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in Hospitalized Patients with Diabetes and Stress Hyperglycemia

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14. ABSTRACT period Regulatory approvals have been obtained and updated from the University's IRB, Army's HSRRB, and FDA (approved IDE) to study the Telemetry Glucose Monitoring System (TGMS) and Vascular Glucose Monitoring System (VGMS) in 12 diabetic patients undergoing major surgery. Study investigators, anesthesiologists, surgeons, research nurses, technicians, and clinical nurses were educated and trained to manage the sensors and collect the required blood samples and clinical data safely. There were significant delays in initiating patient recruitment due to the regulatory approval process and technical problems at Medtronic MiniMed supplying sterile VGMS sensors. We received sterile sensors from Medtronic 11/23/05 and recruited the first diabetic study subject (A2) on 11/28/05. Six TGMS sensors and one VGMS sensor were implanted 1 hour before surgery. Reference blood samples were obtained approximately every 20 minutes from a radial artery (RA) catheter, every 60 minutes from central venous (CV) and RA catheters, and every 3 hours from a capillary fingerstick, CV, and RA catheters. Blood samples were analyzed for glucose, lactate, pH, PaO2, PaCO2, SaO2, hemoglobin, and electrolytes. Plasma samples were frozen for subsequent measurement of insulin and fatty acid levels. In general, all 7 sensors functioned well throughout the 60 hours of data collection. The 7 sensor output signals moved in parallel over a wide range of BG values (63 mg/dl to 218 mg/dl) and clinical situations (Figures 1-3). Technical issues that caused two brief s of sensor data loss have been resolved. Analysis of sensor, glucose, vital sign, and other blood analyte data is ongoing.					
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Table of Contents

Cover	1
SF 298	2
Introduction	4
Body	5
Key Research Accomplishments.....	9
Reportable Outcomes	9
Conclusions.....	9
References.....	9
Appendices	9

Introduction

The overall goal of the research effort is the clinical application of an automated glucose monitoring and insulin delivery system (artificial endocrine pancreas) capable of tightly controlling the levels of glucose and insulin in the blood of hospitalized patients with diabetes and stress induced hyperglycemia. Near-normal glucose control in the hospital setting has been linked to improved outcome (decreased hospital stay, decreased chance of infection and death, and increased wound healing). The current research will evaluate two real-time glucose-monitoring systems (under development by Medtronic MiniMed) in the perioperative setting, as a possible input signal for an in-hospital artificial endocrine pancreas.

The immediate goal of the research is to evaluate the safety and efficacy of two glucose monitoring technologies when applied to human subjects in the hospital environment. The Telemetered Glucose Monitoring System (TGMS) and the Vascular Glucose Monitoring System (VGMS), manufactured by Medtronic MiniMed Inc., will be evaluated in ten diabetic patients undergoing major surgery. Prior to surgery, the subject will be brought into the hospital and one (1) VGMS and up to six (6) TGMS sensors will be implanted. The VGMS will be introduced through a central venous catheter and advanced so that the distal tip floats freely within the superior vena cava. The TGMS sensors will be inserted through the skin with the distal tip located within the subcutaneous tissue of the upper arm, thigh, and/or abdomen. Each subject will receive an infusion of intravenous insulin, titrated by their clinical nurse according to frequent BG measurements. Sensor, reference blood, and clinical data will be collected and recorded pre-op, intra-op, and post-operatively for a total of 60 hours. Blood samples will be obtained every 20 minutes from a radial artery (RA) catheter, every hour from a central venous (CV) catheter and RA catheter, and every 3 hours from a fingerstick, CV catheter, and RA catheter. All samples will be assayed for glucose. Arterial blood samples will be assayed for pH, PaO₂, PaCO₂, SaO₂, electrolytes, lactate, hemoglobin, insulin, and fatty acids. In addition to these reference measurements, the research nurse will record changes in infusion rates of IV fluids, changes in body position, patient state (sedated, awake, sleeping, ambulating, etc.), procedure state (pre-op, surgery, post-op), meals (time, duration, size and content), and medications (time, type and dose). This clinical information and blood chemistry data will be used to understand the clinical conditions that occur during nominal sensor function, dysfunction, and failure. Reference blood glucose and sensor data will be used to investigate recalibration requirements for the VGMS and TGMS to achieve a given measurement accuracy. In addition, methods to improve measurement accuracy using multiple sensors will be explored using the reference blood glucose and TGMS sensor data.

Body

The project to evaluate the Telemetry Glucose Monitoring System (TGMS) and Vascular Glucose Monitoring System (VGMS) in diabetic surgical patients was initiated 02/01/04. Significant effort was required to obtain regulatory approval from Thomas Jefferson University's Institutional Review Board (IRB), The Department of the Army Human Subject Research Review Board (HSRRB), and the Food and Drug Administration (FDA). The principal investigator received an approved Investigational Device Exception (IDE) on 08/16/04, IRB approval on 12/28/05, and HSRRB approval on 01/07/05. The study was approved for one site Thomas Jefferson University (TJUH) and 12 subjects.

We received sterile TGMS and five VGMS sensors from Medtronic MiniMed on 03/15/05 and started patient recruitment. Unfortunately, the VGMS sensors supplied by Medtronic had an expiration date of 04/12/05, only four weeks after receipt of the shipment. We were not able to recruit a study patient during this period of time. The Principal Investigator received multiple reassurances from senior management of Medtronic MiniMed that sterile VGMS sensors would be delivered in a timely fashion. The initial Medtronic delay with supplying VGMS sensors seemed to be related to maintenance on the equipment required to sterilize the sensors. Further delays occurred as Medtronic performed a detailed systematic study to validate that re-sterilization of the original VGMS sensors did not affect performance.

In this time period, the co-investigators developed additional expertise using the sensors and data collection computers in the laboratory setting. We also recruited and trained an additional 14 nurses and technicians to maintain a detailed patient diary, collect the blood/urine specimens according to protocol, and analyze the specimens at the bedside using the study reference device (OMNI 9, Roche Diagnostics). The principal investigator met with approximately 25 surgeons and their office staff to facilitate study subject recruitment. He also met with physicians and staff of the Same Day Surgery Admission Unit to facilitate study subject recruitment. Significant time and effort has been required to maintain the OMNI 9 reference blood analyzer on a daily basis.

TJU received 10 re-sterilized VGMS sensors from Medtronic MiniMed on 11/23/05. We were surprised and dismayed that the expiration date on the 10 VGMS sensors was 01/15/06. This short shelf life also conflicted with patient and investigator schedules due to the holiday season.

The first study subject (A2), a type 2 diabetic patient on insulin, was recruited on 11/28/05 and admitted to the hospital on 12/05/05, through the Same Day Admission Unit. She was transported to an isolated area of the Post Anesthesia Care Unit (PACU) and an intravenous catheter was inserted into a peripheral vein using aseptic technique. The patient was given oxygen via nasal cannula and mildly sedated with Midazolam. Catheters were inserted into the patient's radial artery and internal jugular vein using aseptic technique. The VGMS sensor was easily inserted through the central venous catheter, with the distal tip advanced into the superior vena cava. The proximal end of

the VGMS sensor was connected to an extension lead and transceiver to initiate blood glucose data recording. The distal tip of three TGMS sensors were inserted through the skin into the subcutaneous tissue around the T- 10 to T-11 region of the upper abdomen, using aseptic technique. An addition three TGMS sensors were inserted into the upper arm region using aseptic technique. Each TGMS sensor was attached to a transmitter to initiate interstitial fluid (ISF) glucose data recording. Sterile adhesive bandages were applied. All seven sensors provided an estimate of the patient's blood or ISF glucose concentration once every minute. Blood samples were obtained from the radial artery catheter, central venous catheter, and via fingerstick, and assayed for glucose and a variety of other analytes.

The patient was transported to the operating room under the care of the clinical anesthesiologist, gynecological surgeon, and plastic surgeon to remove a large uterine tumor (benign) and abdominal wall pannus. The anesthesiologist managed the patient's diabetes by titrating continuous intravenous infusions of insulin and glucose. The uterus and pannus were removed over a 6 hour period without incident. The patient's trachea was extubated in the OR and she was transferred to the Surgical Intensive Care Unit (due to the extensive surgery and history of cardiovascular complications). Approximately 10 minutes after arriving in the ICU, the clinical nurse anesthetist and ICU nurse gave the patient an intravenous dose of narcotic to relieve pain. Apparently, the patient developed respiratory depression followed by hypoxemia and bradycardia. She was rapidly ventilated with oxygen by bag and mask and given atropine, followed by tracheal intubation and mechanical ventilation. This adverse event (AE) was immediately reported in writing to the IRB, HSRRB, and the FDA. It was determined by the principal investigator and study monitor that the AE was related to clinical care, and was not related to the study devices or protocol.

The patient remained stable on the ventilator over night and was easily extubated on the following morning. Tissue oxygenation and perfusion were typical for a post-operative patient. The clinical nurse adjusted the rate of intravenous insulin and glucose delivery according to frequent blood glucose measurements. Two small doses of 50% glucose were delivered by the clinical nurse during the 60 hour protocol to treat asymptomatic hypoglycemia (BG < 70 mg/dl). Reference arterial blood glucose levels were maintained within the 63 mg/dl to 218 mg/dl range. The radial artery catheter was removed on the morning of post-op day # 2 due to difficulty withdrawing blood and the hint of inadequate little finger perfusion. The catheter was removed to error on the side of safety. The patient was transferred to the Intermediate Surgical Care Unit on post-op day # 2. After 60 hours of data collection, the central venous catheter and VGMS were removed from the internal jugular vein without incident. The six TGMS sensors were removed from their subcutaneous position without incident. The skin was cleaned and sterile bandages were applied. The patient recovered from surgery in the typical fashion and was discharged to home by the Gynecological surgeon on post-op day # 4.

After an initial period of stabilization, all seven sensors functioned well throughout the 60 hours of data collection. Sensor data (six TGMS and one VGMS) and reference glucose data are summarized in Figures 1 through 3. The output signal from the seven

sensors moved in parallel over a wide range of BG values and clinical conditions. TGMS sensor data could not be collected for two brief periods of time due to technical issues with the computer's power supply. Reference blood analyte data could not be collected for one period of time due to obstruction within the OMNI 9 blood pathway. Plasma samples were frozen and will be assayed for insulin and fatty acid levels in the near future. Analysis of sensor, glucose, vital sign, and other blood analyte data is ongoing.

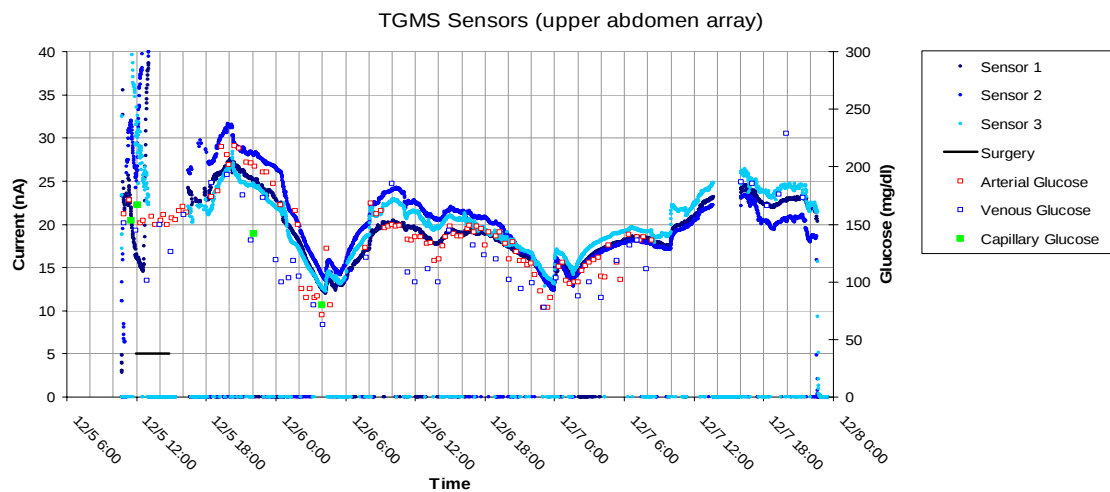


Figure # 1: Output signals from three TGMS sensors implanted in the upper abdomen of patient A2 in relation to arterial, venous, and capillary reference blood glucose measurements.

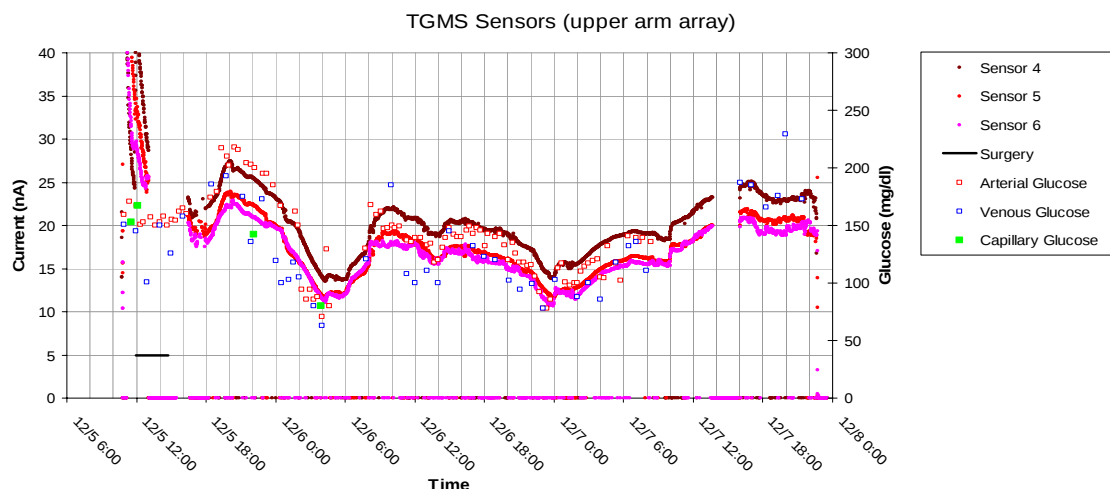


Figure # 2: Output signals from three TGMS sensors implanted in the upper arm of patient A2 in relation to arterial, venous, and capillary reference blood glucose measurements.

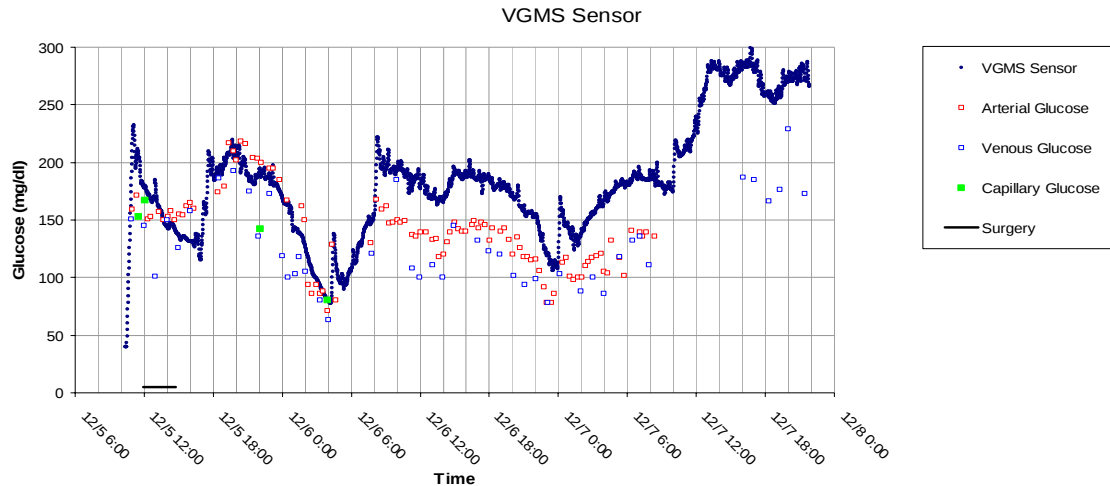


Figure # 3: Corrected output signal from VGMS sensor implanted within the superior vena cava of patient A2 in relation to arterial, venous, and capillary reference blood glucose measurements.

Although the patient recovered well from the surgical procedure, she was admitted to a local hospital two weeks post-operatively to treat a seizure. The principal investigator was told by the patient's primary care physician that she was non-compliant taking her Dilantin for a chronic seizure disorder. She remained seizure free in the hospital while taking Dilantin to increase blood levels. This adverse event (AE) was immediately reported in writing to the IRB, HSRRB, and the FDA. It was determined by the principal investigator and study monitor that the AE was related to clinical care, and was not related to the study devices or protocol.

Issues related to the computer's power supply and OMNI 9 maintenance have been resolved. We were unable to recruit a second study patient over the holidays, before expiration of the VGMS shelf-life and are currently without sterile VGMS sensors. The Medtronic MiniMed study coordinator suggested the possibility of another 3 to 6 month delay to re-sterilize the VGMS sensors and verify sensor performance.

Therefore, the principal investigator has been forced to proceed with the project utilizing the six TGMS sensors, in relation to arterial, venous, and capillary reference glucose measurements. The necessary documents have been prepared to modify the protocol and consent form. A 12 month no-cost time extension has been obtained so we can complete data collection and analysis on the last 9 patients. We are not sure if Medtronic will supply additional sterile VGMS sensors before completion of the study.

Key Research Accomplishments

- Received full regulatory approval from Thomas Jefferson University's Institutional Review Board (IRB), The Department of the Army Human Subject Research Review Board (HSRRB), and the Food and Drug Administration (FDA-approved IDE).
- Evaluated TGMS and VGMS sensors in the laboratory to optimize methods of data collection, recording, and analysis.
- Study investigators, anesthesiologists, surgeons, research nurses, technicians, and clinical nurses were educated to the protocol and trained to manage the sensors, collect the blood samples, clinical data, and manage the OMNI 9 reference blood analyzer.
- Developed an efficient system for outpatient and inpatient study subject recruitment, utilizing the Same Day Admissions Unit staff, surgeon's office staff, and faculty/resident physicians from the Departments of Anesthesiology, Surgery, and Endocrinology.
- Correlated OMNI9 (bedside reference analyzer) measurements with Thomas Jefferson University Hospital clinical laboratory measurements.
- Recruited and studied first human subject utilizing six TGMS sensors and one VGMS sensor for 60 hours. In general sensors functioned well with the 7 output signals moving in parallel over a wide range of BG values (63 mg/dl to 218 mg/dl) and clinical situations.
- Currently analyzing sensor output signal, reference blood chemistry, and clinical data to determine glucose monitoring efficacy.
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Reportable Outcomes

Preliminary data was presented at the Department of Medicine's (Division of Endocrinology) Grand Rounds at Thomas Jefferson University.

Conclusions

The TGMS and VGMS sensors developed by Medtronic MiniMed for continuous glucose monitoring in the ambulatory patient with diabetes have significant potential to continuously monitor the blood or interstitial fluid glucose levels of hospitalized patients over a wide range of glucose values and clinical situations.

References

No references included in this report.

Appendices

No appendices included in this report.