

Absence of an association between glucose levels and surgical site infections in patients undergoing craniotomies for brain tumors

Clinical article

SARA J. HARDY, B.A.,¹ AMY S. NOWACKI, PH.D.,² MARY BERTIN, R.N., B.S.N.,³
AND ROBERT J. WEIL, M.D.¹

¹The Brain Tumor & Neuro-Oncology Center, Department of Neurosurgery, the Neurological Institute;
and Departments of ²Quantitative Health Sciences and ³Quality/Infection Control, Cleveland Clinic,
Cleveland, Ohio

Object. In select patient populations, hyperglycemia has been shown to increase the risk of surgical site infection (SSI), whereas stringent glucose control has improved outcomes. To date, no study has focused on whether SSIs in patients with brain tumors undergoing resection are associated with hyperglycemia.

Methods. The authors performed a retrospective chart review of patients who underwent a craniotomy after receiving a diagnosis of brain tumor. From 2001 to 2008, 2485 patients underwent a craniotomy for tumor resection at the Brain Tumor & Neuro-Oncology Center at the Cleveland Clinic. Fifty-seven of these patients (2.3%) developed SSIs postoperatively. A matched case-control study design was used, with 57 patients who developed SSIs after craniotomy (cases) matched with 57 patients who did not develop SSIs (controls). The results were analyzed using both univariate and multivariate conditional logistic regression.

Results. Glucose level was not a significant factor in postoperative SSI ($p = 0.83$) after adjusting for duration of surgery and adherence to antibiotic prophylaxis. However, duration of surgery was significantly associated with postoperative SSI ($p = 0.047$).

Conclusions. For patients who undergo craniotomy for definitive resection of a brain tumor, duration of surgery described more variation in the model to predict SSI than blood glucose levels. (DOI: 10.3171/2010.2.JNS09950)

KEY WORDS • hyperglycemia • postoperative complication •
surgical site infection • glucose • craniotomy

IN critically ill patients, release of glucagon, epinephrine, cortisol, and catecholamines often leads to hyperglycemia.¹⁶ Critically ill patients who have undergone neurosurgery are particularly prone to hyperglycemia, because many receive supraphysiological doses of corticosteroids perioperatively.¹⁴ This inclination is significant because postoperative hyperglycemia may have consequences for infection rates and mortality risk postoperatively. In 2001, van den Berghe et al.¹⁹ performed a single-center randomized controlled trial that compared IIT to conventional insulin therapy; for both treatments, insulin was given via an infusion pump. In the IIT group, glucose was maintained between 80 and 110 mg/dl, while in the conventional group, glucose was maintained between 180 and 200 mg/dl. This study showed that IIT reduced mortality risk in the ICU from

8.0 to 4.6% ($p < 0.04$), decreased overall hospital deaths by 34% ($p = 0.01$), and lowered the rate of bloodstream infections by 46% ($p = 0.03$). Other studies have also shown benefit from using IIT. In a 2003 prospective observational study, Finney et al.⁶ demonstrated a decreased mortality risk when blood glucose was maintained between 145 and 200 mg/dl. Additionally, a prospective randomized trial by Lazar et al.¹¹ in 2004 found that patients who received IIT (blood glucose maintained between 125 and 250 mg/dl) versus standard insulin control therapy (maintaining serum glucose < 250 mg/dl) experienced a shorter postoperative hospital stay (6.5 vs 9.2 days, respectively; $p = 0.003$) and fewer recurrent wound infections (1 vs 10%, respectively; $p = 0.03$). The randomized controlled trials provided strong evidence in favor of a benefit with using IIT. Although the observational studies and other studies with less rigorous designs carried less impact than the randomized controlled trials, they did corroborate the benefits of using IIT.

Despite this evidence, postoperative control of hyperglycemia remains controversial. In 2008, Brunkhorst et al.² published a randomized controlled trial of IIT for patients with severe sepsis. In this study, the IIT group,

Abbreviations used in this paper: ASA = American Society of Anesthesiologists; BMI = body mass index; CAD = coronary artery disease; DM = diabetes mellitus; ICU = intensive care unit; IIT = intensive insulin therapy; NICE-SUGAR = Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation; SSI = surgical site infection.

which had an average glucose level of 112 mg/dl, was compared with a conventional therapy group, with an average glucose level of 151 mg/dl. The conventional therapy group received a continuous insulin infusion when blood glucose was > 200 mg/dl. The study was discontinued early for safety reasons, because the IIT group had an increased rate of serious adverse events (10.9 vs 5.2%, respectively; $p = 0.01$) and severe hypoglycemia (17.0 vs 4.1%, respectively; $p < 0.001$). Furthermore, in 2009, the multinational randomized controlled trial NICE-SUGAR compared IIT (maintaining blood glucose between 81 and 108 mg/dl) and conventional insulin therapy (maintaining blood glucose below 180 mg/dl). This study found significantly increased mortality risk in the IIT group (27.5 vs 24.9%; $p = 0.02$), as well as no difference in the number of patients with blood cultures positive for pathogenic organisms (12.8 vs 12.4%; $p = 0.57$). Moreover, patients in the IIT group had a higher rate of severe hypoglycemia (6.8 vs 0.5%; $p = 0.02$), defined as blood glucose < 40 mg/dl.⁵ The results of the NICE-SUGAR study had a considerable impact and led to some significant questions regarding the role of IIT in perioperative care.

The NICE-SUGAR study raised 2 major issues. First, even though the NICE-SUGAR study found no advantage to IIT, it is possible that other patient populations may still benefit. Second, insulin therapy may be beneficial when it is used to maintain blood glucose at different values.¹² Several previous studies have established benefit when implementing less stringent cutoff levels. Krinsley¹⁰ showed a mortality risk benefit with blood glucose < 140 mg/dl in a before/after study of an intensive glucose management protocol. Furnary et al.⁸ demonstrated a decreased incidence of infection with a blood glucose goal of < 200 mg/dl with a similar before/after study design.

The conflicting outcomes of various studies have diminished the generalizability of these results. Few studies have investigated the benefits of IIT in the postoperative period after neurosurgical procedures. In 2009, Bilotta et al.¹ reported on a randomized trial of 483 patients, in which there was an increased incidence of hypoglycemic events in those receiving IIT; notably, IIT decreased infection rates as well as length of stay in the ICU. However, this study included a heterogeneous mix of patients admitted to the postoperative ICU who were undergoing neurosurgery for tumors, neurovascular disease, severe head trauma, or intraparenchymal hemorrhage.¹ In a retrospective study, Thiele et al.¹⁸ concluded that strict glucose control had no effect on mortality risk after aneurysmal subarachnoid hemorrhage ($p = 0.132$) but did increase the risk of hypoglycemia ($p = 0.001$).

To date, no study has focused on postcraniotomy SSIs and the potential role of hyperglycemia. In addition, it remains unclear whether information from large ICU studies can be generalized to specialized subpopulations. Thus, we performed a retrospective review of patients with brain tumors who underwent craniotomies and definitive resection to discern whether postoperative glucose levels are associated with SSI. This study also investigated 2 glucose cutoff points (130 mg/dl and 150 mg/dl) that both define moderate glucose control levels. Cutoff point selection was based on ideal blood glucose

ranges for patients at risk for ischemic brain injury identified by Wass and Lanier²⁰ in their 1996 review, as well as an attempt to maintain comparability with the 140 mg/dl cutoff point shown to be beneficial by Krinsley.¹⁰

Methods

Patient Population and Matching

This study was approved by the Cleveland Clinic institutional review board. From 2001 to 2008, 2485 patients underwent a craniotomy for definitive resection of a brain tumor at the Brain Tumor and Neuro-Oncology Center at the Cleveland Clinic. Fifty-seven of these patients (2.3%) developed SSIs postoperatively. The infections were identified by standard criteria from the Centers for Disease Control and Prevention and recorded independently by an experienced member of the Department of Quality/Infection Control at the Cleveland Clinic (M.B.). We completed a retrospective chart review matched case-control study, using the 57 patients who developed SSIs after craniotomy and 57 matched surgical controls who did not develop SSIs. In all 114 patients, the intention of surgery was complete or near-total (definitive) tumor resection. Patients who underwent subtotal resection and biopsy procedures (whether open or stereotactic) were excluded. Cases and controls were matched on 5 criteria: primary versus reoperation,⁴ sex,³ diagnosis, International Classification of Diseases-9 code (intended to approximate supratentorial vs infratentorial procedures), and age ± 6 years.¹⁷ When a perfect match for diagnosis was unavailable, a patient with a diagnosis within 1 WHO grade was used. For example, a patient with a Grade III astrocytoma could be matched with a patient with a Grade IV astrocytoma.

Data Collection

Data were collected using the patient's electronic chart and paper chart, as well as information obtained from the prospective clinical database of the Brain Tumor and Neuro-Oncology Center. This database, and the authors' use of the data, was approved by the institutional review board. In addition to the matching factors, the following parameters were collected: previous diagnosis of hypertension, CAD, DM, tobacco use (ever), ASA classification, duration of surgery (defined as the time [hours] from incision until the end of anesthesia), BMI, postoperative venous blood glucose measurements, and adherence to perioperative antibiotic prophylaxis. Adherence to antibiotic prophylaxis perioperatively was defined as antibiotics provided within 60 minutes prior to the incision, with the exception of vancomycin, which must be given within 2 hours before the incision.^{13,15} For blood glucose measurements, only venous blood glucose measurements from the postoperative period until the end of postoperative Day 2 were used. The beginning of the postoperative period was defined as the end of anesthesia. However, if the end of anesthesia data were unavailable or uncertain, the beginning of the operative period was defined as the time of the first arterial blood gas reading from the intraarterial catheter and the end was defined by the final arterial blood gas reading. The availability of the end of

Hyperglycemia and wound infections after craniotomy

anesthesia data was not significantly different between controls and cases ($p = 0.79$). Management of perioperative glucose levels was left to the discretion of the surgeon and was not controlled. Corticosteroids were used in all patients, but the cumulative daily dose and administration route was not standardized. No trend in corticosteroid administration was discerned between the groups.

Statistical Analysis

The primary study variable of interest was blood glucose level. Time-adjusted glucose was calculated by appropriately weighting the average of all measurements by the length of time a patient was in a particular glucose measurement. Time-weighting is an approach commonly implemented in studies involving glucose measurements.⁶ The time-weighted average is intended to use all available information and adjust for the varying number of glucose measurements per patient. However, for this data set, the majority of patients had only 1 measurement recorded per day. To eliminate potential measurement bias, the variable glucose was additionally defined and calculated as the average of the first measurements taken each day (Day 0, Day 1, and Day 2). Analyses were performed using both definitions of the blood glucose level variable; results were similar, thus only multivariate models utilizing nontime-adjusted glucose are reported.

Bivariate associations between categorical study factors and the development of SSI were assessed using the Fisher exact test. Bivariate associations between continuous study factors and the development of SSI were assessed using the Wilcoxon rank-sum test. The probability of postoperative SSI was modeled as a function of study factors using conditional logistic regression. Univariate conditional logistic regression was performed to identify factors associated with development of SSI. All study factors were entered into a conditional multivariate logistic regression and backwards eliminated according to both statistical and clinical judgment. Models were assessed for collinearity. Clinical interest exists in dichotomizing glucose levels at meaningful cutoff points to classify hyperglycemic levels. Conditional logistic models were used to investigate whether an association exists between hyperglycemic levels (defined by various cutoff points) and development of SSIs. For all conditional logistic models, OR estimates were obtained with corresponding 95% CIs, summarizing the crude and adjusted association of SSI with each of the proposed risk factors. Statistical tests used for computing probability values and significance levels are indicated in the text. All statistical analyses were performed using SAS statistical software version 9.1 (SAS Institute, Inc.). A probability value < 0.05 was considered statistically significant.

Results

A total of 57 patients who developed SSIs after craniotomy (cases) and 57 matched controls were studied. Patient characteristics are summarized in Table 1. Cases and matched controls were not significantly different in terms of the obtained study factors. Demonstrating the

strength of our age-matched design, there was no significant difference between rates of diseases for which the risk is known to increase with age, such as hypertension, diabetes, obesity (BMI), and CAD. No difference in the availability of end of anesthesia data supports our previously defined beginning of the postoperative period. The median time-adjusted glucose level for patients with SSI was 141.6 mg/dl compared with 133.0 mg/dl for matched controls. The median glucose level for the 2-day postoperative period was 143.5 mg/dl for patients who acquired SSIs compared with 138.8 mg/dl for matched controls. Figure 1 further illustrates the relationship between median glucose level and postoperative duration. Whereas the patients who developed SSIs consistently had higher glucose levels, there was not a large difference (in magnitude) in blood glucose levels between the 2 groups.

Table 2 illustrates that no factors in the univariate conditional logistic regression analyses were associated with a higher risk of SSI. The smallest probability values were found for time-adjusted glucose level, venous glucose measurement (Day 0 and Day 1), duration of surgery, and presence of CAD. Reassuringly, the point estimate for each risk factor was directionally aligned with biological plausibility; for example, greater duration of surgery increased risk of SSI, which is plausible because the wound is open and vulnerable to pathogens for a longer time period. Previous diagnosis of hypertension, diabetes, CAD, longer duration of surgery, antibiotic prophylaxis adherence, higher ASA classification, and higher glucose levels all showed ORs suggesting an increased risk of SSI. However, such an interpretation is suspect, because each CI includes the value of 1, thus the absence of an effect of these variables on SSI risk cannot be ruled out.

The multivariate conditional logistic regression analysis (Table 3) showed that duration of surgery ($p = 0.047$) was associated with postoperative SSI. Longer surgical time was directly associated with risk of infection (Fig. 2). Glucose level was not significant ($p = 0.83$) after adjusting for duration of surgery and adherence to antibiotic prophylaxis (Table 3). The information necessary to determine adherence versus nonadherence was missing in 19.3% of controls and in 14.0% of cases. In controls for whom the information was available, 73.9% received antibiotics in accordance with the Centers for Disease Control and Prevention guidelines.^{13,15} In cases for whom the information was available, 81.6% received appropriate antibiotics. The rates of adherence to antibiotic prophylaxis were not different between groups (Table 1; $p = 0.46$). Results were similar when time-adjusted glucose level was used as the blood glucose level measurement (data not shown).

To investigate the effect of blood glucose level cutoffs as insulin therapy targets, we modeled the probability of postoperative SSI as a function of insulin therapy target achievement using conditional logistic regression. Table 4 illustrates that blood glucose levels ≥ 130 mg/dl or ≥ 150 mg/dl were not associated with an increased risk of SSI. Although probability values were nonsignificant, the ORs indicated that glucose levels ≥ 130 or 150 mg/dl increased the odds of having SSI. The association of hyperglycemic levels with the 2 cutoff points and SSI risk remained non-

TABLE 1: Baseline characteristics of study patients*

Variables	SSI Group*	No SSI Group*	p Value†
no. of patients	57	57	
previous diagnosis			
hypertension	18 (31.6)	15 (26.3)	0.68
DM	7 (12.3)	5 (8.8)	0.76
CAD	10 (17.9)	5 (8.8)	0.18
tobacco use ever	31 (57.4)	32 (58.2)	0.99
end of anesthesia data available	48 (84.3)	50 (87.7)	0.79
duration of surgery in hrs	4.3 (3.3–5.2)	4.1 (2.7–5.2)	0.16
adherence to antibiotic prophylaxis	40 (81.6)	34 (73.9)	0.46
ASA classification			0.80
2	12 (24.0)	15 (29.4)	
3	34 (68.0)	33 (64.7)	
4	4 (8.0)	3 (5.9)	
median BMI (IQR)	27 (24.2–31.0)	28.1 (24.4–31.8)	0.88
median time-adjusted glucose level in mg/dl (IQR)	141.6 (129.1–161.6)	133.0 (120.8–153.1)	0.07
median glucose level in mg/dl (IQR)			0.09
Day 0	155.5 (137.5–183.0)	153.0 (125.5–166.5)	0.13
Day 1	139 (124.8–165.5)	134 (114–154.0)	0.16
Day 2	121.0 (109.0–145.0)	117.0 (103.8–141.3)	0.42

* All values given as number of patients (%) unless otherwise indicated. Abbreviation: IQR = interquartile range.

† Probability values for categorical variables (number of patients and percentage) calculated using the Fisher exact test; all others used the Wilcoxon rank-sum test.

significant when entered into multivariate analyses controlling for other risk factors (data not shown).

Discussion

In this study, we sought to discern whether postop-

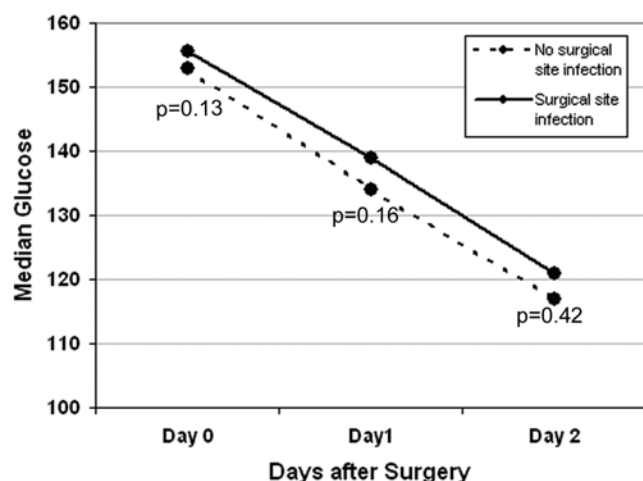


Fig. 1. Graph of glucose levels over time according to infection group for patients undergoing craniotomy. Median glucose levels are shown for each postoperative day. Day 0 is the day of surgery, Day 1 represents the first day after surgery, and Day 2 represents the second day after surgery. There were no significant differences between groups at any time point.

erative glycemic levels are associated with risk of SSI. The goal was not to generalize our study results to other patient populations, but rather to obtain specific information on patients who undergo craniotomy for definitive resection of a brain tumor.

Blood glucose levels were higher for those patients who developed SSI when compared with those who did not, but these differences were not statistically significant. Further classification of hyperglycemic levels resulted in similar conclusions. It is possible that both groups had blood glucose levels below the cutoff point at which treating hyperglycemia is beneficial. In comparison, Furnary et al.,⁸ in a before/after study of subcutaneous insulin versus continuous insulin infusion, compared blood glucose levels 2 days postoperatively for patients who developed deep sternal wound infection with patients who did not. On the first postoperative day, infected patients showed a mean blood glucose level of 209 mg/dl, and noninfected patients had a mean blood glucose level of 190 mg/dl. On the second postoperative day, infected patients had a mean blood glucose level of 206 mg/dl, whereas the mean level in noninfected patients was 188 mg/dl. All of the values in the study of Furnary et al. are higher than the means found for either of the craniotomy patient groups in our study. Patients with intermediate glucose levels were used in a retrospective study by Krinsley¹⁰ in 2004. Krinsley found that with a mean blood glucose level of 152.3 mg/dl for the patients using conventional insulin therapy, and with a mean blood glucose level of 130.7 mg/dl for the patients who received IIT, there were fewer infections in

TABLE 2: Summary of univariate conditional logistic regression analysis of potential risk factors associated with postoperative SSI

Variables	OR (95% CI)	p Value
previous diagnosis		
hypertension	1.33 (0.56–3.16)	0.51
DM	1.40 (0.44–4.41)	0.57
CAD	2.00 (0.68–5.85)	0.32
tobacco use ever	0.86 (0.40–1.85)	0.70
duration of surgery*	1.23 (0.97–1.57)	0.09
adherence to antibiotic prophylaxis	1.22 (0.51–2.95)	0.66
ASA classification		0.79
2	referent	
3	1.36 (0.43–4.33)	
4	1.92 (0.25–14.55)	
BMI	0.98 (0.91–1.05)	0.55
time-adjusted glucose level†	1.32 (0.98–1.81)	0.07
glucose level†	1.29 (0.94–1.81)	0.10
Day 0	1.17 (0.92–1.49)	0.20
Day 1	1.22 (0.98–1.49)	0.07
Day 2	1.08 (0.80–1.49)	0.59

* ORs for duration of surgery are per 1 hour change.

† ORs for glucose are per 20-unit change.

the IIT group (3.4 vs 2.6%, respectively). These glucose levels are similar to those found in patients in our study. Thus, for patients undergoing craniotomy for brain tumor, blood glucose levels may simply be a factor of less importance in the development of SSIs.

For patients with a diagnosis of brain tumor, the variable “duration of surgery” described far more variation in the model to predict SSI than did blood glucose levels. Each additional hour of time in surgery resulted in a 43% increase in the odds of developing an SSI ($p = 0.047$). This finding is consistent with those in previous studies of craniotomy, which found that increased duration of surgery significantly increased risk of SSI after craniotomy.⁹ Adherence to antibiotic prophylaxis was associated with an 80% increase in risk of SSI, but this increase was not statistically significant ($p = 0.30$). Perhaps there was insufficient power to investigate this study factor, or physicians are more careful with antibiotic prophylaxis when patients are perceived as higher risk.

We recognize several potential limitations to the study. This study is retrospective and the number of glucose measurements obtained for each patient varied. Furthermore, although corticosteroids were used in all patients, the dose was not standardized. It is possible that comorbidities other than hypertension, DM, obesity, and CAD are important, although studies of hyperglycemia and infection from cardiac surgery suggest they are by far the most common risk factors associated with major infection.⁷

Sample size per group was determined by the number of cases of postoperative SSIs at the Brain Tumor & Neuro-Oncology Center at the Cleveland Clinic from

TABLE 3: Summary of multivariate conditional logistic regression analysis of potential risk factors associated with postoperative SSI

Variables	OR (95% CI)	p Value
glucose level*	0.94 (0.54–1.49)	0.83
duration of surgery†	1.43 (1.005–2.05)	0.047
adherence to antibiotic prophylaxis	1.80 (0.59–5.46)	0.30

* ORs for glucose are per 20-unit change.

† ORs for duration of surgery are per 1 hour change.

2001 to 2008 (57 per group). Although it appears that patients with an infection tend to have higher glucose levels (Fig. 1), the observed differences failed to achieve statistical significance (Table 1). If the sample size could be increased, it is possible we could have achieved statistical significance for this variable. However, given the small differences observed between controls and cases, the findings would still be unlikely to be clinically significant. This study also includes several advantages. This work is significant because no study of this nature has been reported on this group of patients. The power of the study was increased by the matched case-control design. As recent studies have shown, because control or prevention of hyperglycemia is beneficial in some populations but not in others,¹² it is important to study each patient population of interest.

Conclusions

In patients with a diagnosis of brain tumor, who underwent a craniotomy and definitive resection, we did not find that hyperglycemia was associated with SSI. It is possible that more stringent control of blood glucose levels—with attendant risks of symptomatic hypoglycemia—will demonstrate that levels < 130 mg/dl (the lower limit examined here) may prove beneficial. However, this would require a large, multicenter, prospective trial. A future study that further matches cases and controls to duration of surgery may reveal whether hyperglycemia is

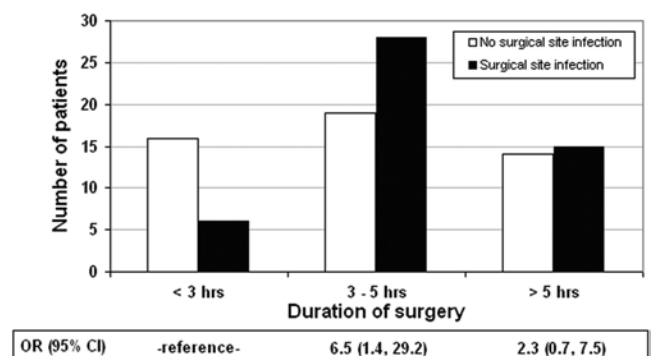


Fig. 2. Bar graph comparing the risk of SSI with duration of surgery, according to infection group, for patients undergoing craniotomy. The duration of surgery was divided into < 3 hours, 3–5 hours, and > 5 hours. An increased risk of SSI was found in the longer surgery duration groups (3–5 hours and > 5 hours).

TABLE 4: Summary of univariate conditional logistic regression analysis of different hyperglycemic levels associated with postoperative SSI

Glucose Level	OR (95% CI)	p Value
≥130 mg/dl	1.25 (0.59–2.67)	0.56
≥150 mg/dl	1.63 (0.67–3.92)	0.28

associated with SSI for patients who undergo craniotomy for definitive resection of a brain tumor.

Disclosure

This study was supported, in part, by the Melvin Burkhardt chair in neurosurgical oncology (R.J.W.) and by research and administrative support from the Karen Colina Wilson research endowment fund within the Brain Tumor and Neuro-Oncology Center at the Cleveland Clinic (R.J.W.).

Author contributions to the study and manuscript preparation include the following. Conception and design: SJ Hardy, RJ Weil. Acquisition of data: SJ Hardy, M Bertin. Analysis and interpretation of data: SJ Hardy, AS Nowacki, RJ Weil. Drafting the article: SJ Hardy. Critically revising the article: SJ Hardy, AS Nowacki, RJ Weil. Reviewed final version of the manuscript and approved it for submission: SJ Hardy, AS Nowacki, M Bertin, RJ Weil. Statistical analysis: AS Nowacki. Study supervision: RJ Weil.

References

1. Bilotta F, Caramia R, Paoloni FP, Delfini R, Rosa G: Safety and efficacy of intensive insulin therapy in critical neurosurgical patients. **Anesthesiology** **110**:611–619, 2009
2. Brunkhorst FM, Engel C, Bloos F, Meier-Hellmann A, Ragaller M, Weiler N, et al: Intensive insulin therapy and pentastarch resuscitation in severe sepsis. **N Engl J Med** **358**:125–139, 2008
3. Bundy JK, Gonzalez VR, Barnard BM, Hardy RJ, DuPont HL: Gender risk differences for surgical site infections among a primary coronary artery bypass graft surgery cohort: 1995–1998. **Am J Infect Control** **34**:114–121, 2006
4. Chang SM, Parney IF, McDermott M, Barker FG II, Schmidt MH, Huang W, et al: Perioperative complications and neurological outcomes of first and second craniotomies among patients enrolled in the Glioma Outcome Project. **J Neurosurg** **98**:1175–1181, 2003
5. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al: Intensive versus conventional glucose control in critically ill patients. **N Engl J Med** **360**:1283–1297, 2009
6. Finney SJ, Zekveld C, Elia A, Evans TW: Glucose control and mortality in critically ill patients. **JAMA** **290**:2041–2047, 2003
7. Fowler VG Jr, O'Brien SM, Muhlbaier LH, Corey GR, Ferguson TB, Peterson ED: Clinical predictors of major infections after cardiac surgery. **Circulation** **112** (9 Suppl):I358–I365, 2005
8. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A: Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. **Ann Thorac Surg** **67**:352–362, 1999
9. Korinek AM, Baugnon T, Golmard JL, van Effenterre R, Coriat P, Puybasset L: Risk factors for adult nosocomial meningitis after craniotomy: role of antibiotic prophylaxis. **Neurosurgery** **59**:126–133, 2006
10. Krinsley JS: Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. **Mayo Clin Proc** **79**:992–1000, 2004
11. Lazar HL, Chipkin SR, Fitzgerald CA, Bao Y, Cabral H, Apstein CS: Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. **Circulation** **109**:1497–1502, 2004
12. Lipshutz AK, Gropper MA: Perioperative glycemic control: an evidence-based review. **Anesthesiology** **110**:408–421, 2009
13. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR: Guideline for prevention of surgical site infection, 1999. Hospital Infection Advisory Committee. **Infect Control Hosp Epidemiol** **20**:250–278, 1999
14. McClelland S III, Long DM: Genesis of the use of corticosteroids in the treatment and prevention of brain edema. **Neurosurgery** **62**:965–968, 2008
15. Odom-Forren J: Preventing surgical site infections. **Nursing** **36**:58–63, 2006
16. Robinson LE, van Soeren MH: Insulin resistance and hyperglycemia in critical illness: role of insulin in glycemic control. **AACN Clin Issues** **15**:45–62, 2004
17. Shinoura N, Yamada R, Okamoto K, Nakamura O: Early prediction of infection after craniotomy for brain tumours. **Br J Neurosurg** **18**:598–603, 2004
18. Thiele RH, Pouratian N, Zuo Z, Scalzo DC, Dobbs HA, Dumont AS, et al: Strict glucose control does not affect mortality after aneurysmal subarachnoid hemorrhage. **Anesthesiology** **110**:603–610, 2009
19. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al: Intensive insulin therapy in the critically ill patients. **N Engl J Med** **345**:1359–1367, 2001
20. Wass CT, Lanier WL: Glucose modulation of ischemic brain injury: review and clinical recommendations. **Mayo Clin Proc** **71**:801–812, 1996

Manuscript submitted July 1, 2009.

Accepted February 25, 2010.

Please include this information when citing this paper: published online April 2, 2010; DOI: 10.3171/2010.2.JNS09950.

Address correspondence to: Sara J. Hardy, Cleveland Clinic Lerner College of Medicine, Cleveland Clinic/NA24, 9500 Euclid Avenue, Cleveland, Ohio 44195. email: hardys2@ccf.org.