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A pilot study of continuous glucose monitoring in critically ill patients: Do they perform well enough for use in glycaemic control?

Matthew Signal*. Liam Fisk, Geoffrey M. Shaw*** and J. Geoffrey Chase******

**University of Canterbury, Christchurch, New Zealand,*
(e-mail: matthew.signal@canterbury.ac.nz)
***University of Canterbury, Christchurch, New Zealand,*
(e-mail: liam.fisk@pg.canterbury.ac.nz)
**** Department of Intensive Care, Christchurch Hospital, New Zealand,*
(e-mail: geoff.shaw@cdhb.health.nz)
***** University of Canterbury, Christchurch, New Zealand,*
(e-mail: geoff.chase@canterbury.ac.nz)

Abstract: Glycaemic control (GC) in the intensive care unit (ICU) has proven difficult and contentious. Continuous glucose monitors (CGM) have been mooted as a solution to provide better control with less clinical effort. The aim of this study was to assess the reliability of CGM devices in critically ill patients, as well as the impact of device type (inter-device) and sensor location (inter-site) on performance. Ten patients were enrolled in this pilot trial and each patient was monitored using 3 concurrent CGM devices: a Medtronic Guardian real-time on their abdomen and Medtronic iPro2 recorders on their abdomen and thigh. The Guardian real-time had an overall MARD of 24%, compared to ~12% for the iPro2 devices. Bland Altman plots showed Guardian SG errors were associated with BG level, but iPro2 SG errors were not associated with BG level. Inter-device SG discrepancies were larger than inter-site discrepancies, when comparing concurrent data and CGM device type, or calibration method, tends to have a larger impact on SG accuracy than sensor location. Three case studies showed several interesting findings regarding CGM behaviour in critically ill patients. CGM devices are capable of performing very well in critically ill patients, but certain illnesses/conditions, as well as drugs/therapies may impact SG data. These factors require further investigation before CGMs can be implemented as standard clinical practice and/or for GC.

1. INTRODUCTION

Hyperglycaemia in intensive care units (ICU) is a prevalent and much debated problem. Glycaemic control (GC) has been mooted as a means to reduce the risk of mortality with some success (Chase et al., 2008, Krinsley, 2004), but has also served to increase the risk of hypoglycaemia and associated mortality (Finfer and Delaney, 2008). What is known is that glycaemic level and variability are each independently associated with increased risk (Egi et al., 2006, Krinsley, 2008), and safe, effective GC has proven difficult.

A major limiting factor in providing effective GC is the burden of relatively frequent blood glucose (BG) measurements (Carayon and Gurses, 2005, Holzinger et al., 2005). Equally, different measurement rates confound comparisons between studies, especially when calculating variability metrics. As a result, continuous glucose monitoring (CGM) devices have been considered as a possible solution for enabling better GC, and better understanding of the evolution and variability of glycaemia in the critically ill (De Block et al., 2006, Price et al., 2008).

However, several issues remain to be addressed. In particular, certain illnesses, medications or therapies that are common in the ICU could potentially affect sensor performance. In addition, the type of sensor and its calibration may also play a role, as some CGM devices do not provide data in real-time, and instead utilize a retrospective calibration scheme. Finally, device location may play a role, particularly as the commonly used abdominal site may not be available for some critically ill patients. Hence, there is a significant need to understand the accuracy of CGM devices, and the impact of sensor location and calibration in these cohorts.

This study presents initial results from an analysis of CGM device reliability in critically ill patients, and the impact of both sensor calibration and sensor location. Each of these factors is assessed independently using multiple sensors in each patient, with both retrospective and real-time calibration. The overall goal is to better understand the variability induced by these factors, and their potential clinical impact in use for GC.

2. METHODS

2.1 Subjects

This study uses data from an ongoing investigation of CGM in patients admitted to the Christchurch Hospital ICU. This preliminary analysis uses CGM and BG data from 10 patients who were recruited into the study. All patients were recruited

by a physician in the ICU and informed written consent was obtained from the next of kin if the patient was unable to consent. Inclusion criteria were two consecutive BG measurements greater than 8mmol/L, indicating the need for insulin therapy using the STAR protocol (Evans et al., 2012). Exclusion criteria were an anticipated ICU admission period of less than 3 days. This study and use of data was approved by the Upper South A Regional Ethics Committee, New Zealand. Table 1 shows the patient demographics.

Table 1. Patient demographics

Patients	10
Age (years)	51 [39 - 64]
Sex (M/F)	5/5
APACHE II	24 [17 - 27]
APACHE III	85 [52 - 99]
SAPS II	52 [30 - 59]
LOS (days)	20 [10 - 33]
Outcome (L/D)	6/4
Diabetes (None/T1/T2)	10/0/0

2.2 Continuous Glucose Monitoring

Each participant in the study was monitored concurrently using 3 CGM devices for a period of up to 6 days. Two sensors were located on the patient's abdomen, one of which was connected to a Medtronic Guardian Real-Time monitor (Medtronic Diabetes, Northridge, CA) and the other connected to a Medtronic iPro2 recorder (Medtronic Diabetes, Northridge, CA). The third sensor was located on the patient's thigh and was connected to a second Medtronic iPro2 recorder. This configuration allowed comparison between different devices and sensor locations within each subject. Medtronic Enlite sensors were used with both types of CGM device. It should be noted that these CGM devices and sensors were not designed for use in the ICU and they were being assessed off label in this study.

One significant difference between the two CGM devices are the calibration algorithms, which use independent BG measurements to convert the raw sensor current (ISIG) into a series of sensor glucose (SG) values for the user. The iPro2 devices store the sensor signal information internally and are retrospectively calibrated. Retrospective calibration allows the calibration algorithm to use information both before and after the time point of interest to obtain an optimal calibration to each reference point. In contrast, the Guardian CGM device displays a glucose value in real time and the calibration algorithm can only use prior data for calibration, but it thus enables real-time glycaemic management.

Calibration BG measurements were obtained by specifically trained ICU nurses at least 3 times per day, (Minimed, 2006). A blood sample was drawn from the patient's arterial line and a blood gas analyser (BGA - ABL90 FLEX, Radiometer, Copenhagen) was used to determine the glucose concentration. This value was immediately entered into the Guardian Real-Time device and then recorded for retrospective calibration of the iPro2 devices.

2.3 Intermittent BG monitoring

In addition to BG measurements used for calibration of CGM data, each patient had intermittent BG monitoring every 1-3 hours for GC. STAR requires, on average, 12-14 BG measurements per day to guide insulin/nutrition therapy. In this study, BG measurements were determined using Super Glucocard II (Arkray, Japan) glucose meters, by the ICU nurses. Several patients had additional BG measurements determined using Nova Statstrip (Nova Biomedical, Waltham, MA, USA) and/or Roche Accu-chek Inform II (F. Hoffmann-La Roche Ltd, Basle, Switzerland) hospital grade glucose meters, which actively measured and adjusted for haematocrit level. Occasionally, a single blood sample was distributed across multiple BG meters to assess precision and in those cases the median value was used as the 'true' BG. All meter BG measurements collected were distinctly separate to BG measurements used for CGM device calibration, giving an independent comparator for CGM data.

2.4 Analyses

CGM data were stratified into 3 subsets by CGM device type and sensor location to allow comparison between the three combinations: Guardian abdomen (Ab.), iPro2 Ab. and iPro2 thigh (Th.). Overall accuracy of SG data in each subset was quantified using mean absolute relative difference (MARD). In addition, Bland Altman plots were produced to show how SG errors were associated with glucose level. Cumulative distribution functions (CDFs) were used to show the overall inter-site and inter-device discrepancies in SG data. Finally, 3 sets of BG and SG data were selected as case studies show interesting aspects of CGM behaviour in critically ill patients.

3. RESULTS

3.1 Overall cohort

The overall results from the analysis of BG and SG data are shown in Table 2. The BG results show that intermittent BG measurements were taken frequently in this study, with a median interval of 1.5 hours. The median [IQR (inter-quartile range)] BG levels were 6.9 [6.2 – 7.6] mmol/L, showing that the STAR protocol controlled BG to a normal level.

The lower section of Table 2 shows results for each combination of CGM device and sensor location assessed in this study. All of these subsets have good CGM duration, with most data sets containing more than 3 days of data. For majority of patients, SG data was calibrated at least every 8 hours, and between calibration BG measurements, reference BG measurements were taken every ~1.8 hours. Overall, the median [IQR] results reported by SG data were very similar to those results reported by BG data. Assessing the overall accuracy SG data, the MARD for the Guardian device in the abdomen was 24%, compared to ~12% for the two iPro2 data sets.

Table 2. BG and CGM results

BG results			
Number of patients	10		
BG interval (hours)	1.5 [0.9 - 2.3]		
Blood glucose (mmol/L)	6.9 [6.2 - 7.6]		
CGM results	*Guardian - Ab.*	*iPro2 - Ab.*	*iPro2 - Th.*
Number SG Data sets	10	10	10
Duration of CGM (days)	4.8 [3.0 - 6.0]	4.8 [2.8 - 6.0]	5.3 [3.0 - 6.0]
Cal BG interval (hours)	7.5 [5.1 - 8.2]	7.5 [3.6 - 9.0]	6.3 [3.0 - 8.1]
Ref BG interval (hours)	1.8 [1.0 - 2.8]	1.7 [1.0 - 2.7]	1.8 [1.0 - 2.8]
Sensor glucose (mmol/L)	6.9 [5.9 - 8.1]	6.7 [6 - 7.4]	6.7 [6.1 - 7.3]
MARD (%)	24.0	11.8	12.4

The Bland Altman plots in Figure 1 show how SG error changes with glucose level. The top subplot shows data from the abdomen Guardian CGM device. The overall mean error is 0.2 mmol/L, but the 95% confidence bounds are at -4.2 and 4.4 mmol/L, suggesting error can be relatively large for this device when monitoring critically ill patients. At lower BG levels the Guardian CGM had a tendency to read low and at high BG levels it had a tendency to read high, shown by the positive slope in the scattered data. The middle and bottom Bland Altman plots show data from the abdomen iPro2 and thigh iPro2 CGM devices, respectively. Both SG data sets have an overall mean error close to zero and the 95% confidence intervals are much tighter than that of the abdomen Guardian real-time device. There appears to be no association between SG error and glycaemic level in iPro2 data.

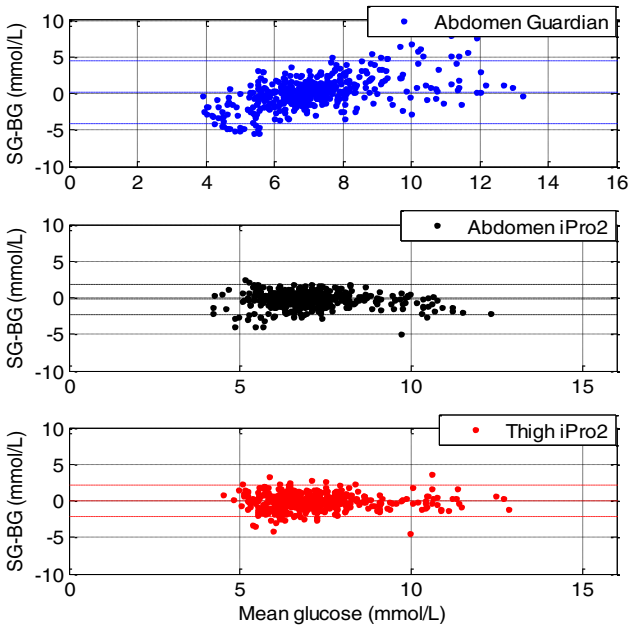

Fig. 1. Bland Altman plots for the three CGM variations

Figure 2 shows two CDF plots, one for inter-site discrepancies in SG data and one for inter-device discrepancies in SG data. At the time of every 5-minute SG measurement, inter-site discrepancy was calculated as thigh iPro2 SG - abdomen iPro2 SG and inter-device discrepancy was calculated as abdomen Guardian SG - abdomen iPro2 SG. The inter-site CDF is steep and narrow suggesting good agreement between the two CGMs, irrespective of sensor location. Conversely, the inter-device CDF is flatter and wider, suggesting the type of CGM device, or calibration method, has a larger impact on SG data. The 5th to 95th percentile interval for inter-site is 3.2 mmol/L, compared to 6.1 mmol/L for inter-device, reinforcing that CGM device type has a substantially larger impact on SG discrepancies.

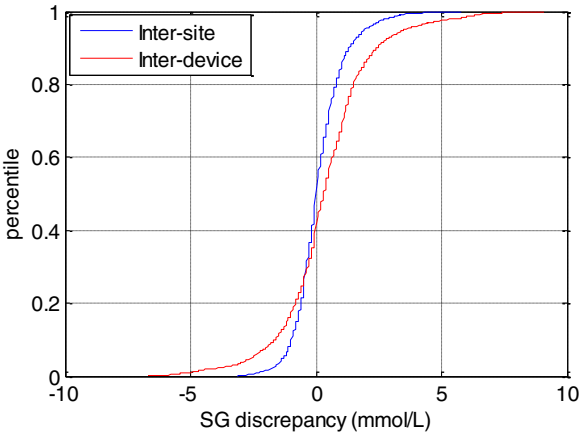

Fig. 2. Inter-site and inter-device discrepancies between SG data. Inter-site discrepancies were calculated as thigh iPro2 SG - abdomen iPro2 SG and inter-device discrepancies were calculated as abdomen Guardian SG - abdomen iPro2 SG

3.2 Individual patient case studies

This study had the unique opportunity to observe several interesting characteristics of CGM behaviour in critically ill patients and 3 case studies are presented in this section. First, Figure 3 shows an example of 3 CGM devices working very well in the critical care setting. During the first ~24 hours of monitoring there was some mismatch between the SG data, but for the remainder of monitoring the SG traces were almost overlapped. This particular patient was an otherwise healthy spinal injury patient with little or no oedema and no signs of sepsis. The CGM devices tracked glycaemic trends well and the Guardian Real-Time device would have provided useful real-time data at the bedside for nurses.

Figure 4 shows SG and BG data collected from a patient with severe oedema. This patient had an estimated 18 litres of additional fluid onboard during the first few days of monitoring, with most of it in the abdominal region. Due to the additional fluid, the simple process of inserting each sensor was made difficult and the first sensor to be inserted in the abdomen failed to adhere to the skin, due to fluid constantly seeping from the insertion site. This sensor was replaced and the other two sensors, one in the abdomen and one in the thigh, were inserted successfully. However, after 2-3 hours, one of the abdominal sensors failed and had to be removed early. Thus Figure 4 contains only two complete SG data sets. It should be noted that this was the only patient in the study to have a sensor adhesion failure.

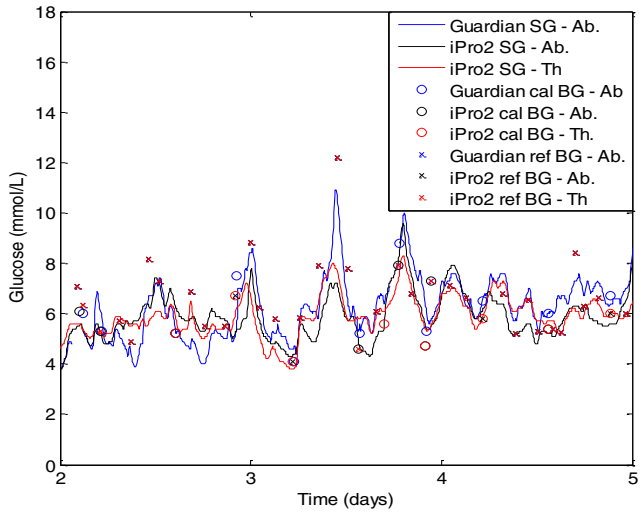

Fig. 3. Three CGM devices monitoring a patient with excellent inter-device/site agreement.

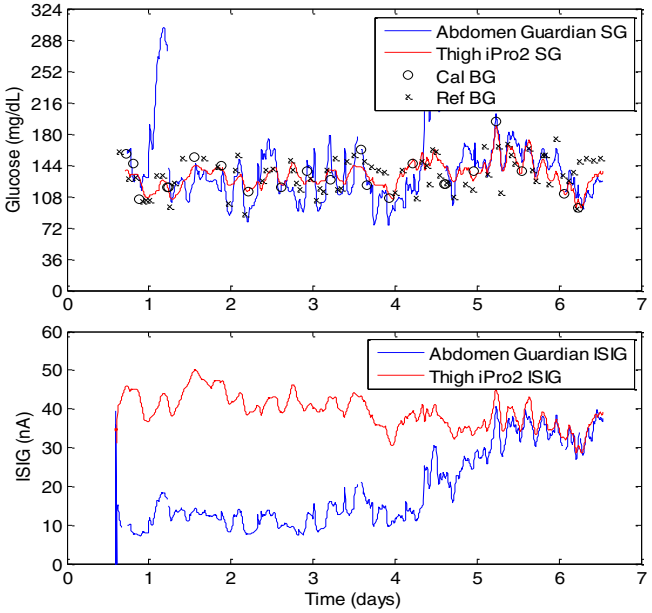

Fig. 4. SG and ISIG data from two CGM devices monitoring a patient with severe oedema

The top subplot of Figure 4 shows SG and BG data collected throughout the monitoring period. Abdominal Guardian SG data is much more variable than the Thigh iPro2 SG data during days 1-4. After day 5, both SG traces reported similar trends in glycaemia. The bottom subplot shows the raw sensor signal, or ISIG, for each CGM device over the monitoring period. The ISIG data shows a clear separation in sensor sensitivity, or glucose availability, over the first 4 days of monitoring. The abdominal sensor current was typically in the region of 10-20nA, compared to the thigh sensor which was between 30-50nA. However, during day 5, the abdomen ISIG rose to the level of the thigh ISIG and for the remainder of the monitoring period both sensors reported similar dynamics in the region of 30-40nA.

Figure 5 shows two examples of large step increases in sensor current and how they appear in the SG data after calibration. The top subplot shows SG data and the bottom subplot shows ISIG data. The box labelled 'A' in Figure 5 illustrates a step increase in the abdominal Guardian ISIG data from ~20nA to ~40nA. In this instance, the real-time calibration algorithm amplified the step causing the SG data to rise from 4.7 mmol/L to above 12.2 mmol/L. At around 1.9 days when the Guardian device was next calibrated, the algorithm detected the SG was too high and adjusted it to the correct level. The box labelled 'B' shows a similar rise in the thigh iPro2 ISIG from ~20nA to ~35nA. However, the retrospectively calibrated thigh iPro2 SG only increased from 4.5 mmol/L to 7 mmol/L and no further adjustments were made at the next calibration at ~3.4 days. Note, there are a few gaps in Guardian SG data, caused by dropouts in wireless communication between the monitor and the sensor.

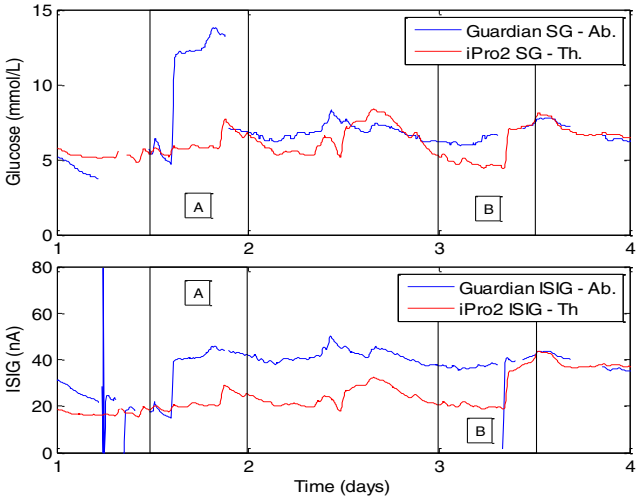

Fig. 5. Examples of un-physiological 'step' increases in ISIG and their appearance in SG

4. DISCUSSION

The interim results presented in this study give a good indication of expected CGM performance in the ICU, while highlighting several aspects that require further investigation.

4.1 Overall cohort

The results in Table 2 show that glycaemia was monitored closely during the study, by intermittent BG measurements and CGM, with both methods producing similar overall glycaemic results. In terms of CGM accuracy, the MARD for the Guardian SG data was approximately twice the MARD of iPro2 SG data, irrespective of whether the iPro2's sensor was located in the abdomen or thigh. This result strongly suggests that the accuracy of the device, in terms of MARD, is dependent on device type, or more likely, calibration algorithm.

The Guardian uses a real-time calibration algorithm that must adjust the 'calibration factor' using only prior data. Thus, any

disturbances that might induce error at the time of calibration could result in substantial inaccuracies in SG data until the time of next calibration. Conversely, the iPro2 is calibrated retrospectively, so one would expect the same disturbances to have less impact on the overall accuracy, as future calibration BG values are known. Overall, the MARD values presented here are all in the region of reported MARD for CGM in outpatients, where the devices were designed to be used (Kovatchev et al., 2008, Larson and Pinsker, 2013), indicating that they otherwise performed as might be expected despite the different cohort.

Despite the relatively high MARD of the Guardian SG data, the clinical impact of those errors was determined to be minor. A Clarke Error Grid analysis of paired SG and reference BG data showed that 99.1% of the points fell in zones A and B, which would not lead to inappropriate treatment. Furthermore, no points fell in the clinically dangerous regions D and E. The same analysis of iPro2 SG data showed similar clinical results, with 100% of points in zones A and B. However, compared to the Guardian analysis, there were a higher proportion of points in zone A for both iPro2 data sets.

The Bland Altman plots in Figure 1 highlight another interesting difference in the error characteristics of each CGM device type. The Guardian SG error appears to be associated with BG level, but the iPro2 error appears independent of BG level. At low BG levels the Guardian tended to report under the true value and at high BG levels it tended to over report glycaemia. Interestingly, there have been reports of associations between CGM error and BG level, but they typically show the CGM to report high at lower BG levels and low at higher BG levels (Beardsall et al., 2013). A larger data set is required from patients that cover a wider range of glycaemia before the association observed in this study can be confirmed. Patients on the STAR protocol are generally very well controlled (89% of BG measurements in 4.4-8 mmol/L and 0.9% < 4 mmol/L) so it is difficult to conclusively assess error characteristics during hypoglycaemia or hyperglycaemia.

To determine the impact of inter-site and inter-device variations on the data produced by CGM devices, SG data from one device were compared directly to SG data from another, over the entire monitoring period. Figure 2 shows that the discrepancy in SG data between two different devices is generally much more significant than the discrepancy in SG data due to sensor location. Again, this outcome is likely due to the calibration scheme used, as in this study the sensor technology for all three CGM devices was the same. Without an accurate reference BG measurement every 5 minutes, it is impossible to determine the true underlying BG level. However, the true BG is likely some combination of the SG data produced by all three CGM devices.

4.2 Individual patient case studies

Three case studies are presented in this manuscript, to show some of the interesting observations in data collected from the first 10 patients of this study. First, as shown in Figure 3, CGM devices are capable of working very well in critically ill patients. However, there are still several questions that need to be answered before they are implemented as normal clinical practice, such as:

- Which patients stand to benefit from CGM?
- What conditions/drugs/therapies (if any) have a negative effect on sensor performance?
- What are the performance characteristics of CGM in the ICU and how can data be utilized?

Fortunately, several researchers have already started asking these questions, among others, in an effort to improve healthcare for critically ill patients (Kovatchev et al., 2008, Roberts et al., 2012).

Second, as shown in Figure 4, it is possible that severe oedema could have an effect on sensor performance. While the data in Figure 4 represents evidence from a single patient in this study, it still presented an interesting case study from a topic that has not been thoroughly investigated. The main focus for this discussion is the ISIG produced by each sensor. The ISIG produced by the abdominal sensor is much lower than the ISIG produced by the sensor in the thigh, where there is much less excess fluid. Interestingly, after a few days of monitoring as the patient's condition improved and excess fluid was removed, the ISIG from the abdominal sensor rose to the level of the iPro2 ISIG. In addition, for the remainder of monitoring the ISIG from both sensors tracked each other well. However, these observations could have been due to other factors such as the sensor itself, drugs/therapies, and these other factors cannot be ruled out by this study. Further investigation with a larger cohort containing patients with severe oedema is required to determine whether or not it has an effect on sensor performance.

Third, as shown in Figure 5, it is possible for spurious, non-physiological changes in the ISIG data to occur without warning. In addition, the way these 'step changes' appear in SG data is dependent on the calibration algorithm used. In box 'A' of Figure 5, the 20nA increase in ISIG caused a ~7.8 mmol/L increase in SG data, whereas in box 'B', a 15nA increase in ISIG only caused a ~2.5 mmol/L increase in SG data. In box 'A', the rise occurred in the sensor that was monitored by the Guardian real-time CGM. As previously mentioned, the Guardian algorithm could only prior data to estimate the calibration factor which converted ISIG data into SG data. Consequently, the calibration factor remained fairly constant at approximately 0.31, both before and after the rise in ISIG. It was not until next calibration BG was entered 6 hours later that the calibration factor was reduced to 0.17.

Conversely, the rise in ISIG shown in box 'B' of Figure 5, occurred in a sensor connected to an iPro2 with a retrospective calibration scheme. Therefore, at the time of the rise in ISIG, the calibration algorithm used future data to determine that the calibration factor should be reduced from 0.24 to 0.18. This adjustment prevented the SG data from rising significantly above reference BG measurements. These two examples clearly illustrate one of the major tradeoffs between real-time and retrospective calibration of SG data.

Finally, in Figure 5, there are several drop outs of ISIG to ~0nA in the sensor that was connected to the Guardian CGM device. These drop outs are frequently observed at the start of monitoring when a voltage is first applied to the sensor. It is possible that a loose connection between the sensor and transmitter could have caused the dropouts in ISIG later in the monitoring period. Fortunately, the calibration algorithms recognize that these dropouts are unusual and omit SG data.

4.3 Limitations

There are three main limitations to this study that need to be addressed. First, this study uses BG and CGM data from a relatively small cohort of 10 critically ill patients. These patients are broadly representative of the patients admitted to Christchurch ICU, but a larger study is required to provide conclusive evidence regarding the results presented here. Second, patients on the STAR GC protocol tend to remain in the 4.4-8 mmol/L glycaemic band, and consequently, a wide range of BG levels are not included in this cohort. Again, a larger study with a more broad population, potentially from multiple centres, would likely provide the data required to assess CGM characteristics in hypoglycaemia and hyperglycaemia. Third, it was not possible in this study to have a high accuracy reference BG measurement from a YSI or blood gas analyzer taken every 5-15 minutes, as this was a pilot study done in the unit as observed. Thus, we cannot conclude whether all large rises/falls in SG were due to glycaemia or sensor artefacts.

5. CONCLUSIONS

This study used CGM and BG data from 10 patients to assess the reliability of CGM in critically ill patients. Overall cohort results and three case studies were used to show several important findings from this study to date. First, CGMs devices can monitor certain patients with a high degree of accuracy, but some illnesses, drugs and therapies might affect sensor performance. Second, severe oedema could potentially affect sensor performance, but further investigation is required to confirm this. Third, CGM device type can have a significant effect on the accuracy of SG data, but sensor location tends to have less impact.

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