

## Insulin for Perioperative Glucose Control: Settled Science?

To the Editor:

We read with interest the recent Clinical Concepts and Commentary article on perioperative glucose control.<sup>1</sup> However, we worry that it overstates available evidence with respect to the benefit/risk ratio of using insulin to target specific intraoperative glucose levels in patients undergoing surgery.

The authors rightly note that most studies find a strong correlation between hyperglycemia and poor perioperative outcomes in cardiac and noncardiac surgery.<sup>2</sup> However, they do not mention that this correlation may not be as tight in diabetic patients<sup>3</sup> who are most likely to experience perioperative hyperglycemia. Although the mechanism for this variability is incompletely understood, one possibility is that poorly controlled diabetics “reset” their hypoglycemic response to a higher glucose threshold.<sup>4</sup> A uniform target for glucose management thus ignores that, for some patient groups, aggressively targeting a single value may cause harm both chronically<sup>5</sup> and in the perioperative period.<sup>6</sup> Existing intensive care unit studies clearly demonstrate that overly tight glucose control can increase mortality so the risk/benefit of any specific glucose target should be empirically tested to permit the clinician to deliver optimal care. Studies of the 200 mg/dl threshold used in the Surgical Care Improvement Project Infection-4 metric find no benefit to Infection-4 compliance,<sup>7</sup> indicating that 200 may not be the right number. More recent data further complicate benefit/risk balance, observing that although mixed perioperative hyperglycemia and hypoglycemia worsened mortality after cardiac surgery, hyperglycemia alone (more than 180 mg/dl) had no effect.<sup>6</sup>

Duggan *et al.* may also understate the risks of aggressive insulin therapy. The Medmarx adverse drug event database identifies insulin and heparin as the two drugs most associated with adverse events resulting from administration error.<sup>8</sup> In cardiac surgery patients, aggressive insulin treatment does not improve cardiac function,<sup>9</sup> may worsen delirium,<sup>10</sup> and increases the risk of hypoglycemia.<sup>11</sup> For ambulatory surgery patients, the risk calculus is even more complex. Duggan *et al.* reference current Society for Ambulatory Anesthesia guidelines, which by definition are for patients going home after surgery.<sup>12</sup> Should such patients really receive an intraoperative insulin infusion targeting a specific glucose level, only to go home afterward where control is likely to be less tight? And is the benefit from controlling glucose only in the operating room worth the risk? Society for Ambulatory Anesthesia guidelines suggest with a 2A level of evidence that “in patients with poorly controlled diabetes, if the decision to proceed with the surgery is made, the blood glucose levels should be maintained around their preoperative baseline values rather than temporarily (*i.e.*, perioperatively) normalizing them.”<sup>12</sup> Approximately 98,000 insulin dosing errors occur every year,<sup>13</sup> and a dosing error causing a patient to not emerge from anesthesia due to severe intraoperative hypoglycemia is eerily plausible.

Although the authors argue that insulin “has been shown” to improve outcomes when administered perioperatively, few prospective, randomized trials exist, some trials do not control for diabetic status, and other nonrandomized trials find no effect of insulin use.<sup>14</sup> In light of the potentially disastrous consequences of perioperative hypoglycemia and logistical issues, including postoperative step-down beds for aggressive hyperglycemia treatment, widespread implementation of intravenous insulin infusions targeting a specific glucose level may be concerning. We do not believe that any single threshold represents settled science, and we worry that risk/benefit ratios remain too imprecise to justify widespread adoption of single-target protocols.

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### Competing Interests

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#### *In Reply:*

We would like to thank Drs. Gerlach and Tung for their thoughtful commentary regarding our article on perioperative glucose control.<sup>1</sup> A large body of evidence has clearly established the association between hyperglycemia and increased risk of perioperative morbidity and mortality in patients with and without diabetes.<sup>2,3</sup> The risk of complications in surgical patients experiencing stress hyperglycemia appears to be higher in nondiabetic patients than in diabetic patients.<sup>4,5</sup> Randomized controlled trials examining cardiac surgery patients demonstrate better outcomes in nondiabetic patients when their blood glucose target is achieved *versus* diabetic patients controlled to the same glycemic range.<sup>6,7</sup> However, patients labeled as “nondiabetic” often are undiagnosed diabetics or prediabetics,<sup>8</sup> and those without a formal diagnosis of diabetes are much less likely to be treated with insulin when hyperglycemic *versus* their diabetic counterparts.<sup>9</sup> This may confound our understanding of current data comparing diabetics to nondiabetics. We do not yet have conclusive evidence to determine best hyperglycemia treatment or prevention strategies during the perioperative period in general surgery patients; continued work is needed in both diabetic and nondiabetic cohorts. Stratification is expected to be complex and treatment targets are likely to be based not only on diabetic, prediabetic, and nondiabetic status, but also on type of surgery, acuity of illness, degree of hyperglycemia, and sensitivity to insulin.

Drs. Gerlach and Tung are certainly correct in identifying the increased risk of hypoglycemia, as well as potential source

of medication error, with insulin administration in the hospital setting. There is no argument that aggressive insulin therapy has the potential to cause harm. Current guidelines for the management of inpatient hyperglycemia advocate for a blood glucose target less than 180 mg/dl. At this target, randomized controlled clinical trials demonstrate that the risk of hypoglycemia is significantly reduced.<sup>10</sup> We advocate against tight blood glucose control and do not recommend perioperative use of insulin until blood glucose is greater than 140 to 180 mg/dl. We do advocate with the Society for Ambulatory Anesthesia (SAMBA) recommendations that subcutaneous insulin therapy can aid in blood glucose control without the need to start a continuous insulin infusion.<sup>11</sup> Likewise, coincident with the SAMBA statement, we do not suggest that “normalization” of blood glucose should be achieved on the day of surgery. Additionally, although insulin-dosing errors are undoubtedly associated with significant morbidity, avoiding insulin entirely due to fear of a medication error is a suboptimal solution for a considerable problem.

Recognizing the risks of hypoglycemia, insulin therapy alternatives (*i.e.*, oral antidiabetic agents) are actively under investigation in hospitalized medical and surgical patients. Our group recently reported that in medical and general surgery patients the use of dipeptidyl peptidase 4 (DPP4) inhibitors, alone or in combination with basal insulin, is equally safe and effective when compared to multidose insulin (basal bolus) regimens.<sup>12,13</sup> In addition, the Linagliptin Surgery trial (NCT02004366) recently presented at the American Diabetes Association meeting in June 2017, compared the use of DPP4 inhibitors to insulin therapy in 280 general surgery patients with type 2 diabetes. Compared to insulin therapy, DPP4 inhibitors show equal efficacy in treatment of mild-to-moderate hyperglycemia, but result in significantly less hypoglycemia (12% *vs.* 2%).<sup>14</sup> We agree with Drs. Gerlach and Tung that forthcoming studies need to continue to explore and identify safe treatment options and protocols.

Management of perioperative hyperglycemia is neither straightforward nor simple. There is not a single approach to all surgical patients due to the wide complexity of the issues that impact glycemic management. Our article attempts to provide anesthesiologists with a variety of patient, surgical, and treatment considerations based on current available evidence. These include diagnosis of diabetes and recommendations for hemoglobin A1C testing, insulin and oral agents for glycemic control, assessment of baseline insulin sensitivity, and anticipated operating room variables (hemodynamic changes, use of pressors, and temperature shifts). We appreciate Drs. Gerlach and Tung’s careful review of our article and agree with them that a single protocol would be “imprecise.”

#### Competing Interests

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