CAN TAKE TRIAL

CONTINUATION OF METFORMIN TO IMPROVE AND KEEP PERI-OPERATIVE GLYCEMIC CONTROL

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Rational for Study

• There are currently 60 million Europeans and 2 million Canadian with diabetes the majority of which have type II DM.

• The Incidence of Diabetes has tripled over the past decade and will most likely triple again in the next couple decades.

• Prevalence of patients with DM undergoing surgery and the incidence of peri-operative dysglycemia continue to rise
Rational for Study

- Diabetic patients require surgical procedures at a rate higher than non-diabetic patients.

- The surgical stress response leads to metabolic perturbations, which alter glucose homeostasis in patients who may already have poor glycemic control.

- In three recent studies the incidence of peri-operative hyperglycemia in patients with type II DM ranged from 15.3% to 66%[1-3].


Rational for Study

- Peri-operative hyperglycemia has been linked to numerous negative adverse consequences, including wound infection, impaired wound healing, endothelial dysfunction, neurocognitive dysfunction, sepsis, prolonged hospital stay and increased mortality.

- Even though the knowledge with regard to negative outcomes and peri-operative hyperglycemia is substantial, almost all oral hypoglycemic medicines are held in the pre-operative period due to fear of adverse consequences related to patient fasting and hemodynamic shifts during surgery.
Metformin

- The majority of individuals who have type II DM take oral hypoglycaemic medications to control their BG and minimize retinopathy, nephropathy, neuropathy, cardiovascular, peripheral vascular and cardiovascular complications.

- The ADA and EASD both recommend Metformin as the first line agent in the treatment of Type II DM[4, 5].

- Metformin acts as both an antihyperglycemic agent and an insulin sensitizer in Type II DM patients.

- Despite the fact that this drug was introduced in 1950 and is prescribed to millions of individuals, its exact molecular mechanism of action has failed to be elucidated.

- It is able to lower blood glucose concentrations without causing overt hypoglycaemia.

Patients who take metformin for daily diabetic control have historically been told to hold their doses of medication on the night prior to surgery and on the day of surgery to avoid possible hypoglycaemia and MALA.
Metformin alone is not [6, 7] or only rarely [8] associated with hypoglycemia.

According to a recent systematic review by Bennett et al.[9], the reported risks of hypoglycemia for metformin users varied between 0 and 21%.

Hypoglycemia and Metformin

- There is no consensus about the definition of hypoglycemia and a confusing variety of definitions makes the comparability of the various studies dealing with frequencies of hypoglycemia difficult.

- A recent clinical review [10] examining the management of diabetic patients wanting to fast for Ramadan has advocated that patients continue to take metformin during this month due to virtually no adverse risk of hypoglycemia and benefits of glycemic control observed.

• Metformin promotes the conversion of glucose to lactate in the splanchnic bed of small intestine

• Metformin inhibits hepatic gluconeogenesis from lactate, pyruvate, alanine, resulting in additional lactate and substrate for lactate production. (mainly by decreased pyruvate carboxylase activity, a rate limiting enzyme in the formation of glucose from lactate)
Metformin and MALA

Diagram showing the metabolism of glucose in skeletal muscle, blood, and liver. The process involves the conversion of glucose into lactate through the Krebs cycle and the electron transport chain, with ATP production and NAD+ and NADH involvement.
• Salpeter et al. [13] identified all trials and cohort studies conducted between 1959 and 2002 and did not find a single case of lactic acidosis in 36,893 person-years of metformin exposure.

• 200 trials evaluated for the incidence of lactic acidosis among patients prescribed metformin vs non-metformin antidiabetes medications. Of 100,000 people, the incidence of lactic acidosis was 5.1 cases in the metformin group and 5.8 cases in the non-metformin group. The authors concluded that metformin is not associated with an increased risk for lactic acidosis.

• Lalau and Race [14] analyzed 49 cases of lactic acidosis associated with metformin use; overall mortality was not correlated with plasma metformin concentrations. Interestingly, plasma metformin concentrations were, on average, three times higher in patients who survived.

• All case subjects with lactic acidosis had, in addition to metformin use, acute or chronic comorbidities predisposing to lactic acidosis.

• Controversy remains whether the use of metformin is a cause or a coincidence in lactic acidosis of DM patients.

“Probably the most common mechanism by which metformin elevates blood lactate is by inducing catecholamine release in those who regulate or prescribe it”

Peter W Stacpoole, Editorial, Diabetes Care 1998
Moreover, the most recent guidelines from the ADA

<table>
<thead>
<tr>
<th>Medication</th>
<th>AM Surgery</th>
<th>PM Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>Hold AM dose if NPO</td>
<td>Give AM dose if eating breakfast</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>Hold AM dose if NPO</td>
<td>Give AM dose if eating breakfast</td>
</tr>
<tr>
<td>Metformin</td>
<td>Take normal dose</td>
<td>Take normal dose</td>
</tr>
<tr>
<td>Solfonylurea</td>
<td>Hold AM dose if NPO</td>
<td>Hold AM and PM dose</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Take normal dose</td>
<td>Take normal dose</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>Omit on day of surgery</td>
<td>Omit on day of surgery</td>
</tr>
<tr>
<td>GLP-1 Analogue</td>
<td>Omit on day of surgery</td>
<td>Omit on day of surgery</td>
</tr>
</tbody>
</table>

Other Potential Benefits of Metformin

- In epidemiological studies metformin has been shown to have atherosclerotic and cardioprotective effects have recently been confirmed in prospective and retrospective studies, and appear to reflect a collection of glucose-independent mechanisms.

- Palva et. Al. have shown that Metformin has cardioprotective effects in experimental models of ischemia reperfusion, which is partially mediated through nitric oxide (NO) synthesis in mice.

- Taleb et. Al. have shown that Metformin treatment can improve skin flap survival through an NO dependent pathway in mice.
O’Connor et al. reviewed the records of 474 patients who were taking metformin and came for preoperative evaluation prior to surgery (December 1995-March 2000).

Of the 474 patients, 406 were instructed by the anesthesiologist to withhold taking metformin on the morning of surgery, 8 were told to take it the evening before, 38 were told to ingest it the morning of surgery, 2 were told to bring the medication with them, 19 were given no instruction, and one was told to stop taking metformin 7 days prior to the procedure.
Metformin Perioperatively

- What is your practice with Metformin in the peri-operative period?
- WHY?

- Guidelines (UK, Australian, Some European, Canadian?)
- Fear or Hypoglycemia and MALA
- NO TRIALS WHICH SHOW THAT THIS IS SAFE AND EFFECTIVE!!!
CAN TAKE TRIAL

Study Recruitment → Randomization

Group A: Metformin → Group B: Placebo

PRIMARY OUTCOME: Incidence of Peri-operative Hyperglycemia

SECONDARY OUTCOMES

1. Incidence of hypoglycemia
2. Acidosis
3. Lactate
4. AKI
5. Wound infection
6. Length of hospital
Patient Selection and Recruitment

- Patients with Type II DM on Metformin presenting to the preoperative anesthesia clinic at McMaster University Medical Centre

- Inclusion criteria are: ages 35 – 75, using metformin for control of Type II DM, ASA I, II and III, informed consent, and Surgery in which minimal hypovolemic/blood loss is expected.

- Exclusion criteria include: renal failure, liver failure, CHF, respiratory failure, previous episodes of hypoglycaemia, conditions which mask symptoms of hypoglycaemia, low-normal or low CBG at pre-operative appointment date, history of lactic acidosis and any patient who received contrast dye within 2 days of the planned surgery or during surgery.
The incidence rate of peri-operative hyperglycemia was based on previous studies, which varies from 15.3% to 66% [1-3]. We based our estimate on a rate of 42%, which is the mean incidence calculated from the aforementioned studies.

Although no peri-operative studies which show a percentage reduction in hyperglycemia with metformin exist an effect size reduction of 50% was considered appropriate based on results of studies in critically ill traumatized diabetic and non-diabetic patients which showed a 52% mean reduction in stress induced hyperglycemia.[15-17]

A total sample size of 168 patients (84 in each group) was calculated with the following assumptions. Baseline event rate of 42%; 50% reduction in peri-operative hyperglycemia with metformin; Alpha error = 5%; Beta error = 20%; and an additional 10% due to accounting other reasons of attrition.

**Study Recruitment** — Randomization

**Group A: Metformin** — **Group B: Placebo**

**PRIMARY OUTCOME:** Incidence of Peri-operative Hyperglycemia

**SECONDARY OUTCOMES**

1. Incidence of hypoglycemia
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3. Lactate
4. AKI
5. Wound infection
6. Length of hospital
The recruited patient is randomized on the day of pre-operative assessment.

Randomization will be done from a central place using a computer generated table, with an allocation ratio of 1:1, using random permuted block sizes.

The allocation will be known to the pharmacist involved in the study. The pharmacist will issue the medication to the RC upon confirming the allotment, concealed through a unique identification number.

The RC will pick up the allotted medication with UIN specific to each patient and hand the medication to the patient to take on his or her regular dosing schedule.
The study allocation will be blinded to patients, treating nurses, physicians, research assistant and investigators.

The allocation list will be available only to the person responsible for randomizing and the pharmacist involved in the study.
Study Logistics

- In the operating room patients will be placed under standard monitoring including invasive blood pressure, heart rate, and oxygen saturation.
- Any additional monitoring will be at the discretion of the anesthesiologist on the day of surgery.
- Anesthesia will be administered in the preferred manner of the patient’s anesthesiologist for the surgery.
- Intravenous crystalloids in the form of NS or lactated Ringer’s solution shall be administered as appropriate. Approximate blood loss shall be recorded.
**Primary Outcome**: Incidence of Peri-operative Hyperglycemia

**Secondary Outcomes**

1. Incidence of hypoglycemia
2. Acidosis
3. Lactate
4. AKI
5. Wound infection
6. Length of hospital
## Planned Outcomes

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Type</th>
<th>Measurement</th>
<th>Time of Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome Glycemic Control</td>
<td>Continuous</td>
<td>Mean CBG score difference between 2 groups</td>
<td>7 Measurements: Pre-op, Intra-op, 1, 3, 6, 9, 12 hours post-op</td>
</tr>
<tr>
<td>Lactic Acidosis</td>
<td>Binary</td>
<td>Presence of Lactic Acidosis post-operatively: pH of $&lt;7.35$ and Lactate $&gt;5$. [18]</td>
<td>pH and Lactate measured at 1, 6, 12, 24 and 48 hours post-op</td>
</tr>
<tr>
<td>Acute Kidney Injury (AKI)</td>
<td>Binary</td>
<td>Presence of AKI: Absolute increase in creatinine by 27μmol/L over 24 hrs or 44μmol/L over 48 hrs. [19]</td>
<td>Creatinine measured at 1, 6, 12, 24 and 48 hours post-op</td>
</tr>
<tr>
<td>Wound infection</td>
<td>Binary</td>
<td>Wound infection present at follow-up visit</td>
<td>At follow up visit with surgeon at approx. 6 weeks post-surgery</td>
</tr>
<tr>
<td>Length of Hospital Stay</td>
<td>Continuous</td>
<td>Mean length of stay</td>
<td>Following discharge from hospital</td>
</tr>
</tbody>
</table>

Statistical Analysis

- The study will be analyzed using an intention to treat approach.

- The dichotomous outcomes will be reported as proportions and analyzed using a chi-square test to detect a significant difference (p<0.05).

- Continuous outcomes will be analyzed using an unpaired 2-tailed student t test for significance (p<0.05).
Trial Management

- This trial will be conducted at Juravinski Hospital, and Hamilton General Hospital, Hamilton.
- The trial will enlist support and collaboration from surgeons and fellow anesthesiologists.
- Study data shall be securely stored at the anesthesia research office, McMaster University. A research coordinator will be employed to work for the study for patient recruitment and data collection.
Questions/Suggestion

- Thanks to Dr. James Paul and Tony Tidy

- Questions/Suggestions??