Title Page

Protocol Cover page

Title:	A Randomized Controlled Trial Comparing Blood Glucose Control Intraoperative Between Insulin Drip vs. Insulin Boluses *(IRB Study # 2023-45)* *IRB Approved Study*
Version Date:	Dated 10 Oct 2024
Version:	Version # 2
Sponsor:	King Faisal Specialist Hospital & Research Centre-Jeddah

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2.0 Protocol Synopsis

TITLE:
A Randomized Controlled Trial Comparing Blood Glucose Control Intraoperative Between Insulin Drip vs. Insulin Boluses

SPONSOR

No sponsor for this study

FUNDING ORGANIZATION

King Faisal Specialist Hospital & Research Center-Jeddah

NUMBER OF SITES

Only (King Faisal Specialist Hospital & Research Center-Jeddah)

RATIONALE:

This randomized controlled trial will provide valuable information on the optimal method for achieving blood glucose control intraoperatively. The results of this study may help improve patient outcomes and reduce the incidence of postoperative complications.

STUDY DESIGN:

Randomized Controlled Trial

PRIMARY OBJECTIVE:

Is to compare blood glucose control intraoperatively between patients who receive insulin drip and patients who receive insulin boluses during adult cardiac surgery.

SECONDARY OBJECTIVES:

Is to evaluate the incidence of hypoglycemic events and the need for insulin adjustments during surgery.

PRIMARY OUTCOME:

rate of severe hypoglycemia

SECONDARY OUTCOME:

-duration of ICU stay
-lactate clearance

-wound infection day 7; and day 30 (clinic follow-up)

NUMBER OF SUBJECTS:

If you assume that 6% of the participants receiving boluses will acquire a wound infection and 1% of the participants receiving insulin drip will acquire an infection, you will need to enroll the following number of participants in your study to detect this difference:

Assuming a two-sided test and an alpha = 0.05, to have power = 80% to detect the difference, you need to enroll 192 participants per group for a total of 384 participants.

SUBJECT SELECTION CRITERIA:

Inclusion Criteria:

- All adult patients (above 18 y of age undergoing Cardiac surgery with preoperative blood glucose level (80 -180 mg/dL)
- Patient with History of diabetes and those taking antidiabietic medications.

Exclusion Criteria:

- Patients with known allergy or insulin intolerance.
- Patients with severe hepatic Dysfunction.
- Patient with History of hypoglycemic events in the past 6 month prior to surgery.

TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION:

Insulin drip will be administered at a starting rate of 2 units/hour and titrated to maintain blood glucose levels between 80-180 mg/dL.

CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION:

Insulin boluses will be administered every 30 minutes to maintain blood glucose levels between 80-180 mg/dL.

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY:

Data will be collected 24 hours before the surgery, then patients will be followed up immediately, one week after, one month, 6 months and one year. Overall study duration is estimated to be 4 years.

CONCOMMITANT MEDICATIONS.

No concomitant medications

EFFICACY EVALUATIONS.

SAFETY EVALUATIONS.

Since both methods of insulin delivery are already in use and FDA approved there is no safety concerns at the time being. However, an interim analysis will be carried out throughout the hospital stay and in each visit in the first postoperative year.

PLANNED INTERIM ANALYSES.

An interim analysis will be carried out throughout the hospital stay and in each visit in the first postoperative year.

STATISTICS. Analysis plan:

Using relative risk for statistical analysis and log rank. A P value of less than 0.05 will be considered statistically significant. Statistical analyses will be carried out using the SPSS or SAS.

Rationale for Number of Subjects:

Sample size calculated basis of a two-sided test and an alpha = 0.05, to have power = 80%. The results will be presented as mean (SD), median (interquartile (range), or proportion.

3.0 Main Protocol

BACKGROUND

General Overview:

Hyperglycemia during surgery has been linked to increased risk of postoperative complications, including wound infections, delayed wound healing, and cardiovascular events. Maintaining blood glucose within a target range during surgery has been shown to reduce the incidence of these complications. Two methods commonly used for maintaining blood glucose control intraoperatively are insulin drip and insulin boluses. However, the optimal method for achieving blood glucose control remains unclear. Therefore, we propose a randomized controlled trial to compare blood glucose control intraoperative between two groups using insulin drip in one group and insulin boluses in the other group.

Methodology

Inclusion criteria:

- All adult Diabetic patients (Both type I & Type II) undergoing Cardiac surgery with preoperative blood glucose level (80 -180 mg/dL)
- Patient with History of diabetes and those taking antidiabetic medications.

Exclusion criteria:

- Patients with known allergy or insulin intolerance.
- Patients with severe hepatic Dysfunction.

- Patient with History of hypoglycemic events in the past 6 month prior to surgery.

Randomization:
Simple randomization will be used for randomization. The participants will be randomized into two groups based on methods of insulin delivery.

- Group A: Insulin drip will be administered at a starting rate of 2 units/hour and titrated to maintain blood glucose levels between 80-180 mg/dL.
- Group B: Insulin boluses will be administered every 30 minutes to maintain blood glucose levels between 80-180 mg/dL.

Insulin boluses will be considered as a control group.

Statistical analysis:
The results will be presented as mean (SD), median (interquartile (range), or proportion. Using relative risk for statistical analysis and log rank. A P value of less than 0.05 will be considered statistically significant. Statistical analyses will be carried out using the SPSS or SAS.

4. SUBJECT SELECTION

4.1. Study Population:

All adult patients (above 18 y of age undergoing Elective Cardiac surgery with preoperative blood glucose level (80 -180 mg/dL)

4.2. Inclusion Criteria:

- All adult patients (above 18 y of age undergoing Elective Cardiac surgery with preoperative blood glucose level (80 -180 mg/dL)
- Patient with History of Both Type I & Type II diabetes and those taking antidiabetic medications.

4.3. Exclusion Criteria:

Patients with known allergy or insulin intolerance.
Patients with severe hepatic Dysfunction.
Patient with History of hypoglycemic events in the past 6 month prior to surgery.

4.4. Treatment

- Group A: Insulin drip will be administered at a starting rate of 2 units/hour and titrated to maintain blood glucose levels between 80-180 mg/dL.
- Group B: Insulin boluses will be administered every 30 minutes to maintain blood glucose levels between 80-180 mg/dL.

4.4.1 Material:

Insulin infusion

4.4.2 Preparation:

The medication will be prepared by the pharmacy

4.5. *Supply of Study Drug at the Site*

Insulin delivery are already in use and FDA approved there is no safety concerns at the time being

4.6. Storage: The hospital pharmacy

5. STUDY PROCEDURE

5.1. Study schedule

All adult patients (above 18 y of age undergoing Cardiac surgery with preoperative blood glucose level (80 -180 mg/dL) Patient with History of diabetes and those taking antidiabetic medications. On admission, all patient will stop all preoperative anti diabetic medications and will be converted to Insulin short acting sliding scale as per protocol according to insulin requirement preoperatively. Patient requiring < 40 unites/ day will receive Low dose Insulin sliding scale, Patient requiring 40-80 unites/ day will receive Medium dose Insulin sliding scale and Patient requiring >80 unites/ day will receive High dose Insulin sliding scale. (Appendix 1)

5.1.1 Schedule of events

All demographic data, diagnosis, procedure (insulin delivery), surgery and hospital course details

Age, Sex, DM, HTN, NYHA class, HbA1C, Pre op FBS, Intraop lactate,Postop lactate, wound scale, BMI, BSA, Preop insulin, CKD, Pre antibiotic, Intraop antibiotic and length of stay will be collected from the day of admission to the day of discharge.

Data will be collected 24 hours before the surgery, then patients will be followed up immediately, one week after, one month, 6 months and one year.

Blood sugar level will be monitored hourly in the first postoperative day and every 4-6 hours during hospital stay.

6. SAFETY ASSESMENTS

Blood sugar level

6.1. Adverse Effects/Events (AEs)

Table 3. AE Relationship to Study Drug

6.1.1 Adverse event reporting period

The period for recording AEs in the CRF begins when signs the ICF and ends at the end of study visit.

6.1.2 Adverse Event Reporting

Both serious and non-serous AEs are to be reported on the AE page of the CRF as specified in the CRF data entry guidelines.

Relationship to Drug	**Comment**
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

The only foreseen adverse may be of the mouthwash giving a bitter taste.

6.2. Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

1. Death
2. A Life-Threatening Adverse Experience
3. Inpatient Hospitalization or Prolongation of Existing Hospitalization
4. A Persistent or Significant Disability/Incapacity
5. A Congenital Anomaly/Birth Defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

6.2.1 Serious Adverse Experience Reporting:

1. Designee investigator(s) will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

2. In accordance with the standard operating procedures and policies of the KFSHRC's Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the investigators will report SAEs to the IRB/IEC.

7. STATISTICAL ANALYSIS:

7.1 Sample size

This study will include a total of 384 adult patients randomly assigned to each arm (192 per arm).

7.2 Definition of study population

All adult patients (above 18 y of age undergoing Cardiac surgery with preoperative blood glucose level (80 -180 mg/dL) Patient with History of diabetes and those taking antidiabetic medications.

7.3 Overall statistical and analytical plan

This study will include a total of 384 adult patients randomly assigned to each arm (192 per arm). Sample size calculated basis of a two-sided test and an alpha = 0.05, to have power = 80%. The results will be presented as mean (SD), median (interquartile (range), or proportion. Using relative risk for statistical analysis and log rank. A P value of less than 0.05 will be considered statistically significant. Statistical analyses will be carried out using the SPSS or SAS.

8. DATA COLLECTION, HANDLING AND RECORD KEEPING

8.1 Case Report Form

All demographic data, diagnosis, procedure (insulin delivery), surgery and hospital course details Age, Sex, DM, HTN, NYHA class, HbA1C, Pre op FBS, Intraoperative lactate, Postop lactate, wound scale, BMI, BSA, Preoperative insulin, CKD, Pre antibiotic, Intraoperative Intraop antibiotic and length of stay will be collected from the day of admission to the day of discharge.

8.2 Source Data

Source documentation is defined as the first time data appear, and may include original documents, data and records (e.g., hospital records, clinical and office charts, procedure reports, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, subject files, and records kept at the pharmacy, at the laboratories). Information in source documents (i.e., medical history/physical condition) dated prior to the Patient Information and Informed Consent Form signature date may be used to verify patient eligibility criteria.

Clinical records must be marked to indicate a subject has been enrolled into the clinical study. The Investigator must ensure the availability of source documents from which the information on the CRFs was derived. Where printouts of electronic medical records are provided as source documents, or where copies of source documents are retained as source documents, they should be signed and dated by a member of the investigational site team indicating they are a true reproduction of the original source document.

Clinical Investigation Plan

The source documents must be made available for monitoring or auditing.Copies of source documents will be requested to support event adjudication.

Data will be collected through ICIS power chart and will be entered into a secured database. A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection, cleaning and validation. Concurrent manual data review will be performed based on parameters dictated by the plan. High quality standards will be maintained, and processes and procedures utilized to repeatedly ensure that the data as clean and accurate as possible when presented for analysis.

8.3 Protocol Deviations

A study deviation is an event where the investigator or site personnel did not conduct the clinical study according to the Clinical Investigational Plan. The investigator is not allowed to deviate from the above-mentioned documents except with prior approval and under emergency circumstances. All deviations shall be documented and explained, regardless the reason for the deviation.

In this study where all patients receive standard hospital care, reporting of deviations is only required in case informed consent cannot be obtained before data entry. No further data should be entered until the issue has been resolved. Failure to obtain consent from the patient to release personal information might ultimately result in removing the patient from the study.

The investigator is obliged to comply with Ethical Committee procedures and/or local laws for reporting deviations.

9. ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

9.1. Investigator Responsibilities

Informed consent is defined as a legally effective documented confirmation of a subject's or their legally authorized/designated representative's voluntary agreement to participate in a particular study after information has been given and explained to the subject on all aspects of the study that are relevant to the subject's decision to participate.

Here and throughout the document, "EC/IRB" is the term that will be used collectively in reference to an Institutional Review Board (IRB), Ethics Committee (EC).

It is the responsibility of the investigator to confirm the approval requirements of the hospital and local regulations for this observational study with his/her EC/IRB prior to start of the study. As a minimum, it is strongly recommended notifying the local Ethics Committee about the conduct of this study.

Patients' confidentiality will be maintained, removing any identifying informations from the data set by the data controller before further usage and analysis. The data of both variables and their values were coded into Alpha-numeric format for concealment with few designated persons having the coding key.

The study will be conducted according to the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines. It will also follow the International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines

Patient engagement and withdrawals:

A participant may withdraw from the study at any time, at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Regulatory and Ethical Considerations:

•This study will be conducted in accordance with the protocol and the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International
- Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations

•The Investigator must submit the protocol, protocol amendments (if applicable), ICF,

and other relevant documents to an IRB/IEC and the IRB/IEC must review and approve them before the study is initiated.

•Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.

•The Investigator will be responsible for the following:

o Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures.

o Notifying the IRB/IEC of SAEs or other significant safety findings, as required by IRB/IEC procedures

o Providing oversight of the study conduct at the site and adherence to requirements of ICH guidelines, the IRB/IEC, for clinical studies (if applicable), and all other applicable local regulations

Publication:

•The results of this study may be published or presented at scientific meetings. If this is Foreseen.

•The investigator will comply with the requirements for publication of study results. Per standard editorial and ethical practice.

•Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Data Quality Assurance:

•All participant study data will be recorded on printed or electronic CRFs or transmitted to

the designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF.

•The Investigator must maintain accurate documentation (source data) that supports the information in the CRF.

•The Investigator must permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.

•Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements.

•Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion, unless local regulations, institutional policies. No records may be destroyed during the retention period without the Sponsor's written approval.

Protocol adherence and amendments:

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Informed Consent Form:

If full Informed Consent is requested by local laws or by the EC/IRB, a signed "Patient Informed Consent" (PIC) document should be obtained. In this case, a patient informed consent form will be given to each patient, which includes all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study.

The informed consent form will be translated into the appropriate language of each country in which the study will be conducted.

Each patient and Principal Investigator or authorized delegated designee obtaining informed consent must personally sign and date, in the appropriate local language a “Patient Informed Consent Form”.

The physician must keep the original informed consent form signed by the patient (a signed copy is given to the patient). For subjects that are unable to read or write, the informed consent shall be obtained through a supervised oral process. The independent witness shall be present throughout the entire process. The informed consent form and any other information shall be read aloud and explained to the subject, and whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

Where a patient has initially verbally consented or a patient’s legally acceptable representative has consented on behalf of the patient, written consent should be sought from the patient as soon as, in the investigator’s opinion, the patient is capable of understanding the process and capable of signing the consent form.

10. REFERENCES:

1. Hovorka R, Kremen J, Blaha J, Matias M, Anderlova K, Bosanska L, Roubicek T, Wilinska ME, Chassin LJ, Svacina S, Haluzik M. Blood glucose control by a model predictive control algorithm with variable sampling rate versus a routine glucose management protocol in cardiac surgery patients: a randomized controlled trial. J Clin Endocrinol Metab. 2007 Aug;92(8):2960-4. doi: 10.1210/jc.2007-0434. Epub 2007 Jun 5. PMID: 17550955.
2. Rao RH, Perreiah PL, Cunningham CA. Monitoring the Impact of Aggressive Glycemic Intervention during Critical Care after Cardiac Surgery with a Glycemic Expert System for Nurse-Implemented Euglycemia: The MAGIC GENIE Project. J Diabetes Sci Technol. 2021 Mar;15(2):251-264. doi: 10.1177/1932296821995568. PMID: 33650454; PMCID: PMC8256075.
3. Blaha J, Kopecky P, Matias M, Hovorka R, Kunstyr J, Kotulak T, Lips M, Rubes D, Stritesky M, Lindner J, Semrad M, Haluzik M.Comparison of three protocols for tight glycemic control in cardiac surgery patients. Diabetes Care. 2009 May;32(5):757-61. doi: 10.2337/dc08-1851. Epub 2009 Feb 5.
4. Cordingley JJ, Vlasselaers D, Dormand NC, Wouters PJ, Squire SD, Chassin LJ, Wilinska ME, Morgan CJ, Hovorka R, Van den Berghe G.Intensive insulin therapy:

enhanced Model Predictive Control algorithm versus standard care. Intensive Care Med. 2009 Jan;35(1):123-8. doi: 10.1007/s00134-008-1236-z. Epub 2008 Jul 26.

5. Roubícek T, Kremen J, Bláha J, Matias M, Kopecký P, Rulísek J, Anderlová K, Bosanská L, Mráz M, Chassin LJ, Hovorka R, Svacina S, Haluzík M. [Pilot study to evaluate blood glucose control by a model predictive control algorithm with variable sampling rate vs. routine glucose management protocol in peri- and postoperative period in cardiac surgery patients]Cas Lek Cesk. 2007;146(11):868-73.

6. Vogt AP, Bally L. Perioperative glucose management: Current status and future directions. Best Pract Res Clin Anaesthesiol. 2020 Jun;34(2):213-224. doi: 10.1016/j.bpa.2020.04.015. Epub 2020 May 11. PMID: 32711830.
7. Ferrari LR. New insulin analogues and insulin delivery devices for the perioperative management of diabetic patients. Curr Opin Anaesthesiol. 2008 Jun;21(3):401-5. doi: 10.1097/ACO.0b013e3282faa2f0. PMID: 18458562.
8. Corney SM, Dukatz T, Rosenblatt S, Harrison B, Murray R, Sakharova A, Balasubramaniam M. Comparison of insulin pump therapy (continuous subcutaneous insulin infusion) to alternative methods for perioperative glycemic management in patients with planned postoperative admissions. J Diabetes Sci Technol. 2012 Sep 1;6(5):1003-15. doi: 10.1177/193229681200600503. PMID: 23063025; PMCID: PMC3570833.
9. Kuntschen FR, Galletti PM, Hahn C, Arnulf JJ, Isetta C, Dor V. Alterations of insulin and glucose metabolism during cardiopulmonary bypass under normothermia. J Thorac Cardiovasc Surg. 1985 Jan;89(1):97-106. PMID: 3880848.
10. Schmeltz, L.R., DeSantis, A.J., Thiyagarajan, V., et al. (2007) Reduction of Surgical Mortality and Morbidity in Diabetic Patients Undergoing Cardiac Surgery with a Combined Intravenous and Subcutaneous Insulin Glucose Management Strategy. Diabetes Care, 30, 823-82
11. Furnary, A.P., Wu, Y. and Bookin, S.O. (2004) Effect of Hyperglycemia and Continuous Intravenous Insulin Infusion on Outcomes of Cardiac Surgical Procedures: The Portland Diabetic Project. Endocrine Practice, 10, 21-33. http://dx.doi.org/10.4158/EP.10.S2.2
12. Van den Berghe, G., Wouters, P.J., Bouillon, R., et al. (2003) Outcome Benefit of Intensive Insulin Therapy in the Critically Ill: Insulin Dose versus Glycemic Control. Critical Care Medicine, 31, 359-366. http://dx.doi.org/10.1097/01.CCM.0000045568.12881.10
13. Van Den Berghe, G., Wilmer, A., Milants, I., et al. (2006) Intensive Insulin Therapy in Mixed Medical/Surgical. Heal, 55, 3151-3159. http://dx.doi.org/10.2337/db06-0855

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