Glycaemic dysregulation in nondiabetic patients after major lower limb prosthetic surgery

S. Pili-Floury a, F. Mitifiot a, A. Penfornis b, N. Boichut a, M.-H. Tripart a, J.-L. Christophe a, P. Garbuio c, E. Samain a,∗

a Department of Anesthesiology and Intensive Care Medicine, Jean Minjoz Hospital, University of Franche Comté, 3, boulevard Alexander-Fleming, 25000 Besançon, France
b Department of Endocrinology and Diabetology, Jean Minjoz Hospital, University of Franche Comté, 3, boulevard Alexander-Fleming, 25000 Besançon, France
c Department of Orthopedic and Plastic Surgery, Jean Minjoz Hospital, University of Franche Comté, 3, boulevard Alexander-Fleming, 25000 Besançon, France

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Abstract

Aim. – Blood glucose (BG) dysregulation is common after cardiac surgery, but remains poorly described after major noncardiac surgery. The aim of this prospective observational study was to analyze perioperative changes in BG levels in nondiabetic patients undergoing major arthroplasty.

Methods. – Nondiabetic consenting patients scheduled for hip or knee arthroplasty were eligible. BG levels were assessed from the preoperative period to the end of postoperative day 2. Oral feeding was resumed from the evening after surgery. Hyperglycaemia, defined as two sequential BG measurements that were either greater than 7.0 mmol/L during the fasting period or greater than 11.1 mmol/L 2 hours after a meal, was the primary outcome variable. Two groups of patients were identified, depending on the occurrence or not of hyperglycaemia (hyperglycaemic and normoglycaemic groups, respectively). Patients were followed-up for surgical wound infection for one year postoperatively.

Results. – Thirty-eight patients, aged 65 ± 14 years (mean ± S.D.), were included. A significant increase in BG was observed during the fasting period (Anova, P < 0.001), and 74% of patients met the primary outcome variable. In the hyperglycaemic group, the mean number of BG measurements per patient above the thresholds was 5.6 ± 2.8, and 58% of the patients still had a postmeal BG level greater than 11.1 mmol/L at the end of the study period. No surgical wound infection was observed at follow-up.

Conclusion. – This study showed that nearly 75% of nondiabetic patients experience a moderate, but significant, increase in either fasting or postprandial BG levels in the first two days following major arthroplasty.

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Résumé

Dysrégulation glycémique après prothèse de hanche ou de genou chez des patients non diabétiques.

But. – Une dysrégulation de la glycémie est fréquente après chirurgie cardiaque, mais reste mal documentée après chirurgie orthopédique majeure. Le but de cette étude prospective, observationnelle, était d’analyser l’évolution de la glycémie dans la période périopératoire chez des patients non diabétiques opérés de prothèse de hanche ou de genou.

Méthodes. – Les patients non diabétiques, ayant donné leur consentement pour participer, programmés pour une prothèse de hanche ou de genou, étaient éligibles. La glycémie capillaire était suivie de la période préopératoire jusqu’à la fin du deuxième jour postopératoire. Une alimentation orale était proposée dès le soir de l’intervention. La survenue d’une hyperglycémie, définie par deux glycémies consécutives supérieures à 7,0 mmol/L en période de jeûne ou supérieures 11,1 mmol/L, deux heures après un repas, était le critère de jugement principal et permettait de définir un groupe Hyperglycémie et un groupe Normoglycémie. Les patients étaient suivis pendant un an à la recherche d’une infection du site opératoire.

Résultats. – Trente-huit patients, d’âge moyen (± DS) 65 ± 14 ans, ont été inclus. Une élévation significative au cours du temps de la glycémie était observée dans la période de jeûne postopératoire (Anova, P < 0.001). Soixante-dix pour cent des patients ont présenté une hyperglycémie. Les patients du groupe Hyperglycémie ont eu en moyenne 5,6 ± 2,8 valeurs de glycémie au-dessus des seuils prédéfinis. Cinquante-huit pour cent d’entre eux avaient une glycémie postprandiale supérieure à 11,1 mmol/L à la fin de l’étude. Aucun patient n’a présenté d’infection du site opératoire à un an.

∗ Corresponding author.
E-mail address: e1samain@chu-besancon.fr (E. Samain).

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1. Introduction

Major surgery has been reported to induce several metabolic changes, including greater energy demands, increased protein catabolism and lipid oxidation. In diabetic patients, surgical stress has been shown to induce an increase in glycaemic levels and insulin needs in the perioperative period [1]. Blood glucose (BG) dysregulation has also been reported in nondiabetic patients after major stress such as polytrauma, extensive burns, severe sepsis or cardiac surgery. Several studies have suggested the deleterious impact of stress hyperglycaemia on patient outcomes [2,3], and a longer inhospital stay has been reported in nondiabetic cardiac surgery patients presenting with postoperative hyperglycaemia [4]. Several well-designed, controlled studies have demonstrated that perioperative intensive insulin therapy aiming to achieve strict glycaemic control does improve patients’ clinical outcomes in the postoperative period [5–9]. These data have led some authors to recommend tight glycaemic control in patients admitted to the intensive care unit especially after cardiac surgery [10].

In the light of such results, it would be tempting to extend strict BG control for every patient undergoing major surgery, including lower limb prosthetic surgery, to reduce perioperative morbidity. However, it is not possible to directly extrapolate results observed in the setting of cardiac surgery to other types of surgery, as the level of surgical stress and the incidence of postoperative complications may differ substantially from one type of surgery to another. Furthermore, whatever the BG targets considered, lowering BG after major surgery remains a difficult and time-consuming task. The protocols required to achieve stringent BG control in a clinical trial are complex and may involve a risk of hypoglycaemia [11,12]. Thus, it appears reasonable, before evaluating the effect of perioperative BG control on patient outcome, to precisely describe the BG changes following different types of surgery.

Accordingly, Hall et al. have shown a progressive increase in BG levels during the first 24 hours following hip or knee arthroplasty [13]. However, the patients in that study were fasting for the first 24 hours, and the changes in BG levels observed with the more current clinical practice that resumes oral intakes shortly after surgery are not known. For this reason, it was the aim of our study to describe intra- and postoperative changes in BG levels in nondiabetic patients undergoing hip or knee arthroplasty.

2. Patients and methods

2.1. Study design and inclusion criteria

This prospective study took place over a 3-month period at the Department of Orthopedic Surgery of the University Hospital of Besançon. The study was conducted according to the French bioethics law (Article L. 1121-1 of law n° 2004-806, August 9, 2004). All patients gave their informed consent to participate in the study and, because the study was only observational and did not modify the current diagnostic or therapeutic strategy, authorization was given to waive the participants’ written informed consent. Sequential patients scheduled for total hip or knee arthroplasty were eligible to participate. Patients with a past medical history of diabetes mellitus (DM), defined as chronic glucose intolerance that was either insulin-dependent or non insulin-dependent at the time of operation, were not included. Preoperatively, venous blood was sampled for subsequent measurements of BG and glycated haemoglobin (HbA1c), using high performance liquid chromatography (HLC-723Ghb G7, TOSOH Bioscience Inc, South San Francisco, CA), in fasting patients several days before the planned surgery. Patients with BG and HbA1c levels greater than 7.0 mmol/L and greater than 6.1%, respectively, were excluded.

2.2. Perioperative management

The patients’ perioperative management was according to a specific written protocol for lower limb arthroplasty in use at our institution. Briefly, after an overnight fast of 6–8 hours, patients are premedicated with oral hydroxyzin (0.75–1.00 mg/kg) 1 hour before surgery. Upon arrival at the operating room, patients are placed under a forced air-warming blanket to prevent hypothermia; an intravenous infusion of saline is also started. Cefuroxime is given intravenously 45 minutes to 1 hour before the skin incision, and no antibiotic prophylaxis is given after surgery.

Anesthesia consisted of general anaesthesia with mechanical ventilation following orotracheal intubation with regional anaesthesia using either an ipsilateral lumbar plexus block, or a sciatic and/or femoral nerve block. For knee surgery, a femoral nerve catheter was placed whenever possible for postoperative pain control by continuous infusion of ropivacaine. Intraoperative noninvasive blood pressure values were recorded on a hard disk for subsequent recognition and duration determination of intraoperative arterial hypotension, defined as a decrease in systolic blood pressure lower than 30% of resting value, or lower than 90 mmHg. A pneumatic tourniquet was used for knee surgery. Intravenous fluid replacement was undertaken using a crystalloid and/or colloid infusion at a rate adjusted to maintain haemodynamic stability. Blood was transfused to maintain haemoglobin (Hb) concentrations above a value determined on a patient-by-patient basis, according to the more recent French recommendations on red cell transfusion (http://afssaps.sante.fr/pdf/5/rbp/glreco.pdf) [14].
Postoperative pain was evaluated using a visual analogue scale, and multimodal analgesia was provided by intravenous paracetamol (1 g, four times per day), ketoprofen (100 mg, twice daily) and patient controlled intravenous morphine together with, if available, a continuous infusion of ropivacaine 0.2% through the femoral nerve catheter.

Upon arrival at the recovery room, an intravenous dextrose (5% solution) infusion was started on the basis of 75 g/day of dextrose, and maintained until oral feeding (proposed from the evening after surgery if the patient was doing well) was considered sufficient. Thromboprophylaxis was started 6–8 hours after surgery using low molecular weight heparin.

Fingerstick blood samples were obtained for BG measurement, using a standard hospital glucose meter (Medisense Optium, Abingdon, Oxon, UK), calibrated according to the manufacturer’s specifications. During the study period, BG levels were measured at the following times (Fig. 1):

- upon arrival at the operating room (Preop);
- hourly during the Intraop period (Intraop₁, Intraop₂);
- upon arrival at the postanaesthesia care unit (PACU) and 2 hours later (PACU₀, PACU₂);
- before (POD₀fasting) and 2 hours (POD₀dinner) after dinner on the day of surgery; and on the postoperative day (POD) before breakfast (BF) (POD₁fasting);
- 2 hours after BF (POD₁BF), lunch (POD₁lunch) and dinner (POD₁dinner).

The same schedule was repeated on the second day after surgery (POD₂fasting, POD₂BF, POD₂lunch and POD₂dinner). In cases where the patient did not resume oral feeding, postmeal BG measurements were omitted.

2.3. Outcome and measurements

The primary outcome variable was hyperglycaemia, defined as two sequential BG measurements that were either greater than 7 mmol/L during the fasting period or greater than 11.1 mmol/L 2 hours after a meal. These cutoff values were selected because they are similar to those used in the Association de langue française pour l’étude du diabète et des maladies métaboliques (ALFEDIAM) study and by the American Diabetes Association for the diagnosis of DM [15]. According to the occurrence or not of the primary outcome during the study period, patients were grouped as either hyperglycaemic or normoglycaemic, respectively.

Secondary outcome measures after surgery included:

- clinically significant venous thromboembolic events, confirmed by either lower limb venous Doppler echography and/or thoracic spiral computed tomography (CT) scans;
- myocardial damage, defined as an increase in cardiac troponin I (measured on POD 1, 2 or 3, or when clinically indicated) to above the upper plasma concentration limits considered to be normal at our institution;
- repeated surgery for haematoma or bleeding in the surgical field.

Patients were followed by the medical team for one year after surgery to determine the occurrence of either surgical wound infection, defined by the criteria of the US Centers for Disease Control and Prevention (CDC) or death [16].

2.4. Insulin therapy

Intravenous insulin therapy was started in cases of severe hyperglycaemia, defined as two sequential fasting BG levels greater than 11.1 mmol/L, or in cases of a diabetes related complication such as osmotic polyuria, acidoketosis or hyperosmolar coma.

2.5. Statistical analysis

Results are given as means ± standard deviation (S.D.) or medians (interquartile). Intergroup comparisons for demographic data were by Fisher’s exact test for categorical variables and by the Mann-Whitney nonparametric test for continuous variables. The analysis over time of BG levels during the fasting period from Preop to POD₀fasting was by the Anova test for repeated measures with Bonferroni-Dunn posthoc analyses. P < 0.05 was considered significant.
Table 1
Demographic and perioperative data for patients in the normoglycaemic and hyperglycaemic groups.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Normoglycaemic group</th>
<th>Hyperglycaemic group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (% hip arthroplasty)</td>
<td>38 (71)</td>
<td>9 (77)</td>
<td>29 (68)</td>
<td>0.99</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 ± 14</td>
<td>56 ± 19</td>
<td>68 ± 11</td>
<td>0.14</td>
</tr>
<tr>
<td>Gender ratio (M/F; %)</td>
<td>60/40</td>
<td>88/12</td>
<td>52/48</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26 ± 5</td>
<td>24 ± 3</td>
<td>27 ± 6</td>
<td>0.36</td>
</tr>
<tr>
<td>Patients with more than a T2DM risk factor (%)</td>
<td>47</td>
<td>44</td>
<td>51</td>
<td>0.99</td>
</tr>
<tr>
<td>ASA classification (I–II/III–IV) (%)</td>
<td>74/26</td>
<td>77/23</td>
<td>72/28</td>
<td>0.99</td>
</tr>
<tr>
<td>Preoperative HbA₁c (%)</td>
<td>5.3 ± 0.4</td>
<td>5.3 ± 0.6</td>
<td>5.3 ± 0.4</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Intraoperative variables

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<th></th>
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<tbody>
<tr>
<td>Surgery duration (minutes)</td>
<td>99 ± 50</td>
<td>70 ± 29</td>
<td>108 ± 51</td>
<td>0.01</td>
</tr>
<tr>
<td>Total hypotension duration (minutes)</td>
<td>26 ± 25</td>
<td>14 ± 12</td>
<td>29 ± 27</td>
<td>0.28</td>
</tr>
<tr>
<td>Total dose of ephedrine (mg)</td>
<td>13 ± 14</td>
<td>6 ± 5</td>
<td>15 ± 16</td>
<td>0.26</td>
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<tr>
<td>Blood loss estimation (mL)</td>
<td>767 ± 631</td>
<td>392 ± 239</td>
<td>908 ± 677</td>
<td>0.02</td>
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</tbody>
</table>

Postoperative variables

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<tbody>
<tr>
<td>Duration of perioperative fasting (hours)</td>
<td>28 ± 12</td>
<td>27 ± 6</td>
<td>28 ± 13</td>
<td>0.65</td>
</tr>
<tr>
<td>Hb level (within 1 hour postoperative)</td>
<td>11.6 ± 1.5</td>
<td>13.1 ± 1.3</td>
<td>11.2 ± 1.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Blood transfusion (%)</td>
<td>16</td>
<td>0</td>
<td>20</td>
<td>0.30</td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>15 ± 10</td>
<td>12 ± 4</td>
<td>28 ± 13</td>
<td>0.69</td>
</tr>
<tr>
<td>Wound infection 1 year after surgery</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

BMI: body mass index; T2DM: type 2 diabetes mellitus; HbA₁c: glycated haemoglobin; ASA: American Society of Anesthesiologists; Hb: haemoglobin.

3. Results

Of the 47 eligible patients, seven were either treated for DM or had a preoperative fasting BG level greater than 7.0 mmol/L, and two had an HbA₁c > 6.1%. Demographic data for the remaining 38 patients included in the study are presented in Table 1. Altogether, 19 patients had one or more risk factors for type 2 DM:

- seven had a past medical history of DM in the family;
- 17 had a body mass index (BMI) greater than 27 kg/m²;
- one had a past medical history of fetal macrosomia.

Immediately prior to surgery, BG levels (Preop) were greater than 7.0 mmol/L in four patients, and 94% of the BG measurements dictated by the study protocol were carried out, corresponding to a mean (± S.D.) of 14 ± 1.7 BG determina-
tions per patient during the study period. A significant increase in BG levels was observed during the fasting period (ANOVA $F = 8.564, P < 0.001$), and 28 (74%) patients had at least two sequential BG levels above hyperglycaemic thresholds, and were included in the hyperglycaemic group. Variations in BG levels over the study period are shown in Fig. 2. Oral feeding was resumed in the evening of the day of surgery in 90 and 76% of patients in the normoglycaemic and hyperglycaemic groups, respectively. The mean duration of perioperative fasting was $28 \pm 12$ hours in both groups (difference not significant).

The mean number of BG measurements per patient above the predefined thresholds was $5.6 \pm 2.8$ in the hyperglycaemic group. Fasting and postprandial BG levels were increased in 78 and 22% of cases, respectively. At the end of the study period, 58% of the patients in the hyperglycaemic group still had a postmeal BG level greater than 11.1 mmol/L.

Of the patients in the normoglycaemic group, 44% had a single BG value above the threshold level during the study period.

During the hospital stay, three patients underwent repeat operations in the first few POD because of surgical wound haematoma, and one patient had clinically patent sural thrombophlebitis, confirmed by venous Doppler echography, and was treated with heparin. No patient met the criteria for wound infection or myocardial damage.

One year after surgery, there were no deaths or surgical wound infections among the patients included in the study.

4. Discussion

This study showed that nearly 75% of nondiabetic patients had a significant increase in either fasting or postprandial BG levels in the first two days following hip or knee arthroplasty. In most cases, these variations occurred early after surgery, and were sustained in 58% of the patients by the end of the second POD.

Noncardiac surgery is a well-characterized cause of alterations in BG regulation in diabetic patients, but its impact on glycoregulation in nondiabetic patients has been less extensively described [1,17]. In a short series of 12 otherwise healthy patients, Thorell et al. reported an increase in BG levels after cholecystectomy or inguinal hernia repair [17]. In nondiabetic patients, Hall et al. reported an increase in BG levels that started at 4 and 12 hours after hip and knee arthroplasty, respectively [13]. However, in that study, patients were fasting throughout the whole of the study period, a situation that is not consistent with the current clinical practice in most institutions.

The present study showed that lower limb arthroplasty was associated with frequent and severe alterations in postprandial BG levels in nondiabetic patients taking oral food in the evening after surgery. Furthermore, 17% of patients with a clinically uneventful postoperative period still had increased postprandial BG levels 60 hours after surgery. These results suggest a prolonged, relative resistance to endogenous insulin and are in accordance with previously reported data from Thorell et al. [17]. Surgical durations and blood loss were greater in the hyperglycaemic group, and these patients also required more blood transfusions.

Although the present study was not designed to identify factors associated with the increase in BG levels, these differences may be related in part to more surgical stress in hyperglycaemic patients. This is in accordance with the findings of Thorell et al. reporting a greater increase in BG levels after cholecystectomy than after inguinal repair, suggesting a relationship between the degree of surgical stress and changes in BG levels [17].

For the purposes of our study, it was important to ascertain that the patients included were not diabetic. For this reason, we chose to exclude patients who had HbA1c > 6.1%, as determined in the study by Bennett et al. [18]. Although this parameter is not useful for the diagnosis of type 2 DM, Herdzik et al. have reported the high negative predictive value of a normal HbA1c to exclude DM in observational studies [15,19]. Intraoperative and postoperative BG measurements were based on capillary blood. This may be open to criticism as it has been shown that measurements based on capillary blood may differ from those using venous blood [20]. However, any variability has been recently shown to be moderate – lower than 0.5 mmol/L – and we found that using capillary BG measurement was the only way to make the study acceptable to the patients.

The impact of perioperative BG variations on patient outcomes after major orthopaedic surgery is an interesting consideration. No patient included in our series experienced any severe septic complications, including surgical wound infections, in the postoperative period up to the first year after surgery. This low incidence of surgical wound infection is in accordance with data from the French national survey network for nosocomial infection [http://www.invs.sante.fr/publications/2008/iso_raising/index.html], which recently reported a mean incidence of postoperative wound infection of 0.8% after hip surgery and 0.4% after knee arthroplasty [21]. Our results suggest that there is no clinically relevant relationship between increases in perioperative BG levels, which are very common, and wound infections, which occur rarely. This interpretation, however, should be taken with caution, as the relatively small number of patients included in our study does not allow statistical assessment of the relationship between BG increases and surgical wound infections. Also, the impact of hyperglycaemia on outcome may depend on the criteria used to define glycaemic dysregulation. We have arbitrarily chosen the values that define DM and which have been associated with a higher rate of complications in large series of patients [15]. Clearly, however, these values do not carry the same risk when they occur for only a short period of time in the perioperative period.

As no patient included in the present study experienced a major increase in BG level or complication directly related to hyperglycaemia, none received insulin therapy in the postoperative period. However, if tight control of BG had been based on, for instance, the BG target level proposed by Van den Berghe et al., then intravenous insulin therapy would have been administered to more than 75% of our patients [6,22].

In conclusion, our study shows that moderate, but significant, increases in BG levels above normal values occur frequently in nondiabetic patients undergoing lower limb arthroplasty, but they appear to be unrelated to severe postoperative complications, the incidence of which remains low. This sug-
gests that any improvement in postoperative outcomes using tighter BG control by insulin therapy is not likely to be seen with this type of surgery.

References