The Research on Perioperative Blood Glucose and Insulin Levels of Patients with Single Insulinoma

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Research Article

Keywords: insulinomas, predict, insulin, glucose, resection effectiveness

Posted Date: December 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1149826/v1

Abstract

Background The blood glucose level is an important biochemical parameter for evaluating the resection effectiveness of insulinomas. However, whether other biochemical parameters have better evaluating ability remains unclear. The current study aims to compare the evaluating capability of blood glucose and insulin levels at several aspects, such as the accuracy and response time.

Methods Between September 2017 and July 2018, 21 insulinoma patients with single tumor who underwent surgical resection were enrolled. Peripheral venous blood samples were assayed for blood glucose and insulin levels on the day of surgery and at 30 minutes, 60 minutes, 1 day, and 7 days after surgery. The evaluating abilities of blood glucose and insulin levels for resection effectiveness were recorded and compared.

Results The evaluating performance of the insulin level was better than that of the blood glucose level (100% for 21 patients vs 82.4% for 17 patients), as well as the response time ($p<0.0001$). Furthermore, the insulin level was not effected by intravenous glucose infusion compared to the blood glucose level.

Conclusions Comparing with blood glucose level, insulin level is a better parameter for evaluating resection effectiveness of insulinomas with faster response and regardless of perioperative intravenous glucose infusion.

Background

Pancreatic neuroendocrine tumors (PanNETs) arise from neuroendocrine cells, which are a heterogeneous group of tumors(1). The incidence and prevalence appears to be increasing with development of imaging technologies(2–4). PanNETs include non-functional PanNETs (NF-PanNETs) and functional PanNETs, according to whether they secrete excess functional hormones(5, 6).

Insulinomas are the most common functional PanNETs, with a reported incidence of 1-4/1,000,000 persons(7–11). The hypersecretion of insulin causes serious hypoglycaemic and neuroglycopenic symptoms, including fatigue, headache, sweating, and dizziness(12, 13). For insulinomas, complete resection of tumor achieves the dual goals of hormone control and oncological benefit. The first goal requires special attention due to the tumor's relatively indolent biological behavior(14). At present, surgical resection is the only potentially curative treatment(15–18). It has previously been observed that surgical management was satisfactory for most patients with insulinoma, with a 7% recurrence after surgery(19). Failure to achieve symptomatic improvement after resection has been associated with worse recurrence-free survival (RFS)(20). Considering these points together, surgeons should confirm resection outcomes after the surgical procedure(21).

It has been demonstrated that blood glucose monitoring can diagnose insulinomas and insulinoma-induced hypoglycemia(22, 23). Rebound hyperglycemia was regarded as a biochemical cure for insulinoma after surgery(24). Continuous glucose monitoring (CGM) might be useful for evaluating

surgical outcomes. That blood glucose levels increase to more than 5.56 mmol/L or double postoperatively was considered the criteria for complete resection(25–27).

The present study aimed to explore the evaluating ability of blood glucose and insulin levels for the complete resection of insulinomas. Finally, the superiority of insulin level for evaluating resection effectiveness was observed, both in predictive accuracy and response time.

Methods

Patient selection and sample collection

The study was approved by the Institutional Review Board of Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences. All of the patients provided signed informed consent before participation.

The inclusion criteria were as follows: 1) clinical diagnosis of insulinomas according to the published criteria(28, 29); 2) pathological diagnoses of G1, G2, or well-differentiated G3 PanNETs. The exclusion criteria were as follows: 1) clinical diagnosis of Multiple endocrine neoplasm - Type I (MEN-I); 2) without pancreatic imaging (computed tomography or magnetic resonance imaging) to evaluate the surgical outcome at follow-up. Then the study enrolled a total of 21 patients with insulinoma who underwent surgical procedure, which was conducted at PUMCH between September 2017 and July 2018.

Peripheral venous blood samples were assayed for blood glucose and insulin concentrations on the day of surgery and at 30 minutes, 60 minutes, 1 day, and 7 days after surgery. The assay method for blood glucose level is the hexokinase method, while the insulin level is tested by chemiluminescent immunoassay. The standard levels of blood glucose and insulin are defined as 3.9-6.1 mmol/L and 5.2-17.2 μIU/mL, respectively. At follow-up, the tumor was considered to be completely resected if patients were asymptomatic, and imaging workups confirmed no abnormal pancreatic lesions 6 months after surgery.

Statistical analysis

The Shapiro-Wilk test was used to test the normality of the data. Continuous data following a normal distribution are presented as the mean ± standard deviation (SD). Non-normally distributed data are presented as the median and interquartile range (IQR). Student's *t*-test was used for continuous data with normal distributions, while the continuous variables that failed the normality test were tested using the Mann-Whitney *U* test. While comparing the response speed for complete resection, parameters were $\log_{10}$ transformed to eliminate the enormous differences in the order of magnitude and the slope of transformed value was used. The statistical significance was set at $p<0.05$. All of the statistical analysis was performed using SPSS software, version 24.0.

Results

Clinicopathological characteristics

The present study included 21 insulinoma patients consisted of 7 men and 14 women. Their basic characteristics are shown in Table 1. The mean age of the study population was 47.1±11.6 years old and the mean body mass index (BMI) was 27.8±3.2 kg/m^2. Open surgery was performed on two patients, and the others underwent laparoscopic surgery. Four patients were treated with intravenous glucose infusion to avoid severe and life-threatening hypoglycemia before surgery.

Pathological reports showed that the average tumor size was 13.3±3.3 mm. Tumors were located in the pancreatic head (n=6), pancreatic body (n=7), pancreatic tail (n=5), and uncinate process of the pancreas (n=3). The tumors of all patients were considered to be completely resected with a median follow-up of 25 months.

Table 1
Characteristics of 21 patients with insulinoma

Race	Chinese
Age (years)*	47.1 (11.6)
Male: Female	7: 14
BMI (kg/m^2)*	27.8 (3.2)
Tumor size (mm)*	13.3 (3.3)
Tumor location (n,%)	
Pancreatic head	6 (28.6%)
Pancreatic body	7 (33.3%)
Pancreatic tail	5 (23.8%)
Pancreatic uncinate process	3 (14.3%)
Operations (n,%)	
LS-EN	15 (71.3%)
LS-SP	3 (14.3%)
LS-SPDP	1 (4.8%)
OS-SP	1 (4.8%)
OS-PD	1 (4.8%)
Glucose infusion	
Yes	4 (19%)
No	17 (81%)
Histological grade (n,%)	
G1	11 (52.4%)
G2	10 (47.6%)

*Mean (standard deviation). LS, laparoscopic surgery; EN, enucleation of the insulinoma; SP, segmental pancreatectomy; SPDP, spleen-preserving distal pancreatectomy; OS, open surgery; PD, pancreaticoduodenectomy.

The perioperative changing trends of blood glucose and insulin levels in patients

Intravenous infusion of glucose could affect the actual condition of the blood glucose level. Therefore, patients with and without glucose infusion were separated into two groups. The preoperative blood glucose levels of patients with glucose infusion were significantly higher ($p<0.001$). However, there was

no difference between the two groups after 30 minutes after surgery. The blood glucose level of both two groups reached the highest level at 1 day after surgery, then decreased to the standard level and was maintained (Fig. 1A).

The insulin level was not affected by glucose infusion and decreased over time after surgery. There was no statistical difference in the insulin level between the two groups. The level of blood insulin decreased rapidly after the tumor was resected and fluctuated mildly within the standard range (Fig. 1B).

The eavluating ability of different criteria of blood glucose levels

In consideration of the effect of exogenous glucose, the blood glucose level should only be used in patients without preoperative glucose infusion. The blood glucose level increased to more than 5.56 mmol/L or doubled 1 hour after resection was considered as the criteria for complete resection as previously reported. There were 52.9% (9/17) and 76.5% (13/17) patients meet the criteria above at 30 and 60 minutes after surgery, respectively.

The Superiority Of Insulin Levels For Evaluating Complete Resection

As mentioned before, no statistical difference in insulin levels was found between patients with or without glucose infusion before surgery. The response speed of insulin levels was also compared between these two groups, as a result, there was also no significant difference at postoperative 30 minutes (p=0.4237, Fig. 2A). Therefore glucose infusion didn't affect the ability of insulin level to evaluate complete resection.

For all patients, there was an apparent decrease in insulin levels after tumor resected, which was maintained within the standard range at 30 and 60 minutes after surgery. The evaluating abilities were both 100% (21/21) if an insulin level less than the upper limit of the standard range was considered as the criterion for complete resection.

The blood glucose and insulin levels of 17 patients without glucose infusion were used to compare the response speed for evaluating resection completeness (Fig. 2B). The decreasing speed of insulin levels was much faster than the increasing speed of blood glucose levels at 30 minutes after surgery (-0.85±0.38 vs +0.23±0.17, p<0.0001. "+" and "-" indicate an increase or a decrease in levels). However, there was no statistical difference at 60 minutes after surgery (-0.19±0.28 vs +0.08±0.11, p=0.1183).

Discussion

Currently, blood glucose monitoring after surgery is routinely used to evaluate the complete resection of insulinomas. However, there are prerequisites for the application of blood glucose levels: firstly, the preoperative blood glucose level must be low so that it is easier to observe the increasing change.

Secondly, a portion of patients need intravenous glucose infusion to avoid life-threatening hypoglycemia, which would disturb the actual condition of endogenous blood glucose levels. Accordingly, under this circumstances, blood glucose monitoring could not be used for these patients. Therefore, the effectiveness of blood glucose levels is limited in acting as a parameter for evaluating the effect of complete resection of insulinomas.

As the aforementioned data demonstrated, the insulin level is relatively free from intravenous glucose infusion compared with the blood glucose level. In order to avoid severe hypoglycemia, patients with insulinoma can be treated with intravenous glucose infusion routinely before and during the operation without the worries of affecting the endogenous blood glucose level. Therefor it makes the insulin level more generally applicable to evaluating the complete resection of insulinoma.

Insulinomas are functional PanNETs automatically secreting insulin, and the insulin level can directly reflect the status of the tumor. The insulin level decreases sharply at 30 minutes after surgery and then it increases gradually, indicating that the insulin level was minimized within 30 minutes postoperatively. Compared with the insulin level, the response speed of the blood glucose level was relatively slower. The evaluating ability of the insulin level was better than that of the blood glucose level, both for the predictive accuracy and for response speed.

Previous studies have demonstrated that intraoperative insulin monitoring can reliably evaluate the complete removal of insulinomas(21, 30). However, these studies mainly described the application of insulin level. In our study, we compared the evaluating ability at multiple aspects between the blood glucose and insulin levels, confirming the superiority of insulin level in to blood glucose level.

The utility of insulin levels for evaluating complete resection of insulinoma is a trend. Perhaps insulin levels assayed less than 30 minutes after resection also have excellent predictive ability. It is possible to evaluate resection effectiveness earlier, which will be the next step of our study. The blood glucose level can be assayed within only 5 seconds. However, the test method of insulin level is more complicated than the blood glucose level. More convenient and rapid methods for testing insulin levels should be explored to allow for a broad range of applications, including for evaluating the complete resection of insulinoma.

About 10% insulinomas are with multiple leisions. We included insulinoma patients with single leision in this research in order to easily insure that the complete resection has been achieved definitely. Obtaining above-mentioned data, we are going to include insulinomas with multiple leisions in the further research, and study the effect of measuring the insulin level on evaluating the complete resection of multiple insulinomas.

Conclusions

In conclusion, peripheral blood insulin level is a better parameter, with faster response and regardless of perioperative intravenous glucose infusion, for evaluating resection effectiveness of insulinomas compared to blood glucose level.

Abbreviations

PanNET
pancreatic neuroendocrine tumor
NF-PanNET
non-functional pancreatic neuroendocrine tumor
RFS
recurrence-free survival
CGM
continuous glucose monitoring
PUMCH
Peking Union Medical College Hospital
MEN-I
Multiple endocrine neoplasm - Type I
SD
standard deviation
IQR
interquartile range
BMI
body mass index.

Declarations

Ethics approval and consent to participate All methods and clinical data during the current study were performed in accordance with the Declaration of Helsinki.Meanwhile, verbal informed consent was obtained from all participants and the study protocol was approved by the Institutional Review Board (IRB) of PUMCH, Chinese Academy of Medical Sciences (S-K1203).

Consent for publication Not applicable.

Availability of data and materials All data generated and analysed during the current study are included in this published article.

Competing interests The authors declare that they have no conflict of interest.

Funding This work was funded by grants from CAMS Innovation Fund for Medical Sciences (CIFMS) 2017-I2M-1-001, CAMS Innovation Fund for Medical Sciences (CIFMS) 2019-12M-1-001, and CAMS Innovation Fund for Medical Sciences (CIFMS) 2016-I2M-3-005.

Authors' contributions Conception and design: YPZ, WMW, LC, RJ, XFH; Collection and assembly of data: XQC, YYH, JLJ, LC; Data analysis and interpretion: LC, RJ; Manuscript writing: LC, RJ. All authors reviewed and approved the final manuscript.

Acknowledgments Not applicable.

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Figures

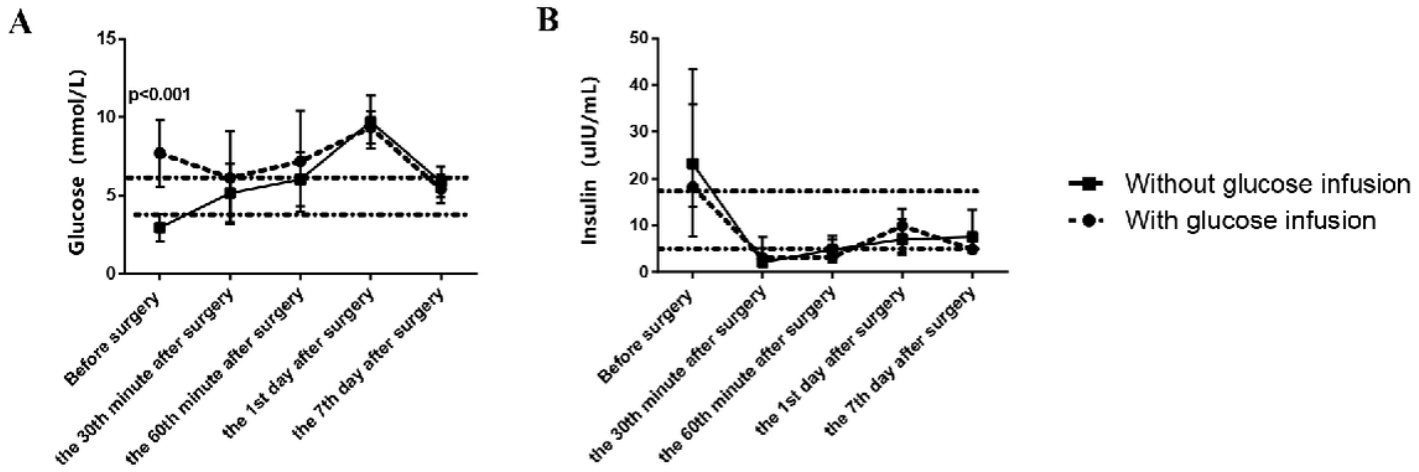

Figure 1

The trends of blood glucose and insulin levels in insulinoma patients. (A-B) The overall trends of blood glucose and insulin levels in patients with or without glucose infusion. The area between the dotted lines represents the standard range.

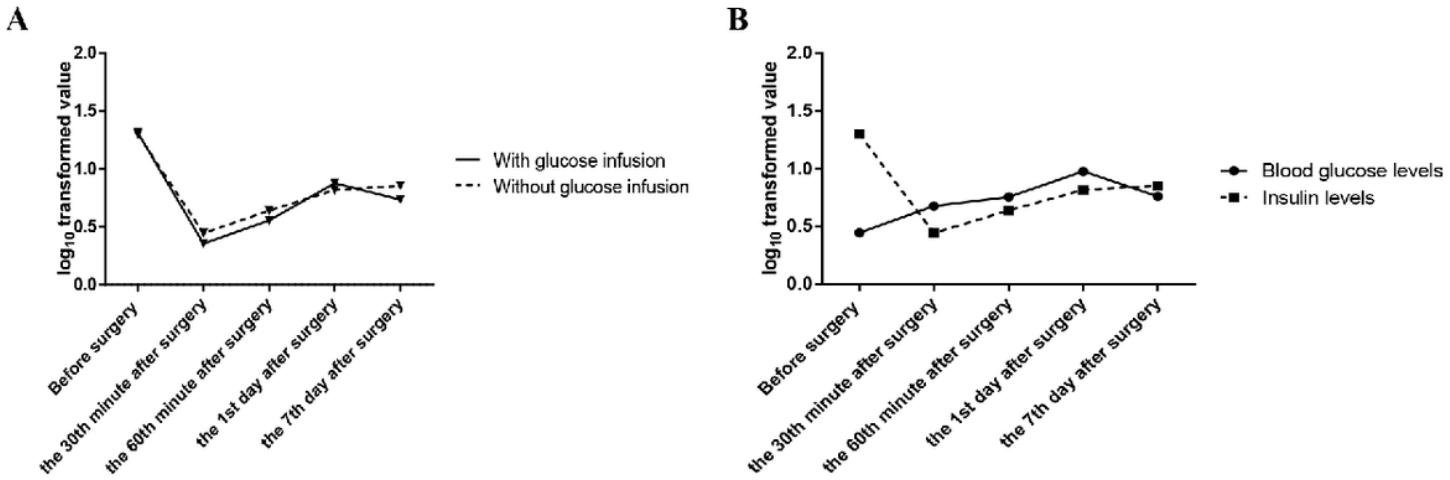

Figure 2

The superiority of insulin levels for evaluating complete resection. (A) The levels were log10 transformed to show the response speed of insulin level. (B) The levels were log10 transformed to compare the response speeds between patients with and without glucose infusion.