All. *Journal of Clinical Anesthesia*. 2013 In Press.
30. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *Journal of Clinical Investigation*. 2005; 115:1111–9. [PubMed: 15864338]
31. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends in Immunology*. 2004; 25:4–7. [PubMed: 14698276]
32. Abdelmalak BB, Bonilla AM, Yang D, et al. The hyperglycemic response to major noncardiac surgery and the added effect of steroid administration in patients with and without diabetes. *Anesthesia and Analgesia*. 2013; 116:1116–22. [PubMed: 23558840]
33. Blackburn GL. Metabolic considerations in management of surgical patients. *Surgical Clinics of North America*. 2011; 91:467–80. [PubMed: 21621691]
34. Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. *Current Opinion in Clinical Nutrition and Metabolic Care*. 1999; 2:69–78. [PubMed: 10453333]
35. DT. Diabetic Ketoacidosis. In: Kellerman, Ba, editor. *Conn's Current Therapy 2012*. 1st. Philadelphia, PA: Elsevier; 2012. p. 735-38.
36. Abdelmalak B, Ibrahim M, Yared JP, Modic MB, Nasr C. Perioperative glycemic management in insulin pump patients undergoing noncardiac surgery. *Current Pharmaceutical Design*. 2012; 18:6204–14. [PubMed: 22762462]

Highlights for Review

- Hyperglycemia is associated with increased risk for morbidity and mortality following major surgery
- Current recommendations thus favor more moderate targets in the range of 140-180 mg dl⁻¹
- The intraoperative period is unique due to the hyperglycemic surgical stress response resulting from the release of stress hormones
- Our primary goal was thus to assess the association between the hypoglycemic effect of intraoperative regular insulin and presence of diabetes mellitus and body weight

Figure 1.
Study flow chart

Figure 2.

The decrease in glucose concentration per unit initial bolus of insulin compared between patients without diabetes, patients with diabetes not requiring insulin, and patients with diabetes treated with insulin. Neither non-insulin treated nor insulin-treated patients with diabetes were significantly different from patients without diabetes on the decrease in glucose concentration per unit initial bolus of insulin. The covariate-adjusted mean difference (97.5% CI) in decrease in glucose per unit initial bolus of insulin was -0.1 (-6.6, 6.4) mg dl⁻¹, -0.01 (-0.37, 0.36) mmol litre⁻¹ between insulin-treated patients with diabetes and patients without diabetes ($P = 0.97$), and 0.2 (-4.0, 4.5) mg dl⁻¹, 0.01 (-0.22, 0.25) mmol litre⁻¹ between non-insulin treated patients with diabetes and patients without diabetes ($P = 0.90$).

Figure 3.

The relationship between decrease in glucose concentration per unit initial bolus of insulin and weight, preoperative CRP concentration, pre-treatment glucose concentration, and presence of metabolic syndrome. None of those factors was significantly associated with the decrease in glucose concentration per unit initial bolus of insulin in the multivariable regression model using Bonferroni correction. CRP = c-reactive protein.

Figure 4.

The relationship between insulin dose and decrease in blood glucose concentration; values of the initial bolus units of insulin were jittered within ± 0.5 to display overlapped points. There was a weak positive correlation between initial dose of insulin and decrease in blood glucose concentrations; the corresponding unadjusted and covariable-adjusted Pearson correlation coefficients were estimated at 0.51 [95% CI: 0.40, 0.61] ($P < 0.001$) and 0.28 [95% CI: 0.14, 0.40] ($P < 0.001$), respectively.

Table 1
Demographics, clinical characteristics and outcomes of 202 patients

Factor	Statistics
Age (yr)	64 ± 11
Weight (kg)	85 ± 20
Female gender	69 (34 %)
Surgical Type	
Abdominal aortic aneurysm repair	37 (18 %)
Colorectal procedures	47 (23 %)
Cystectomy	35 (17 %)
Peripheral Revascularization	37 (18 %)
Whipple / Pancreatic resection	42 (21 %)
Other	4 (2 %)
ASA physical status - %	
II	43 (21 %)
III	130 (64 %)
IV	29 (14 %)
Randomized to Dexamethasone administration	111 (55 %)
Preoperative use of statin	81 (40%)
Diabetes mellitus	68 (34 %)
Insulin-treated diabetes mellitus	16 (8 %)
Non-Insulin treated diabetes mellitus	52 (26 %)
Metabolic syndrome	39 (19 %)
Preoperative C-reactive protein	3.8 [1.8, 8.6] mg litre ⁻¹ (32 [15, 73] mmol litre ⁻¹)
Preoperative glucose concentration	105 [88, 131] mg dL ⁻¹ (5.8 [4.9, 7.3] mmol litre ⁻¹)
Pre-insulin treatment glucose concentration	136 [120, 159] mg dL ⁻¹ (7.6 [6.7, 8.8] mmol litre ⁻¹)
Initial bolus of insulin (units)	2.3 ± 0.8
Total units of the insulin infusion received between the initial bolus and next glucose concentration measurement	1.5 ± 0.8
Time between initial bolus and next glucose measurement (minutes)	36 ± 14
Outcome	
Decrease in glucose concentration per unit initial bolus of insulin	8.3 ± 10 mg dL ⁻¹ (0.46 ± 0.57 mmol litre ⁻¹)
Decrease in glucose concentration at a given initial bolus of regular insulin	21 ± 28 mg dL ⁻¹ (1.2 ± 1.6 mmol litre ⁻¹)

Data are presented as mean ± SD, median [inter-quartiles], or N (%); N = 1 missing for preoperative C-reactive protein; ASA = American Society of Anesthesiologists

Table 2
Univariable and multivariable associations between predictors and decrease in glucose concentration per unit initial bolus of insulin

Outcome: decrease in glucose concentration per unit initial bolus of insulin (mg dl ⁻¹ , mmol litre ⁻¹)			
Primary Factors	Mean ± SD or Pearson's Correlation (97.5% CI)	Adjusted Mean Difference (97.5% CI) or Slope (SE) *	Univariable / Multivariable P value **
Weight (unit – 10kg)	-0.08 (-0.23, 0.08)	0.4 (0.5) / 0.02 (0.028)	0.26 / 0.39
Diabetes mellitus			
No Diabetes	7 ± 10 (0.39 ± 0.56)	reference	
All patients with diabetes	10 ± 10 (0.56 ± 0.56)	0.2 (-3.9, 4.2) / 0.01 (-0.22, 0.24)	0.038 / 0.93
Insulin treated	10 ± 13 (0.56 ± 0.72)	-0.1 (-6.6, 6.4) / -0.01 (-0.37, 0.36)	0.39 / 0.97
Non-Insulin treated	11 ± 8 (0.61 ± 0.44)	0.2 (-4.0, 4.5) / 0.01 (-0.22, 0.25)	0.042 / 0.90
Secondary Factors			
Metabolic syndrome			
No	9 ± 10 (0.50 ± 0.56)	reference	
Yes	7 ± 9 (0.39 ± 0.50)	-4.4 (-9.8, 1.1) / -0.24 (-0.55, 0.06) ^a	0.47 / 0.06
Pre-treatment glucose (unit = 10 mg dl ⁻¹ , 0.56 mmol litre ⁻¹)	0.3 (0.13, 0.44) ^{† a}	0.4 (0.2) / 0.02 (0.01)	<0.001 / 0.028
Preoperative CRP (unit = 1 mg litre ⁻¹ , 8.45 mmol litre ⁻¹)	0.02 (-0.15, 0.19) ^{† a}	0.07 (0.06) / 0.59 (0.51)	0.79 / 0.23

N = 1 missing for Preoperative C-reactive protein; CRP = C-reactive protein; SE = estimated standard error.

* Adjusted mean difference (97.5% CI), slope (SE) from the multivariable model adjusted for gender, age, ASA, surgical procedure, dexamethasone administration, preoperative use of statin, infusion of insulin, and time between bolus and recorded decrease in glucose; the slope describes the mean decrease in glucose concentration for each additional unit of a continuous predictor.

** Bonferroni correction to control type I error for testing 2 primary factors at 0.05 (P values < 0.025 considered as significant), as well as 3 secondary factors (alpha = 0.05/3, P values < 0.017 considered as significant);

^a 98.3% confident interval.

[†] log-transformed pre-treatment glucose and preoperative CRP, respectively

Table 3
Multivariable associations between predictors and decrease in glucose concentration per unit initial bolus of insulin

Outcome: decrease in glucose concentration per unit initial bolus of insulin (mg dl ⁻¹ , mmol litre ⁻¹)			
Primary Factors	Unit	Adjusted Mean Difference (97.5% CI) or Slope (SE) *	P value **
Weight	10kg	0.4 (0.5), 0.02 (0.028)	0.39
Diabetes mellitus	Yes vs. No	0.2 (-3.9, 4.2), 0.01 (-0.22, 0.24)	0.93
	Insulin treated vs. No	-0.1 (-6.6, 6.4), -0.01 (-0.37, 0.36)	0.97
	Non-Insulin treated vs. No	0.2 (-4.0, 4.5), 0.01 (-0.22, 0.25)	0.90
Secondary Factors			
Metabolic syndrome	Yes vs. no	-4.4 (-9.8, 1.1), -0.24 (-0.55, 0.06) ^a	0.06
Pre-treatment glucose	10 mg dl ⁻¹ , 0.56 mmol	0.4 (0.2), 0.02 (0.01)	0.028
Preoperative CRP	1 mg litre ⁻¹ , 8.45 mmol litre ⁻¹	0.07 (0.06), 0.59 (0.51)	0.23

N = 1 missing for Preoperative C-reactive protein; CRP = C-reactive protein; SE = estimated standard error.

* Adjusted mean difference (97.5% CI), slope (SE) from the multivariable model adjusted for gender, age, ASA, surgical procedure, dexamethasone administration, preoperative use of statin, infusion of insulin, and time between bolus and recorded decrease in glucose; the slope describes the mean decrease in glucose concentration for each additional unit of a continuous predictor.

** Bonferroni correction to control type I error for testing 2 primary factors at 0.05 (P values < 0.025 considered as significant), as well as 3 secondary factors (alpha =0.05/3, P values < 0.017 considered as significant);

^a 98.3% confident interval.