Managing hyperglycemia during the COVID-19 pandemic: Improving outcomes using new technologies in intensive care

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Abstract

Hyperglycemia is a significant risk for mortality in COVID-19 infections and is most dramatically noted in critically ill patients. Hyperglycemia and/or diabetes are noted in approximately 30%–40% of patients admitted with COVID-19 infections. Previous studies have shown a marked increase in mortality related to increased glucose concentrations and reduction with improved glucose control. In vivo and in vitro studies reveal the mechanisms by which hyperglycemia increases virulence and how glucose control and insulin reduce it. Optimal glucose control in intensive care is limited by manual sampling of glucose and intravenous insulin adjustment, as well as increased nursing workload and the need of protective equipment. Tools for safe and effective automation of glucose control in intensive care are discussed. A suitable closed loop device could save the lives of thousands of hospitalized hyperglycemic individuals infected with COVID-19 while protecting medical professionals from infection risk.

Introduction

The COVID-19 pandemic presents challenges in glycemic control of critically ill patients. Current methods of glucose control are imprecise, error prone, and labor intensive. New technologies are required to improve outcomes and reduce the need for manual intervention. This review of hyperglycemia, hospitalizations in COVID-19, and automated glucose control in critically ill patients is based on a PubMed search strategy. The following narrative discusses the issues surrounding hyperglycemia in critically ill COVID-19 patients and the development of needed closed-loop technologies.

Effects of hyperglycemia in hospitalized COVID-19 patients

The pandemic of COVID-19 has caused significant disruption in the intensive care unit (ICU) due to inadequate staffing, protective equipment, ventilators, and bed capacity.[1] Demographics reveal that patients at greatest mortality risk are those with diabetes and/or hyperglycemia. Approximately 30%–40% of those hospitalized with COVID-19 had either diabetes or hyperglycemia without previous diagnosis of diabetes.[2–4] The mortality rate is over four-fold higher for those with diabetes and/or hyperglycemia (28.8%) than those without either (6.2%). The mortality was seven-fold greater for those with hyperglycemia and no previous history of diabetes (41.7%).[2] Mortality was not related to prior glucose control as noted by serial hemoglobin A1c measurements[5] but was related to glucose control during the COVID-19 infection. In a subset comparison of age and risk-matched COVID-19 patients with hyperglycemia, there was a reduction in mortality from 11.1% to 1.1% over a 28-day period with glucose control in a range of 3.9–10.0 mmol/L compared to those with >10.0 mmol/L. Approximately 70% of all diabetic individuals with COVID-19 had poor control (blood glucose > 10.0 mmol/L). In those with targeted glucose control of

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3.9–10.0 mmol/L, there was a significantly lower d-dimer, C-reactive protein (CRP), interleukin 6 (IL-6), and occurrence of multisystem failure.[6] An additional study also showed less severe multisystem disease, reduced IL-6 and d-dimer concentrations, and improved survival in those with improved glucose control using intravenous insulin.[7] In addition, glucose variability has been correlated to mortality both in COVID-19[6] and influenza.[8] However, studies on antiviral therapies have included minimal data on glucose control. In the study evaluating remdesivir in COVID-19, 29.6% of the placebo and 32.1% of the treated group had diabetes but no data was published on glucose control in either.[4]

The effects of hyperglycemia on innate and COVID-19-mediated immune responses are complex. Cytokine storm is a major mortality risk in COVID-19.[9] Cytokines are increased in non-infected diabetic and prediabetic individuals.[10] Acute hyperglycemia rapidly increases cytokines in normal and prediabetic individuals.[11] Intravenous insulin reduces cytokine concentrations independent of infection in diabetic individuals.[12] Hyperglycemia also appears to increase the infectivity of the SARS-CoV-2 virus. The viral spike attaches to the angiotensin-converting enzyme 2 (ACE2) receptor as a mechanism to gain access to the cell.[13,14] Hyperglycemia seems to increase the binding affinity, which may be reversible initially with improved glucose control.[15] ACE2 function is critical in protecting vascular endothelium.[16] In post mortem studies, the vascular endothelium in COVID-19 patients showed marked abnormal structural changes.[17] Improved glucose control with intravenous insulin has been shown to protect the vascular endothelium in critically ill patients.[18] In animal models, insulin augments janus kinase-signal transducer and activator of transcription (JAK/STAT) signaling to inhibit viral replication.[19] In the later case, insulin appears to act as an antiviral agent. Hyperglycemia and diabetes have significant adverse effects in COVID-19 infections but the ability to optimally control glucose during an infectious pandemic requires advanced technologies.

Challenges of managing hyperglycemia in COVID-19 patients during intensive care

Many of the challenges of managing hyperglycemia in COVID-19 are similar to those in non-COVID-19-intensive care settings. In intensive care settings, the standard of care for glucose control is the measurement of blood glucose based on an algorithm-determined time schedule, and adjusting manually an intravenous infusion of insulin based on that algorithm.[20] Studies prior to COVID-19 demonstrated that each glucose sample and measurement requires 5 minutes (min)[21] with significant delays or absent determinations 53% of the time.[22] Frequently blood is drawn from arterial lines 6–12 times a day for sampling which leads to anemia and risk of infection.[23,24] In another study prior to COVID-19, 575 US hospital ICUs evaluated 12,176,299 glucose samples

in 653,359 patients with hyperglycemia (>10.0 mmol/L) noted 32.2% of the time and hypoglycemia (<3.9 mmol/L) 6.3% of the time.[25] With the increased nursing workload and addition of protective equipment in COVID-19, the stress on the system to perform optimally is overwhelming. The time in target range of 3.9–10.0 mmol/L was 50%–68% in ICU studies prior to COVID-19,[25–27] and data for glucose control during the pandemic show a lower time in the same target range of 30%–62%.[2,6] While computerized algorithms have improved treatment options, they are still dependent on the manual sampling of blood glucose.[27,28] Hypoglycemia also increases mortality[29] and may go undetected with infrequent glucose determinations. Present techniques are not adequate for ICU settings especially when surges of pandemic proportion tax the hospital resources required. Automated closed-loop systems managed by advanced real-time blood glucose sensing, adaptive algorithms, counterbalancing treatment, and remote monitoring are essential to effectively managing critically ill patients with COVID-19.

Integral development of closed-loop glucose control for the ICU

Requirements for automated closed-loop sensing and treatment of glucose in critical care settings require evaluation of the following specifics.

Sensing

Automated real-time sensing is essential for a closed-loop glucose control system. Based on glucose infusion studies, insulin half-life, glucose disposal rates, and clinical data from critical care, 5 min sampling intervals appear to be required for a sensor in a closed-loop system.[30] Additional factors to be considered include lag between plasma glucose concentrations and sensing results (lag time), as well as the accuracy, durability, and life of the sensor. While a subcutaneous continuous glucose monitor (SCGM) may be adequate for glucose tracking and hypoglycemia prevention in intensive care, this method for closed-loop glucose treatment in critically ill patients appears inadequate. Initial studies showed promise but required frequent sensor site changes and/or recalibration with blood samples every 2–3 hours (h).[31] Subsequent hospital studies of SCGM also showed mean absolute relative difference (MARD) of 12%–15%, a variable but significant sensing lag and the need for frequent readjustment or replacement.[32–36] During rapid changes of blood glucose in clamp studies representing conditions seen in an intensive care setting, the mean glucose lag time with SCGM from plasma glucose was 29 min and MARD range was 13%–24%.[37]

Frequent sampling using an automated ex vivo blood sensing system is one method which could be used. In such a system, blood may be drawn into the sensor and then returned to the patient. The Optiscanner 5000 (Optiscan Biomedical

Corporation, Hayward CA) uses a spectrometric method of glucose sensing but is capable of sampling only every 15 min due to the length of the tubing and time for spectrometric assay.[38] The Glysure sensor (Glysure LTD, Abington UK) uses a boronic acid glucose sensor with a dedicated central venous catheter. The system had difficulties with durability of the sensor and has been discontinued.[39] Automated micro-dialysis-based sensing is another approach that has been developed. The Eirus system (Marquet Getinge Group, Solna Sweden) uses a continuous glucose oxidase sensor integrated with a microdialysis catheter. It has a lag time of 10 min due to equilibration between the microdialysis solution and plasma glucose which is inadequate for real-time sensing in a closed-loop treatment system.[40] Other blood glucose sensors have used a semipermeable membrane embedded in a flow cell window to separate the glucose oxidase sensor from blood[41–46] with some of the devices demonstrating the precision required for a closed-loop sensor in an ICU.[47,48] In such designs, the sensor is integrated in a flow cell window and is connected to a vascular catheter distally and to a bidi-rectional pump proximally. Blood can be withdrawn into the flow cell and then returned to the patient after sensing. The VIA Glucoscout (International Biomedical, Ltd. Austin TX) is a Food and Drug Administration (FDA)-approved device which has a MARD of 5%–10% over a wide range of glu-cose concentrations,[41] but it uses technology which was designed more than 20 years ago. The sensor unit and flow cell are large, difficult to use, and it has been used primarily for research. The Glucoclear (Edwards Lifesciences, Irvine CA) was developed with similar characteristics and MARD but had issues as the sensor was inserted into the peripheral catheter lumen.[43] Smaller flow cell sensors have a correla-tion coefficient of >0.98, insignificant paracetamol interfer-ence and 95% response time <30 seconds.[44,45]

Durability and flexibility of the sensor are other notable factors in an intensive care device. A flow cell glucose oxi-dase sensor with a semipermeable membrane has been used continually for 40 days using in vitro studies[49] and also has been implanted in the aortas of rats and used continuously for 60 days.[50] In addition this design is expandable to other analytes. Lactate oxidase sensing can be added to the same sensing unit to monitor trends of lactate[49] which is a risk fac-tor for mortality in COVID-19 infection.[51]

Vascular access

One limiting factor has been the durability of venous access for such a closed-loop system. Peripheral veins may be used but repeated infusion and frequent withdrawal of blood reduces the functionality in many patients.[43] Central venous catheters are also used but are frequently designed for each system.[38–40] In addition, the central venous catheters require a physician rather than a nurse to place them, and they are left in place for the shortest time possible due to risks of prolonged use. Arterial catheters also must be placed by a

physician and development of arterial glucose sensors has proven unsuccessful.[52]

Midline catheters offer some of the benefits of both peripheral and central access devices. They are placed by nurses at the bedside using ultrasound guidance in approxi-mately 5 min. They are positioned proximal to the elbow which reduces the risk of being dislodged, and they can be used in emergency centers, intensive care, and non-critical care units.[53] Limiting factors for vein durability are pH and osmolality of infusions, volume and rate of infusion, and catheter size relative to vein diameter. This catheter/vein ratio is less than 0.33 needed for preservation of vein func-tion.[54,55] The insertion of a midline catheter, for example, would reduce blood flow in the vein from 250 to 130 mL/min which is still adequate for dilution of infusions.[56,57] Intravenous fluids required at 2 mL/min would be diluted by blood flow at a ratio of 65:1. Maximal reduction in vein occlusion has been noted with infusions of pH > 6.5 and osmolality < 500 mOsm/L.[58,59]

Treatment

Standard treatment of hyperglycemia uses intravenous insu-lin infusion as an unopposed biologic. This is usually diluted in normal saline per a hospital protocol and infused by an intravenous infusion pump. The settings for the infusions are adjusted manually by the nurse after each glucose determina-tion. One study showed a significant error rate of 5.3% of mismatching rate adjustments and entry of these values into the pump.[60] The use of an unopposed biologic (insulin) does not allow for raising and supporting low or falling blood glu-cose concentrations with the implications for patient safety. Treatment of hypoglycemia is manually directed by dextrose infusion and may be prolonged between infrequent glucose determinations. The Biostator (Miles Laboratory Inc., Elkhart IN, USA) was the first device developed in 1979 for use in a semi-closed-loop manner.[61] It was discontinued within a decade. Newer versions of the same device have been developed for clamp research (Glucostator, Olmatic GmbH, Nagold Germany). The use of glucose clamp proto-cols initiated the development of algorithms for targeted glu-cose control using frequent real-time blood glucose sensing.[62] Nikkiso Corporation (Tokyo Japan) has developed a closed-loop glucose control system which has been used in research for more than 30 years in Japan as a glucose clamp and clini-cally since 2006. It was originally the STG 22 and then mod-ified to the present STG 55. It is only available in Japan and used in only a few major medical centers for patients having surgery for liver and pancreas transplants, non-cardiopulmo-nary bypass cardiac surgery, and major gastroesophageal surgery. The system uses a continuous glucose sensor which withdraws blood from a peripheral catheter. The system measures the glucose and automatically adjusts infusion of dextrose and/or insulin using a proprietary algorithm. In a study of 107 esophageal resection patients, the mean, and

standard deviation of blood glucose perioperatively was 7.6 and 1.1 mmol/L, respectively.[63] In 72 cardiac surgery patients, the STG 55 controlled plasma glucoses with mean and standard deviation of 9.3 and 1.2 mmol/L, respectively.[64] In 50 patients undergoing major abdominal resections or transplants, the mean plasma glucose and standard deviation were 6.8 and 0.9 mmol/L, respectively. It prevented hypoglycemia in all studies.[65] In addition to cost issues, it requires significant effort and time to set up the device and it has a sensing lag due to the long length of tubing from catheter to sensor.[37] It is used in patients requiring transfusions during surgery as the device produces blood loss during sensing.[66–71] In a study of hepatic resection patients, the STG system over 18 h significantly exceeded glucose control results for standard of care, reduced infection risks and decreased cost of hospitalization by 43%.[72]

Algorithm

A closed-loop glucose control system requires sophisticated control logic, with its central function being dosage optimization. Various approaches to this are possible, with modern designs largely being classified as artificial intelligence (AI).

An adaptive counterbalancing system by Admetsys (Admetsys Corporation, Boston MA) has been shown in clinical trials of 43 insulin-requiring diabetic individuals to control plasma glucose in a target range of 4.4–6.9 mmol/L for 97% of the time without hypoglycemia (<3.9 mmol/L) during protocols which attempted to destabilize glucose control.[73,74] Additional in silico studies have confirmed a similar counterbalancing algorithm that achieves comparable results. Based on a total of 126,000 5-day simulations using 107,000,000 glucose samples, the time in target range (3.9–7.8 mmol/L) was 97.8%, hyperglycemia (>7.8 mmol/L) was noted 2.1% and hypoglycemia (<3.9 mmol/L) 0.09%.[75]

Nursing workload and allocation of resources

During this pandemic, multiple issues have occurred which have altered optimal care in critically ill patients. Bed occupancy was increased with those having high acute physiology and chronic health evaluation II (APACHE II) scores causing a severe stress on nursing personnel.[1,76] Nurses were recruited from less-affected areas to work in unfamiliar surroundings and were often not trained in critical care. It was difficult to adequately prepare them for the emerging pandemic.[1,77] Protective equipment was limited and improvisation was necessary. The use of such equipment requires increased time preparing to have patient contact and impairs a nurses ability to perform a blood glucose measurement and to adjust an insulin infusion. Continuous glucose monitoring using an intravenous sensor with an open-loop treatment system could improve glucose control but at the expense of a significant increase in nursing

workload. Increased frequency of glucose measurements can increase time needed for glucose control as much as 44% using an open-loop method.[78] This occurs from the more frequent responses required by nurses to verify accuracy of tracked glucose measurements and adjust the insulin infusions. Healthcare personnel have had significant rates of COVID-19 infection due to their exposure.[79] Automated closed loop glucose control could reduce nursing workload and allow remote monitoring of sensing and treatment.

Discussion

Hyperglycemia is a significant risk factor for mortality in COVID-19 and optimal control can change outcomes. The inadequacies of present methods are compounded due to the use of protective equipment, increased nursing workload and limits on bed occupancy. An automated system can advance intensive care treatment of these patients. In addition, coexisting conditions such as myocardial infarction and secondary infections in COVID-19 patients also respond to control of hyperglycemia.[80–82] At present, no antiviral therapies have proven effective in reducing mortality in COVID-19. Remdesivir has shown improvement in recovery time but not in overall mortality.[4] Treatment in the remdesivir group was initiated a median of 9 days after the onset of symptoms and 89% had severe disease. The effect of remdesivir if initiated earlier is unknown. However, if glucose control was suboptimal in the treatment group, the resultant hyperglycemia could reduce the effectiveness of the antiviral agent. A recent trial using dexamethasone in ICU on COVID-19 patients showed significant improvement in mortality in those with severe respiratory issues requiring ventilatory and/or oxygen support. There was no benefit to those without these severe conditions. In the dexamethasone-treated groups, mortality was still significant at 23.3% in oxygen supported and 29.3% in ventilator supported patients.[83] In hospitalized patients receiving glucocorticoids such as dexamethasone, >50% of non-diabetic and >90% of patients with diabetes develop hyperglycemia.[84,85] In the dexamethasone COVID-19 study, as with the remdesivir trial, no data on glucose control was noted. It is possible that optimal glucose control could improve the effectiveness of dexamethasone treatment by reducing the negative effects of hyperglycemia. In vitro data suggest that hydroxychloroquine can reduce glycosylation of the ACE2 receptor and also can lower blood glucose concentrations, both which could be possible mechanisms of antiviral activity.[15] However clinical evaluation of hydroxychloroquine has shown mixed results with some studies showing reduced mortality[86,87] and others no benefit.[88,89] While variance in glucose control could at least in part explain the difference in the results, these studies did not evaluate prevalence or control of hyperglycemia. The Centers for Disease Control and Prevention (CDC) CovidView cumulative hospitalization rate estimates a total

number of COVID-19 hospitalizations at 562,000 as of 12 September 2020.[90] Approximately 30%–40% of the COVID-19 admissions in the United States have had diabetes and/or hyperglycemia.[2,3] In the Bode et al.[2] study using data from Glytec (Glytec, Waltham MA) blood glucose was in the target range of 3.9–10.0 mmol/L 62% of the time. The Glucommander glucose management system used in this study has been shown to improve control[27,28] over conventional methods. Comparisons of poorly and well-controlled patients suggest a marked reduction in mortality by achieving this glucose target range. In one study, a subset comparing poorly and well-controlled diabetic individuals and using 1:1 age/sex/risk-matched analysis, there was a 90% reduction in mortality.[6] In a second study, the mortality rate was reduced by approximately 75%.[7] Using the mortality rates for those with diabetes and/or hyperglycemia in 88 US hospitals of 28.8%,[2] and the data from the above studies,[2,3,6,7,90,91] the mortality rate for those with diabetes and/or hyperglycemia could have been reduced by approximately 23%–36% using targeted glucose control. This equates to a reduction in mortality of an estimated 18,000 COVID-19 infected individuals or 15% of the 118,000 COVID-19-related deaths in US hospitals as of 12 September 2020.[90,91] Studies from additional countries confirm the need of improving glucose control in hospitalized patients with COVID-19 infections. In an Italian study, 42% of patients hospitalized with COVID-19 were diabetic,[7] and in the United Kingdom, one-third of all COVID-19-related deaths in the hospital were in diabetic patients.[92] In Wuhan, targeted glucose control in the range of 3.9–10.0 mmol/L was achieved only 30% of the time. Based on comparison with the Glytec control system data,[2] the Wuhan data[6] suggest an even greater number could have been saved with improved glucose control. In a recent multi-center study, the incidence of pulmonary complications was 56%, and the mortality was 26% in diabetic patients with COVID-19 during perioperative care.[93] Other studies have illustrated the need for optimal glucose control to reduce perioperative and pulmonary mortality.[94–97] Use of a closed-loop system to improve glucose control could be beneficial perioperatively. While detailed data for review is limited, inadequate glucose control of hospitalized COVID-19 patients appears to be a serious global issue. Data on severity of COVID-19 symptoms demonstrate a progression over the first 2–3 days and that the hospital mortality also begins to rapidly increase during the same time period.[6,98] Mean duration from admission to death in those with hyperglycemia and/or diabetes was 8.7 days.[2] Well and poorly controlled hyperglycemic groups showed divergence in mortality rates after the first 2–3 days suggesting that early glucose control could make a significant difference in outcomes.[6] Hyperglycemia markedly increases the virulence of COVID-19 as compared to other respiratory viruses such as H1N1 influenza and respiratory syncytial virus (RSV)[99] which could account for the rapid rate of deterioration. In addition, early glucose control could improve the effectiveness of antiviral agents. Dexamethasone and remdesivir treatment protocols have been used in those with severe disease after a prolonged course.[4,9] The authors of the remdesivir trial concluded: "However, given high mortality despite the use of remdesivir, it is clear that treatment with an antiviral drug alone is not likely to be sufficient. Future strategies should evaluate antiviral agents in combination with other therapeutic approaches or combinations of antiviral agents to continue to improve patient outcomes in Covid-19."[4]

Conclusion

The use of closed-loop automated glucose control in intensive care could reduce mortality while limiting the workload and exposure of healthcare workers. The use of advanced technology could significantly alter outcomes in the critically ill during the COVID-19 pandemic. It can be effective in patients critically ill with both COVID-19 and non-COVID conditions. There are limitations in this review using the estimates of reduced mortality. These estimates are based on data from the US CDC and peer-reviewed studies but the actual data is unknown. Other limitations are related to the device itself. This includes the ability to integrate the components rapidly into a functional device and scalability over a large number of hospitals. The development of such a system in the United States could require the efforts of the Biomedical Advanced Research and Development Authority (BARDA), the FDA, and healthcare industry in partnership as was done in the manufacture of ventilators, vaccines, and protective equipment. While individual components have been discussed, an approved closed-loop system has yet to be completed and evaluated. A significant unaddressed risk factor for mortality in COVID-19 is hyperglycemia, and the development of a closed-loop glucose control system could have a major impact on outcomes in COVID-19.

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