Spring 5-12-2017

Is Intense Glycemic Control Really Better?

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Abstract

The following paper and presentation have been put together in my pursuit of finding out whether or not intense glycemic control has proven more beneficial when compared to a more conventional type of glucose control in hospitalized adults in an intense care unit (ICU). It is important to note that this paper and the following studies look at acute or short term hyperglycemia, not chronic. Chronic hyperglycemia has many detrimental effects and therefore tight blood glucose control is essential for optimal health when discussing long-term control of glycemic levels. Inspiration came for this project while taking care of ICU patients in my capstone clinical experience. By the end of this paper, it is hoped that I will have educated the reader well enough to convince them that conventional glycemic control in acute hospitalized adults in the ICU proves to have less morbidity rates than intense glycemic control.

Is Intense Glycemic Control Really Better?

In hospitalized patients, does intense glycemic control result in better outcomes when compared to conventional glycemic control? After a study done in 2001 in Belgium that researched a similar topic, many ICUs worldwide adopted protocols supporting the idea that intensive insulin therapy proved beneficial and had better outcomes for patients when compared to conventional glycemic control (Marik & Bellamo, 2013). Despite many limitations in the 2001 study, many healthcare decisions were altered due to the results found from this single center study. In the following paper, this study will be analyzed along with others whose goal was to disprove or prove the findings were accurate and reproducible. The following paper will also go into detail about the human body's adaptive response to stress and why it is beneficial for the body to increase its blood sugar levels in order to promote optimal healing.

Stress Response

The human body is extremely adaptive and has mechanisms in place to heal itself in times of sickness and stress. To review, euglycemia is the goal in day-to-day life. This ideal value should be 70-110 mg/dL and can vary dependent on time of day, such as if the reading is taken pre-prandial or postprandial (Lewis, Heitkemper, Dirksen, & Bucher, 2014, pg 1160). In times of illness, glycemic levels can rise and fall to certain extremes. Critical results of hyperglycemia or hypoglycemia can result in serious outcomes. Less than 40 mg/dL in females (less than 50 mg/dL in males) is considered a critical glycemic value whereas greater than 450 mg/dL is considered the critical glycemic value for both males and females (Pagana & Pagana, 2014, pg 254). As one can see, the lower level of euglycemia is much closer to the critical value for hypoglycemia than is the higher level of euglcemia to critical hyperglycemia.

When hyperglycemic, an individual may have the following signs and symptoms: weakness, fatigue, headache, blurred vision, nausea, vomiting, and abdominal cramps (Lewis et. al., 2014. pg 1175). When hypoglycemic, an individual may have: numbness of fingers, toes, and mouth, tachycardia, emotional changes, nervousness, tremors, dizziness, unsteady gait, seizures, and these patients can even fall into a coma. Comparing the symptoms of hyperglycemia and hypoglycemia, one can see that hypoglycemia can have much worse effects on the body. "It would therefore appear that in critically ill patients, hyperglycemia is not desired, but that 'low' blood glucose is even less desired (Marik, 2009, pg 4)."

The primary source of energy for the brain is glucose (Marik & Bellamo, 2013). The most imperative organ to keep functioning is the brain seeing as it keeps the human body breathing and the heart beating and therefore, delivering oxygen to the entire body. In times of stress, the body is aware of the need to keep the brain energized and therefore takes immense measures to give the brain the energy it needs to survive. The body's sympathetic (fight or flight) system kicks in and raises levels of glucagon, growth hormone, catecholamines, glucocorticoids, cytokines/interleukins, and tumor necrosis factor (TNF-alpha) (Marik, 2009). Increasing cortisol and catecholamines from the adrenal cortex, as well as the increase in growth hormone, leads to insulin resistance (Marik & Bellamo, 2013). Inflammatory mediators such as C-reactive protein (CRP) increase and cause peripheral insulin resistance and thereby shunts more glucose away from the peripheral body where it is not necessarily needed at this time. The human body also stimulates gluconeogenesis; there is an increase in hepatic output of glucose and glycemic levels rise even more.

Glucose, as a solute, moves into the cell by a passive diffusion gradient from areas of high concentration to low concentration (Lewis et. Al., 2013). Therefore, by raising blood levels

of glucose, the body is maximizing its ability for cellular glucose uptake by supporting the transfer of more glucose molecules to be attracted into the cell because less sugar is in this area (when compared to the blood). By doing so, the cell has more energy than it did before. Glucose molecules also have the help of glucose transporters that are expressed on cell surfaces. The pro-inflammatory mediator, TNF-alpha, affects the expression of the glucose transporter on the cell surface and facilitates movement of glucose into the cell (Marik & Bellamo, 2013). Furthermore, acute hyperglycemia in the cells protects against ischemia and apoptosis or cell death. The extra available energy promotes the cell's already existing anti-apoptic pathways as well as supports angiogenesis and increases cell plasticity. The above mechanisms make available the glucose/energy needed to keep the brain, nervous system, and immune cells functioning to optimally heal the body.

Van Den Berghe Study

A randomized control study done in Belgium 2001, set out to prove that intensive insulin therapy in hospitalized adults reduced mortality rates when compared to conventional insulin therapy (Berghe et. al., 2001). The randomized control study included 1,548 participants/patients, all of whom were surgical ICU patients on mechanical ventilation and hospitalized five or more days (the vast majority of patients were post-cardiac surgery). Participants were broken into two groups. One group received intensive insulin therapy and blood sugar levels were kept between 80-110 mg/dL, while the other group took part in conventional insulin therapy with an insulin infusion being initiated if the patient's blood sugar level read 215 mg/dL or above. For the conventional insulin therapy, once the insulin infusion was started, caregivers maintained glycemic levels between 180-200 mg/dL. Both groups had

arterial blood gases drawn every four hours and blood glucose checked on admission and 0600 every day.

Results showed that in the intense group, all participants required exogenous insulin in order to achieve glycemic levels between 80-110 mg/dL (Berghe et. al., 2001). In the conventional group, only 39% of participants required exogenous insulin to maintain a blood sugar level below 215 mg/dL. Bringing mortality statistics into play, thirty-five patients died in the intensive group and sixty-three died in the conventional group. According to the above mortality statistics, the study concluded that intensive insulin therapy resulted in decreased mortality rates when compared to conventional insulin therapy. Important to note, thirty-nine participants in the intensive group experienced hypoglycemic episodes whereas only six participants in the conventional group experienced hypoglycemic episodes. In summary, there were more episodes of hypoglycemia in the intensive insulin therapy group. Considering that the conventional group was allowed to be much further from the critical values of 40-50 mg/dL, this makes sense. The vast majority of deaths in this study were attributed to multiple organ failure related to sepsis. A relationship/causation between the use of TPN and sepsis was not mentioned in the study. Readers may then wonder if exogenous administration of TPN may have contributed to the higher rates of sepsis and therefore multiple organ failure which led to death.

Post-release of this study, many, if not all, ICUs around the globe adopted likewise thinking and glycemic levels were tightly controlled in hospitalized adults admitted to the ICU (Bellomo & Egi, 2009). The Van Den Berghe study was done with surgical ICU patients; therefore, the question arises as to whether or not it is appropriate to extend these findings to medical ICU patients as well. Other limitations to the Van Den Berghe study exist. First, the study done in Belgium was a single-center study; it was also not blinded. This means that the

investigators and researchers were aware of what participants were in what groups and leaves the possibility for bias and skewing of results. Second, the Van Den Berghe study had all participants on 200-300 grams of TPN over 24 hours every day while participating in the study (2001). According to Bellomo & Egi, this was an extremely unusual practice (2009). Third, it was found that the mortality rate of the participants who had undergone cardiac surgery was more than twice the national average for Australia at the time; therefore, the argument of whether or not the group chosen in Belgium was representative or not of the whole population, was at question. Lastly, Bellomo & Egi also brought up in their editorial the Hawthorne effect (2009). The Hawthorne effect relates back to the idea that the entire Belgium study was investigator initiated and that if given more attention and knowing every detail of the study, would that alone be enough to skew the results?

NICE-SUGAR Study

In an attempt to find the optimal target blood glucose range in critically ill patients, the NICE-SUGAR study investigators involved forty-two hospitals world-wide, involving a total of 6, 104 participants (2009). All participants were placed in one of two groups; characteristics of these patients and their conditions were accounted for to optimize similarities between the two groups. The difference between the two groups was the target glycemic levels. The intense insulin therapy group's target range was between 81-108 mg/dL. The conventional group's target was to remain under 215 mg/dL; if therapy had to be initiated, it was then stopped once the patient reached a glycemic level of 144 mg/dL. The criteria to be included in the study was that the patient was admitted to the ICU for a minimum of three days; the patient was discontinued from the study once eating or discharged from the ICU. It is important to note that this study included both medical and surgical ICU patients.

Results were inconsistent to the 2001 study by Van Den Berge. Twenty-seven and five tenths percent of participants in the intensive insulin therapy group died whereas 24.9% of participants in the conventional insulin therapy died. The NICE-SUGAR study proved that the 90-day mortality rate was increased if treated with intense insulin therapy while hospitalized (2009). It is important to note that most of the deaths in the study were attributed to cardiovascular causes. The episodes of extreme hypoglycemia (blood glucose less than 40 mg/dL) were much higher in the intensive insulin therapy group as well. There were 272 hypoglycemic episodes in the intense group compared to sixteen episodes in the conventional group.

Although the NICE-SUGAR study disproved the finding that Van Den Berghe had back in 2001, ICUs were/still are leery to adopt these new ideas and change their ways of thinking and doing so quickly. It is important to note than many other researchers attempted to perform studies to replicate Van Den Berghe's, but failed to do so. Attempts to replicate were "prematurely discontinued due to an alarmingly high rate of hypoglycemia" (Marik, 2009, pg 4). According to current research, no study done has been completed that backs up the results of the 2001 Van Den Berghe study, concluding that intensive insulin therapy has proved to be more beneficial in the hospitalized adults admitted to the ICU when compared to conventional insulin therapy.

Conclusion

The human body is adaptive and can identify when the body is ill and under stress. It has mechanisms in place to attempt to heal itself by conserving its energy resources and shunting them to places in most need, i.e. the brain. The fight or flight adaptive response has proved beneficial to the body and we therefore should allow the mechanism to attempt to heal itself to

some point before we intervene. Since hypoglycemia is much less desired than hyperglycemia, we should avoid hypoglycemic episodes at all costs (Marik, 2009). According to Pagana & Pagana, the critically low values for hypoglycemia is 40-50 mg/dL and below; the critical value for hyperglycemia is 450 mg/dL and above (2014). Seeing that optimal euglycemia levels are 70-110 mg/dL on a day-to-day basis, one can analyze these numbers and see that there is much more room available to ride hyperglycemic without approaching the critical hyperglycemic levels than there is for hypoglycemia.

It is imperative to recognize that the human body uses up more energy in times of stress than in times of wellness (or everyday life). Because glucose is the brain's primary source of energy, we must allow the brain to have more glucose in order for healing to occur (Marik & Bellamo, 2013). Relating back to the passive diffusion gradient knowledge, more glucose in the blood directly affects the cell in that more glucose will diffuse into the cell because it is an area of lesser concentration. Recognizing that ICU patients are extremely sick, it is important to acknowledge that these patients need more energy (in the form of glucose). Therefore, we should not be controlling their glycemic levels as tightly as they would in everyday life.

Just because one study proved that intensive insulin therapy in hospitalized adults in the ICU had better outcomes than conventional glucose control, does not warrant the adoption of these practices in ICUs worldwide, especially because the NICE-SUGAR study has since found conflicting data. It is imperative that all members of the healthcare team stay up-to-date with published evidence and further research the pathophysiology behind different mechanisms that they may see every day in their work lives. By doing so and supporting the idea of always learning, we, as a team, can continue to improve patient outcomes and provide the best, safest care possible.

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