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Effect of Glucose Administration on the Metabolism during Surgery

Shoko Kitamura, Jun Hirokawa*, Saori Sako and Takeshi Yokoyama

Kyushu University, Department of Dental Anesthesiology, Fukuoka, Japan

Corresponding author: Jun Hirokawa, Faculty of Dental Science, Kyushu University, Department of Dental Anesthesiology, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan, Tel: +81-92-642-6480; Fax: +81-92-642-6481; E-mail: hj8823@dent.kyushu-u.ac.jp

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Abstract

Background and aim: Glucose is stored mainly in the liver and muscles as glycogen. However, the total calories are less than basal energy expenditure for one day. Overnight fast before surgery may be stressful for patients. Therefore, we investigated the effect of glucose administration on the metabolic state during anesthesia.

Methods: After getting written informed consent, patients undergoing maxillofacial surgery were randomly assigned to two groups throughout the surgical procedure, G group receiving acetated Ringer solution with 1.5% glucose (n=12) and R group receiving acetated Ringer solution without glucose (n=11). Anesthesia was maintained with remifentanil and sevoflurane. Blood glucose level was monitored continuously using the STG-22TM from after the induction of anesthesia. Plasma ketone bodies were evaluated before and after surgery. Respiratory quotient (RQ) was monitored continuously during anesthesia using the indirect calorimetry V-Max.

Results: In G group (n=12), patients received 0.17 ± 0.03 g/kg/hr of glucose. But hyperglycemia did not observed during surgery. The mean blood glucose levels were maintained stably <150 mg/dL during surgery. The plasma concentration of ketone bodies was significantly higher at T4 in R group than in G group (p=0.027). However, it decreased from T1 to T3, T4 in G group. RQ decreased significantly from 0.93 ± 0.14 to 0.78 ± 0.11 in the R group (p=0.037), while it was kept at 0.88 ± 0.09 in the G group. There is no significant difference between group R and group G in REE during operation.

Conclusion: Intraoperative 0.17 ± 0.03 g/kg/hr of glucose administration may suppress ketogenesis and can maintain glucose metabolism successfully without causing hyperglycemia.

Keywords: Metabolism; RQ; Indirect calorimetry; Ketogenesis; REE

Introduction

There are some postoperative complications about general anesthesia. One of them is hyperglycemia, which causes reperfusion injury in the tissues [1-5] and causes the immune suppression [6-8] and may worsen prognoses of surgical procedures especially in neurosurgery [1,5]. The postoperative hyperglycemia is caused by increased insulin resistance (IR). Brandi reported that 8 times more insulin is necessary for maintenance of normoglycemia postoperatively than before surgery [9]. In our previous study [10] we proved that the infusion of 1.5% glucose solution during surgery may attenuate postoperative IR without causing hyperglycemia. However, though we understood the importance of the glucose supply, the metabolism during surgery is not clear today. Increasing blood glucose concentration due to glucose administration is regularly reported, although it has not been possible to evaluate to what extent exogenous glucose is metabolized. One of the metabolic indicators is measuring Respiratory quotient (RQ). RQ is the ratio of carbon dioxide produced to oxygen consumed. When glucose is consumed mainly, RQ should be 1.0. In the case of proteins and lipids, RQ should be 0.81 and 0.71 respectively. Since it is not usual that only one substrate is metabolized, therefore, RQ frequently exists between these values. In the body fluid, ketone, free fatty acid and urine urea nitrogen are also the indicators of metabolism. Sandstrom et al. studied whether intraoperative supply of glucose influences the dominating metabolic pathway as reflected by the RQ during pediatric anaesthesia [11]. If no glucose is administrated, increased fat metabolism, such as free fatty acids and ketones, have been observed in young children [12,13] We reported that small-dose of glucose administration, around one-third of basal metabolism, could reduce ketogenesis [14].

The aim of this study was to evaluate the effects of intraoperative infusion of 1.5% glucose solutions on RQ and the other metabolic indicators during maxillofacial surgery over three hours. RQ and energy expenditure, with and without intraoperative glucose administration, were calculated. Blood glucose, ketone bodies and free fatty acid concentrations were measured to indicate any difference of substrate metabolism during surgery.

Materials and Methods

After obtaining approval from the Ethics Committee of Kyushu University Hospital, we got written informed consent from patients undergoing elective maxillofacial surgery, American Society of Anesthesiologists physical status I or II. Patients with diabetes and/or obesity [Body Mass Index (BMI) > 25 kg/m^2] were excluded from this study. Patients were randomly assigned to two groups: those receiving acetated Ringer solution with 1.5% glucose (G group) during surgery or those receiving acetated Ringer solution with no glucose (R group) (Figure 1).

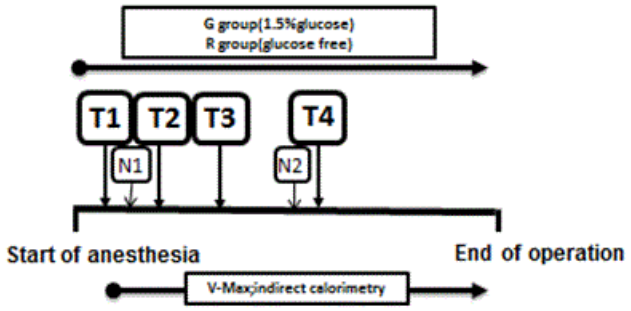

Figure 1: Timetable for this study.

Evaluation of RQ

V-Max is equipped with O_2 and CO_2 concentration meter. O_2 concentration is galvanic battery and CO_2 concentration meter is infrared absorption. RQ is defined by the ratio of carbon dioxide production (VCO_2) to oxygen consumption (VO_2). It is possible to measure RQ breath-by-breath, while the sampling tube connects the ventilation sensors.

Anesthetic management

No Patients received premedication and intravenous fluid infusion after overnight fasting. In the operating room, routine monitoring was applied, including pulse oximetry, noninvasive blood pressure, electrocardiography, and capnography. For anesthetic induction, 4 μg/kg fentanyl and 0.1 mg/kg midazolam were used. Intubation was facilitated with 0.1 mg/kg of vecuronium. Anesthesia was maintained with 1-2% sevoflurane in 50% oxygen and 50% air to keep bispectral index (BIS) levels < 60. Intermittent administration of fentanyl and continuous administration of remifentanil were performed for analgesia.

After intubation, patients were connected to the artificial breathing machine, and ventilated by 8 mL/kg at one time. The times of ventilation were 10, I:E was 1:2, peep was 0. During operation, settings were timely changed to be $<P_aCO_2$ 40 mmHg in blood gas test.

After anesthetic induction, a 20G IV catheter (InsyteTM, 20GA 1.16 IN, Becton Dickinson Infusion Therapy System, Sandy, UT) was inserted into the antebrachial vein and connected to the STG-22TM (Nikkiso Company, Tokyo, Japan) for continuous blood glucose monitoring. A 20G catheter was inserted into the radial arterial to collect blood samples intermittently. Patients in R group were infused acetated Ringer solution without glucose, while patients in G group were infused 1.5% glucose Ringer solution during anesthesia. The infusion rate of these Ringer solutions was 20 mL/kg/h at the start of anesthetic induction. Then, the infusion rate was decreased to 5 mL/kg/h one hour after the start of infusion however it was changed depending on situations and freely adjusted by the anesthesiologist in charge. All patients received no other fluids, such as plasma or colloids except of 100 mL of saline for administration of antibiotics. The blood glucose levels of all patients were continuously monitored by the STG-22TM, and insulin therapy was permitted intraoperatively when a glucose level exceeded 180 mg/dL. A rectal probe was inserted for core temperature monitoring. Ambient temperature was maintained at approximately 23-24°C. Patients were covered with a single cotton blanket during the study period. Rectal temperatures were recorded every 15 min after the start of surgery. When rectal temperature decreased to 36°C, patients received intraoperative forced air warming using upper body blanket (Bear Hugger Blanket; Augustine Medical, Eden Prairie, MN, USA) and the rectal temperature were maintained between 36°C and 37°C. (Measurements of plasma glucose, ketone bodies, lactic acids, pyruvic acids, free amino acids and urine urea nitrogen).

Blood samples were collected at the induction of anesthesia (T1), 1h after the induction of anesthesia (T2), 3h after the induction of anesthesia (T3), at the end of surgery (T4) to determine plasma glucose, ketone bodies, catecholamine, lactic acids, pyruvic acids and free fatty acids. The samples were centrifuged at 3,000 rpm for 10 min and the serum and plasma obtained were frozen (-20°C) until analysis. Plasma glucoses were measured at the same time using ABL System 625 (Radiometer, Copenhagen, Denmark). Ketone bodies were measured by enzymatic techniques. Thus, urine samples were collected 1.5 h after the induction of anesthesia (N1) and at the end of surgery (N2) to determine urine urea nitrogen.

Statistics

Data values are expressed as mean ± standard deviation (SD). Nonparametric variables were compared between the groups using Mann-Whitney's U test. Parametric data were compared between the groups using unpaired Student's t test. Each blood sample parameters and hemodynamic data were evaluated with two-way repeated measures analysis of variance (ANOVA). When a significant difference was indicated with the ANOVA, Tukey test or Games-Howell test was performed. A p value of <0.05 was considered as statistical significance.

Results

	R group (n=11)	G group (n=12)
Male / Female	7/4	7/5
Age (year)	32.5 ± 9.6	32.2 ± 10.6
Height (cm)	164.8 ± 8.4	163.6 ± 9.4
Weight	57.8 ± 10.0	58.3 ± 10.1
BMI (kg / m^2)	21.1 ± 2.2	21.7 ± 2.5
Fasting time (min)	675	675
Anesthesia time (min)	340.6 ± 70.6	382.2 ± 82.5
Operation time (min)	255.0 ± 64.4	285.0 ± 77.8
Fentanyl (μg/kg)	7.3 ± 1.7	6.4 ± 1.7
Remifentanil (μg / kg)	90.4 ± 43.9	76.8 ± 22.5
Infusion (mL / kg / h)	10.0 ± 3.1	8.4 ± 1.3
Urine output (mL / kg / h)	1.8 ± 1.5	1.9 ± 1.0
Blood loss (mL / kg / h)	1.2 ± 0.9	1.3 ± 0.8

Table 1: Patient characteristics and intraoperative variables values are given as the mean ± standard deviation (SD).There were no significant differences between groups by Student's t test. BMI: Body Mass Index

Twenty-three patients, 12 in G group and 11 in R group, participated in this study. No other fluids were infused except of autologous blood transfusion and insulin was not administrated for all patients. There were no significant differences in terms of demographic data (Table 1). There were no significant differences in hemodynamic status, BIS values and rectal temperature (Table 2).

	T1	T2	T3	T4
HR (bpm)				
R group	81.9 ± 18.6	63.9 ± 6.9	67.5 ± 10.1	74.9 ± 14.6
G group	79.3 ± 12.4	65.9 ± 7.4	66.0 ± 10.6	76.4 ± 14.5
SBP (mmHg)				
R group	115.3 ± 21.0	90.5 ± 7.2	87.3 ± 5.5	103.8 ± 18.0
G group	109.7 ± 23.2	88.2 ± 9.6	90.1 ± 8.0	110.2 ± 8.5
DBP (mmHg)				
R group	65.7 ± 21.1	47.0 ± 7.2	46.0 ± 4.9	52.8 ± 13.3
G group	65.5 ± 17.6	48.4 ± 9.1	47.3 ± 5.5	56.3 ± 10.5
BIS values				
R group	98.4 ± 0.7	45.1 ± 9.9	49.3 ± 12.0	67.6 ± 14.9
G group	97.5 ± 1.5	50.6 ± 7.4	52.9 ± 11.9	64.9 ± 5.2
Rectal temperature (°C)				
R group		36.6 ± 0.3	36.7 ± 0.5	37.4 ± 0.5
G group		36.5 ± 0.3	36.6 ± 0.4	37.2 ± 0.5

Table 2: Hemodynamic status and BIS values of patients. Values are given as the mean ± SD. There were no significant differences between groups by ANOVA. T1; Anesthetic induction, T2; 1h after anesthetic induction, T3; 3h after anesthetic induction, T4; at the end of surgery HR: Heart Rate, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, BIS: Bispectral Index.

Blood glucose level was monitored continuously for all patients during operation using the STG-22TM. Intermittent measurement of the plasma glucose levels was also performed. RQ and REE were monitored continuously for all patients during operation using the V-Max. There were no significant differences in both groups (Figure 2). Hyperglycemia was not observed and blood glucose level was maintained stably less than 150 mg/dL in both groups during surgery.

RQ was decreased from 1h after start of operation in both groups. In R group, it was significantly decreased 0.78 ± 0.11 (p=0.037) at 3h after start of operation. In G group, it was significantly decreased from T1 (1.00 ± 0.11) to T4 (0.87 ± 0.09) (p=0.022) (Figure 3). REE was almost maintained during operation in both groups (Figure 4). There were no significant differences in both groups.

The plasma concentration of total ketone bodies was significantly higher in R group than that in G group at T4 (p=0.027) (Figure 5). In G group, it decreased from T1 to T4. That of Acetoacetic acid and 3-Hydroxybutyric acid was significantly higher in R group than that in G group at T4 (p=0.028, p=0.045). In all patients, acetone was not detected at any measurement.

The plasma concentration of free fat acids (FFA) was significantly decreased from 672.3 ± 252.3 μEq/L (T1) to 331.7 ± 220.7 μEq/L (T4) (p=0.012) in G group (Figure 6). FFA was significantly higher in R group than in G group at T3, T4 (p=0.026, p=0.008).

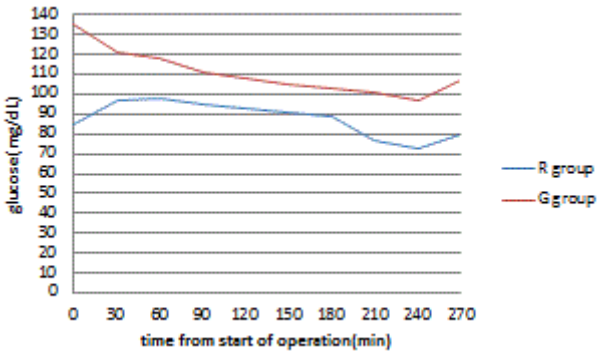

Figure 2: Continuous blood glucose monitoring using the STG-22TM. Alteration of mean blood glucose levels of G group (n=12) and R group (n=11).

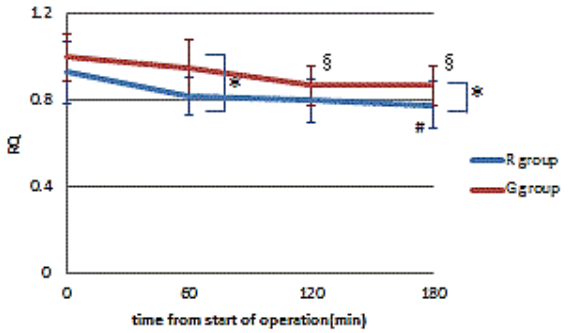

Figure 3: Changes in RQ. Differences between groups were significant for plasma ketone bodies concentrations by ANOVA repeated measurement. #p < 0.05 in comparison to that at start of operation in R group using Tukey test. §p < 0.05 in comparison to that at start of operation in G group using Tukey test. *p < 0.05 between groups using unpaired Student's t test. Results are expressed as mean ± SD

Urine urea nitrogen (UUN) decreased in all cases at the end of surgery (Figure 7). In R group, it was decreased from 8.7 ± 6.3 g/day to 5.7 ± 3.3 g/day. In G group, it was decreased from 9.7 ± 9.5 g/day to 6.8 ± 2.9 g/day. However, no significant differences are detected in UUN between two groups.

Discussion

The higher RQ was measured in G group during surgery than in R group, particularly at 1h and 3h after start of operation. The results have indicated that RQ in patients received glucose is maintained higher than that in patients received no glucose. Brandi et al. reported RQ measurement was useless for metabolic purposes at least for 120

minutes after ventilator resetting [15]. In our results, there were significant differences at 1h, but no significance at 2h. However, significant differences between groups at 3h indicated that patients receiving glucose preferentially metabolized it as an energy source during surgery. In pediatric anesthesia, RQ of the patients given glucose was significantly higher than that of the patients without glucose [11]. The impact of intraoperative glucose administration on RQ has been studied in adult patients immediately after surgery. In the study, RQ of the patients receiving intraoperatively glucose-containing solutions administration was postoperatively higher than the patients receiving normal saline [16]. Our results suggested that no glucose administration reflects the importance of lipids as a major energy source 3h after start of operation.

Intraoperative glucose administration is assumed to prevent ketogenesis and lipolysis. We reported that overnight fasting and administration of no glucose increased in serum ketone bodies during surgery, however, intraoperative low-dose of glucose, corresponding to 43% of estimated basal energy expenditure, effectively suppressed ketogenesis in orthopedic surgery [17]. There were significant differences between the two groups in the free fatty acids and ketone bodies during surgery. Those results suggested that patients received no glucose during surgery was actively lipid metabolism. This would be evidence to prove the decrease in RQ is moving towards a lipid metabolism.

UUN is one of the protein metabolic indicators. Thus, in our study, significant differences were not detected in UUN. A certain study reported UUN did not significant change during perioperative period [18]. We think more studies about protein metabolism are need to do.

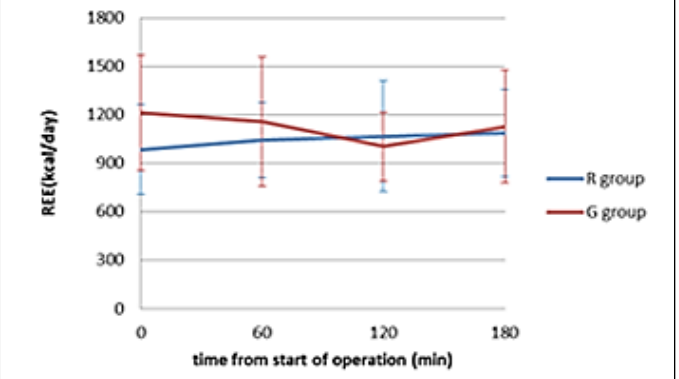

Figure 4: Changes in REE. There were no significant differences between groups by unpaired Student's t test. Results are expressed as mean ± SD.

As nutrient especially for brain tissue, glucose is the most important. However, storage of glucose in our body is usually less than basal energy expenditure for one day. Even in young patients, therefore, more than one-third of glucose production depends on gluconeogenesis after 22 hours of fasting [19]. However, intraoperative glucose administration has not been performed routinely because high dose of glucose infusion might cause hyperglycemia [20-24] When the benefit of intraoperative glucose administration is assumed, lower amounts are now recommended [25]. However, aggressive glycemic control increased the incidence of hypoglycemic events and did not result in any significant improvement in clinical outcomes that can be achieved with moderate control [26].

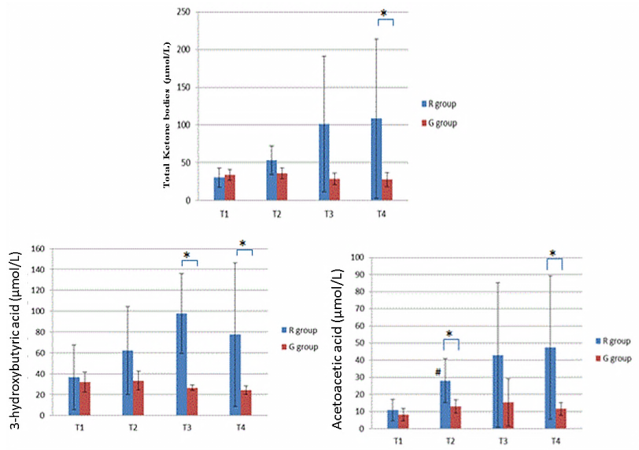

Figure 5: Changes in ketone bodies at anesthetic induction (T1), 1 h (T2), 3 h after anesthetic induction (T3), at the end of surgery (T4). Differences between groups were significant for plasma ketone bodies concentrations by ANOVA repeated measurement. #p<0.05 in comparison to T1 in R group using Games-Howell test and *p<0.05 between groups using Mann-Whitney U test. Results are expressed as mean ± SD.

In the current study, hyperglycemia was not observed. The mean blood glucose level in G group increased to almost 150 mg/dL in 1h after the induction of anesthesia due to the rapid infusion at 20 mL/kg/h. The infusion rate was changed from 20 mL/kg/h to 5 mL/kg/h at one hour after the start of infusion and the average administration rate of glucose was about 0.17 g/kg/h intraoperatively.

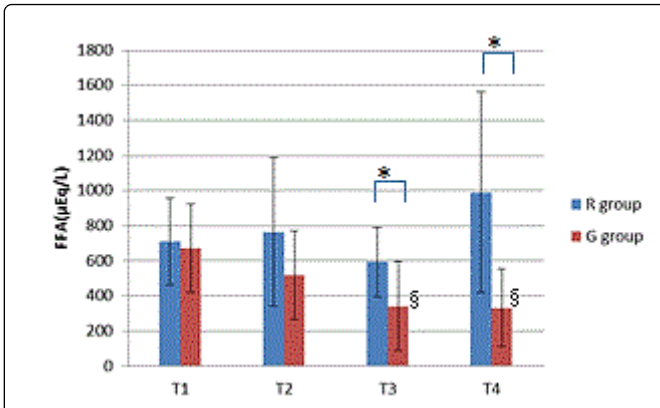

Figure 6: Changes in free fat acids at anesthetic induction (T1), 1h (T2), 3h after anesthetic induction (T3), at the end of surgery (T4). Differences between groups were significant for plasma ketone bodies concentrations at p<0.05 by ANOVA repeated measures between groups. §p < 0.05 in comparison to T1 in G group using Tukey test. * p<0.05 between groups using Mann-Whitney U test. Results are expressed as mean ± SD

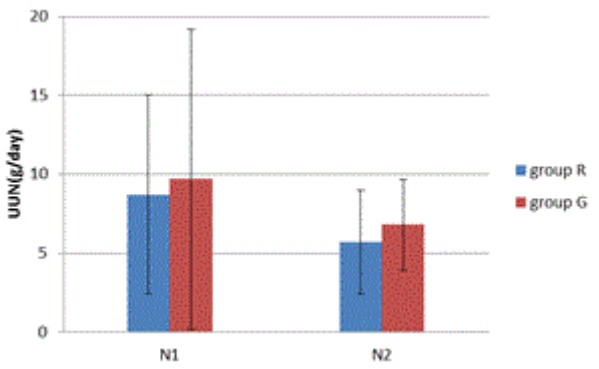

Figure 7: Changes in UUN at 1.5 h after the induction of anesthesia (N1) and at the end of surgery (N2). There were no significant differences between groups using unpaired Student's t test.

This small-dose of glucose did not cause hyperglycemia during surgery and that covers about 82.4% of basal energy expenditure. However, it effectively suppressed ketogenesis and increase ofdecreased plasma FFA at 3h after the induction of anesthesia and the end of surgery.

Depression of whole body protein and glucose metabolism are caused by surgery, independently of the anesthetic technique [27]. The emotional stress of being brought to the operating theatre and the stress of surgery seem to be more important than anesthesia in causing a rise in blood sugar and plasma FFA [28]. However, we suggest the anesthetic management in this study, particularly in nutrition, could control the metabolic changes induced by surgical stress. If patients take some stress as invasive surgery and fasting, it is likely the required amount of nutrients to change. Terashima et al. explained about the energy dynamics in the critical illness [29]. It has been reported that when patients take the invasion, they are supplied an endogenous energy depending on the size of the invasion as a primitive physiological responses.

Bio energy is replenished by the endogenous and exogenous energy. The higher invasion is because stress hormones and cytokines are released, endogenous energy increases. And if we administer the energy greater than REE, remaining surplus energy is mainly used for lipogenesis because it is impossible to change from dissimilation to anabolic [29,30]. Therefore, we should control the glucose administration by checking REE and RQ during surgery. Stephen et al. reported that RQ should not be used to finely adjust the nutrition support regimen, however comparing calories infused with REE was the best way [17]. We think indirect calorimetry is useful during surgery for nutrition management.

In conclusion, the infusion of 1.5% glucose solution during surgery did not cause either hyperglycemia or hypoglycemia, suppressed ketogenesis, and may maintain glucose metabolism successfully. The RQ measurements by indirect calorimetry indicate utilization of glucose administration during anesthesia and surgery.

Acknowledgements

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Author Disclosures

The authors declare that we have no conflict of interest with regard to this manuscript.

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