Kidney Injury, Insulin Therapy, and Hypoglycemia

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Abstract: The intent of this review is to evaluate the literature with respect to increased risk for hypoglycemia for critically ill patients with acute kidney injury or chronic kidney disease who are given insulin therapy. The unique pathophysiology of insulin and glucose metabolism during renal failure that predisposes patients for hypoglycemia is reviewed. Studies that contribute to the understanding and clinical relevance of renal dysfunction upon glycemic control during intensive insulin and continuous nutrition therapy are evaluated. Some practical suggestions for management of hyperglycemia with insulin therapy for critically ill patients with renal failure are given.

Keywords: Renal failure, parenteral nutrition, enteral nutrition, trauma, critical illness, hemodialysis, hyperglycemia.

INTRODUCTION

Over the past decade, a substantial number of studies have examined the impact of glycemic control upon clinical outcome for critically ill patients. Despite the plethora of clinical studies, the “best” target blood glucose concentration (BG) range to achieve an improvement in clinical outcome remains an enigma. The “best” target BG range depends on the patient population (e.g., surgical/injured patients versus medical patients) as well as the institution’s ability to effectively achieve that target BG range in an effort to improve clinical outcomes without causing adverse effects such as hypoglycemia. Pursuit of achievement of “tight” BG control (e.g., 80 to 110 mg/dL or 4.4 to 6.1 mmol/L) is often complicated by a significant portion of critically ill patients developing severe hypoglycemia (BG < 40 mg/dL or 2.2 mmol/L). Since “tight” BG control has been associated with poorer clinical outcomes in one large randomized, controlled trial [1], a more modest target BG range (140 mg to 180 mg/dL or 7.8 to 10 mmol/L) has been advocated by the American Diabetes Association consensus panel [2]. However, the consensus group acknowledged that more stringent goals, such as a target BG range of 100 to 140 mg/dL (5.6 to 7.8 mmol/L), may be appropriate for selected patients as long as this can be achieved without significant hypoglycemia [2].

The latter scenario best describes optimal glycemic management for critically ill patients with traumatic injury whereby improved outcomes have been demonstrated when BG concentrations are kept less than 140 mg/dL (7.8 mmol/L) [3] or 150 mg/dL (8.3 mmol/L) [4, 5]. Since the majority of our population is critically ill patients with trauma (i.e., patients admitted to the intensive care unit of the Presley Trauma Center at the Regional Medical Center at Memphis), we developed a graduated continuous intravenous regular human insulin (RHI) infusion algorithm for patients receiving enteral or parenteral nutrition therapy with the intent of keeping BG within 70 to 150 mg/dl (3.9 to 8.3 mmol/L) [6]. Our data indicated that the target BG was achieved within 5 ± 3 hours of starting the RHI infusion and we were able to maintain BG within the target range for an average of 20 ± 5 hours daily [6]. Thirty five percent out of 40 patients given the RHI infusion had at least one episode of mild to moderate hypoglycemia (BG 40 to 59 mg/dL or 2.2 to 3.3 mmol/L) for a total of 23 episodes out of 4140 BG measurements. However, none of the patients experienced an episode of severe hypoglycemia (BG < 40 mg/dL or 2.2 mmol/L) [6]. Nursing adherence to our paper-based continuous intravenous RHI infusion algorithm was nearly 90% which indicated excellent nursing compliance [7]. However, one important consideration with our study methodology was that we excluded patients with renal impairment as defined by a serum creatinine ≥ 2 mg/dL (177 µmol/L) or if the patient required hemodialysis [6]. We introduced that exclusion criteria based on our anecdotal clinical observations that patients with renal impairment or those receiving hemodialysis given our conventional continuous intravenous RHI infusion algorithm frequently developed severe hypoglycemia. Thus we sought to develop a graduated continuous intravenous RHI infusion algorithm designed specifically for patients with renal failure [8] concurrently while developing an algorithm for those without renal failure [6].

The intent of this review is: to discuss the pathophysiology of why patients with acute kidney injury or chronic kidney failure are at increased risk for hypoglycemia; examine those studies that implicate acute kidney injury as a risk factor for hypoglycemia;
during insulin therapy; and offer some practical approaches for consideration of implementation into your clinical practice.

**DEFINITION AND CLINICAL RELEVANCY OF HYPOGLYCEMIA**

Hypoglycemia has been defined as a BG < 70 mg/dL (3.9 mmol/L) based on the activation of counter-regulatory hormone secretion of glucagon and epinephrine [2, 9]. Autonomic symptoms to hypoglycemia include anxiety, palpitations, tremor, and diaphoresis and generally do not occur until the BG is < 60 mg/dL (3.3 mmol/L) [9]. At a BG < 50 mg/dL (2.8 mmol/L), neuroglycopenic symptoms (e.g., dizziness, blurred vision, paresthesia, impaired cognition) may occur [9]. Patients can become comatose, experience seizures, develop cardiac arrhythmias, or die when the BG is less than 40 mg/dL (2.2 mmol/L). Since it is difficult to elicit symptoms from a mechanically ventilated and sedated patient in the intensive care unit, many clinicians define hypoglycemia on the basis of BG concentration alone. Mild to moderate hypoglycemia is usually represented as a BG within 40 to 60 mg/dL (2.2 to 3.3 mmol/L) [6-8] and severe hypoglycemia as < 40 mg/dL (2.2 mmol/L) [1, 10, 11].

It has been suggested that even a single episode of severe hypoglycemia is associated with increased risk for mortality during critical illness [12, 13]. But it has been argued that this association is not causal and may be attributable to impending death from multiple-organ failure rather than an incidental episode of hypoglycemia [14, 15]. Episodes of hypoglycemia and increased blood glucose variability during insulin therapy are related to the severity of critical illness or septic episode [16-18]. Therefore, it is the severity of illness that is likely to be associated with mortality for patients receiving intensive insulin therapy and not necessarily the presence of a hypoglycemic episode per se.

Despite this controversy of whether hypoglycemia is associated with mortality or not, the prevalence of hypoglycemia should not be ignored. Persistent episodes of severe hypoglycemia may aggravate residual critical illness-induced neurocognitive dysfunction particularly in the visuospatial skills domain [19]. Prevention of severe hypoglycemia for patients with traumatic brain injury is vitally important. A linear relationship exists between systemic and brain interstitial glucose concentrations with brain concentrations at about 25% of plasma concentrations [20]. During hypoglycemia, brain glucose concentrations may fall to concentrations that are rate limiting to support the increased energy needs and accelerated glucose metabolism by the brain following traumatic brain injury. In a cross-over manner, Vespa and coworkers [21] demonstrated a greater percentage time (40% versus 11%) for critically low brain glucose concentrations (less than 11 mg/dL or 0.6 mmol/L) and an increased lactate to pyruvate ratio (suggesting anaerobic metabolism) when receiving intensive insulin therapy (e.g., BG 80 to 110 mg/dL or 4.4 to 6.1 mmol/L) compared to modest glycemic control (BG 120 to 150 mg/dL or 5.5 to 8.3 mmol/L) in critically ill patients with traumatic brain injury. If patients with traumatic brain injury constitute part of your patient population, then use of a continuous intravenous RHI infusion algorithm that avoids severe hypoglycemia is imperative when managing these types of hyperglycemic patients.

**METABOLIC ABERRATIONS IN GLUCOSE AND INSULIN HOMEOSTASIS DURING KIDNEY FAILURE**

Recent trends towards increased prevalence of hypoglycemia with continuous intravenous RHI infusions have prompted many clinicians to critically re-evaluate their current management of hyperglycemia. This is particularly the case for hyperglycemic patients with kidney failure. Case reports of spontaneous hypoglycemia in non-diabetic patients with end-stage chronic kidney disease have been reported in the literature over thirty years ago [22]. With the advent of aggressive insulin therapy for critically ill hyperglycemic patients, the impact of renal failure has recently been emphasized as a predisposing risk factor for the development of hypoglycemia in the intensive care unit [12, 23]. The exact physiologic mechanism for this increased risk for hypoglycemia is not entirely clear and probably multi-factorial as the kidney is an important organ influencing insulin elimination, insulin receptor sensitivity, and gluconeogenic response to hypoglycemia.

The renal clearance of insulin exceeds the glomerular filtration rate. This phenomenon is reflective of significant uptake and degradation of insulin by the kidney. When the glomerular filtration rate decreases to about 40 to 50 mL/min, renal insulin clearance substantially decreases [24]. Patients with chronic kidney disease may have a doubling or tripling of the half-life of insulin (e.g., from a normal half life of 12 to 15 minutes to a mean of 40 minutes [25] with a resultant 40% to 50% decrease in insulin requirements [26]. Critical illness such as traumatic injury [27], as well as acute [28] or chronic [29] renal failure, have
also been associated with varying amounts of insulin resistance. Changing patterns in plasma insulin pool size due to a prolonged half life combined with variable insulin receptor sensitivity provide a plausible explanation for why plasma insulin and BG concentrations are often erratic for critically ill patients with kidney injury when receiving concurrent nutrition and insulin therapy.

The kidney also contributes a significant role to gluconeogenesis and glucose counter-regulation. It was originally thought that the kidneys only had a minor role in gluconeogenesis accounting for 10% of systemic glucose appearance in response to hypoglycemia. Recent data refutes this historical assumption [30, 31]. Renal glucose release accounts for about 28% of systemic glucose appearance in normal subjects but increases to 40% after an intravenous epinephrine infusion [30]. Similar findings have been observed in normal volunteers rendered hypoglycemic (BG 60 mg/dL or 3.3 mmol/L) by a continuous intravenous insulin-glucose infusion clamp technique [31]. During hypoglycemia, volunteers experienced activation of the autonomic nervous system (increased serum glucagon, epinephrine and norepinephrine concentrations) resulting in a doubling of the net renal glucose production rate [31]. These data indicate that impairment in glucose production by the diseased kidney represents an additional dysfunction in the body's defense against hypoglycemia. Unfortunately, there are no data to indicate at what level of renal dysfunction results in a specified amount of impairment in renal gluconeogenesis.

Given a clinical scenario of combined nutrition and insulin therapy for a critically ill patient with kidney dysfunction, it is very plausible that the patient may be at high risk for both hyperglycemia and hypoglycemia with respect to evolving changes in carbohydrate intake, insulin clearance, and insulin sensitivity. Once the patient with renal failure becomes hypoglycemic, the ability to effectively respond to hypoglycemia may also be impaired.

**HYPOGLYCEMIA DURING INSULIN THERAPY IN PATIENTS WITH KIDNEY FAILURE**

Data to support the potential high risk for hypoglycemia during insulin therapy for patients with renal failure has been described in the literature as early as 1986 [32]. Fisheker and associates found that 46 out of 94 patients (49%) who had chronic renal insufficiency developed hypoglycemia (BG < 50 mg/dL or 2.8 mmol/L) [32]. The most common risk factor was the use of insulin itself (occurring in 90% of all episodes of hypoglycemia) followed by the presence of kidney disease as the second most occurring risk factor. More recent data indicated patients who received continuous veno-venous hemofiltration for acute kidney injury were at increased risk for severe hypoglycemia as defined by a BG < 45 mg/dL (odds ratio (OR) of 3.7) [23].

Despite these recent data indicating acute kidney injury or chronic kidney disease as a significant risk factor for hypoglycemia during insulin therapy, none of the major glycemic control trials adjusted their continuous intravenous RHI infusion algorithms or target BG range for those patients that developed acute kidney injury or had pre-existing chronic kidney disease. Table 1 depicts the incidence of acute kidney injury and severe hypoglycemia for recent large, randomized, controlled intensive insulin therapy trials. It is interesting to note that those studies with the greatest incidence of severe hypoglycemia (i.e., Leuven 2 and VISEP) also had the largest proportion of patients with acute kidney injury. Conversely, those studies with the lowest incidence of hypoglycemia (i.e., Leuven 1 and NICE-Sugar) also had the lowest proportion of patients with acute kidney injury (Table 1). These studies appear to support the relationship between acute kidney injury and increased risk for severe hypoglycemia during intensive insulin therapy.

However, despite this relationship between kidney injury and severe hypoglycemia during insulin therapy, Table 1 tends to over-simplify the myriad of events outside of acute kidney injury that may have contributed to hypoglycemia. For example, there were additional predisposing factors in the Leuven 2 trial for hypoglycemia beyond the difference in patient population (e.g., medical versus surgical patients) or the amount of patients with acute kidney injury compared to the Leuven 1 trial. In the Leuven 1 trial, patients were given parenteral nutrition and insulin therapy was adjusted by a 24 hour a day, 7 days per week insulin infusion nursing team dedicated to glycemic control. In the second Leuven RHI infusion study, patients were fed by enteral nutrition and not predominately by parenteral nutrition as in their first study. This is significant as those fed enterally are apt to have more abrupt and temporary discontinuations in continuous nutrition therapy than those who receive parenteral nutrition due to factors such as gastric feeding intolerance, surgical and diagnostic procedures [33]. Additionally, the Leuven investigators changed from an insulin infusion team (Leuven 1) to a nurse-
driven paper-based algorithm (Leuven 2). Depending on the complexity of the algorithm and amount of nursing inservice training given to using the algorithm, insulin infusion protocol adherence rates by nursing personnel have ranged from 53% to 90% [7]. Misinterpretation of algorithm instructions may result in erroneous decisions in administering insulin therapy. Such is the case with the Glucontrol trial whereby frequent protocol violations by nursing personnel and a high rate of severe hypoglycemia led to its premature discontinuation [34]. Finally, administration of pharmacotherapeutics agents that unknowingly cause kidney damage may also skew interpretation of the efficacy and safety of a RHI infusion algorithm. The VISEP (volume and insulin therapy in severe sepsis and septic shock) trial [35] is an example of this type of confounding factor. In the VISEP study, patients were randomized to receive intravenous crystalloid or pentastarch resuscitation fluid followed by intensive or conventional intravenous RHI infusion therapy. The RHI therapy portion of the study was discontinued due to the increased incidence of severe hypoglycemia. However, the resuscitation portion of the study was also subsequently discontinued after it was discovered that pentastarch resuscitation was associated with a dose-dependent increase in acute kidney injury [35]. Thus, one might speculate whether pentastarch-induced acute kidney injury contributed to the development of hypoglycemia during intensive RHI therapy.

Knowledge of the metabolic changes of insulin and glucose homeostasis during kidney injury, combined with our anecdotal clinical observations of a marked increase in hypoglycemia when using our conventional intravenous insulin infusion algorithm [6] in patients with renal failure, prompted us to seek a safer method for glycemic control for these patients [8]. Table 2 contrasts our conventional intravenous insulin infusion algorithm with our first (discontinued) prototype [8] and current protocol for patients with renal failure. Inspection of the two methods designated for renal failure demonstrates that escalation of the infusion rate for a given BG was less aggressive than our conventional infusion (Table 2). Despite a more conservative escalation in RHI infusion rate, 76% of the studied 21 patients with renal failure (86% with acute kidney injury and 14% with chronic kidney disease) experienced mild to moderate hypoglycemia (BG 40 to 60 mg/dL) and 29% had at least one episode of severe hypoglycemia (BG < 40 mg/dL) with the first (discontinued) algorithm for renal failure [8]. This is in contrast to 35% and 0%, respectively, for those without renal failure despite receiving a more aggressive RHI algorithm (Table 2) [6]. As a result of these findings, we have subsequently modified our algorithm to our current version (described in Table 2) which allows for a higher BG range where there is no change in the insulin infusion rate, a decrease in insulin infusion rate sooner (at a higher BG), as well as continuation of the slower escalation in RHI infusion rate for hyperglycemia (1 unit per hour increase for every 50 mg/dL increase in BG). Whether this algorithm will result in less hypoglycemia yet maintain reasonable glycemic control remains to be established and is currently under investigation.

Table 1: Incidence of Severe Hypoglycemia (BG < 40 mg/dL or 2.2 mmol/L) During Intensive Insulin Therapy and Continuous Nutrition Therapy for Patients with Acute Kidney Injury or Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Prevalence of Renal Failure</th>
<th>Incidence of Severe Hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucontrol [34]</td>
<td>536</td>
<td>519 days of CRRT</td>
<td>8.7%</td>
</tr>
<tr>
<td>Leuven 1 [11]</td>
<td>544</td>
<td>4 patients with dialysis before ICU admission</td>
<td>5.1%</td>
</tr>
<tr>
<td>Leuven 2 [10]</td>
<td>595</td>
<td>6.2% with CRRT before ICU admission</td>
<td>18.7%</td>
</tr>
<tr>
<td>NICE-SUGAR [1]</td>
<td>3504</td>
<td>35% with “renal dysfunction” (SOFA score 1-2)</td>
<td>6.8%</td>
</tr>
<tr>
<td>VISEP [35]</td>
<td>247</td>
<td>8.5% with renal dysfunction at baseline</td>
<td>17.0%</td>
</tr>
</tbody>
</table>

AKI, acute kidney injury; BG, blood glucose concentration; CKD, stage V chronic kidney disease; CRRT, continuous renal replacement therapy; HD, hemodialysis; ICU, intensive care unit; N, number of patients receiving intensive insulin therapy; NICE-SUGAR, normoglycemia in intensive care evaluation-Survival using glucose algorithm regulation; SOFA, sequential organ failure assessment; VISEP, volume substitution and insulin therapy in severe sepsis.
It is recommended that continuous intravenous RHI infusions be used with extreme caution and potentially adjusted for patients with acute kidney injury or chronic kidney disease. Your institution’s continuous intravenous RHI infusion algorithm should be evaluated to insure its safety and efficacy. Our current modified continuous intravenous RHI infusion algorithm anecdotally appears promising and is undergoing critical evaluation after nearly two years of use in our clinical practice. Finally, reconsideration of changing your target BG range to 140 mg/dL to 180 mg/dL (7.8 to 10 mmol/L) may be warranted if your current target BG range cannot be safely achieved [2].

**CONCLUSIONS**

Acute kidney injury or chronic kidney disease presents as a major risk factor for severe hypoglycemia for patients requiring continuous intravenous RHI infusion therapy. Continuous intravenous RHI infusion
algorithms that have been successful for hyperglycemic critically ill patients without renal failure may not be appropriate for use in patients with kidney disease. Clinicians need to have a heightened awareness for the risk of hypoglycemia for hyperglycemic patients who receive insulin therapy. Whether a restructured intravenous RHI infusion, a more liberal BG target range, or if a combination of both of these techniques provide the best clinical outcomes for these complicated patients remains to be determined.

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