Analysis of a series for surgical management of insulinomas in central China

Running title: Surgical management of insulinomas

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Abstract

The aims of this study were to summarize the characteristics of insulinoma in central China and to present our experience with surgical management in the Department of Hepatobiliary and Pancreatic Surgery of The First Affiliated Hospital of Zhengzhou University. 617 patients were enrolled in this retrospective analysis, including 89 cases of insulinoma and 528 cases of other pancreatic tumors. All patients had been confirmed by histopathology reports and underwent surgical treatment. Medical data and operative notes were incorporated into the database. Among the 617 patients, 4 died during the perioperative period. In the insulinoma group, no deaths occurred. The average size of the insulinoma tumor was 1.4±0.8 cm. The ratio of open surgical procedure (57) to laparoscopic resection (32) was 1.8/1. The mean interoperation blood loss was significantly lower in the laparoscopic group (LA) (mean 35.2±17.4ml, range from 10 to 170ml) than that in the open surgical (OA) group (mean 64.7±38.6ml, range from 25 to 400ml). The mean postoperative hospital stay was also lower in the LA group (mean 8.1 ± 3.2days, range from 5 to 20 days) than that in the OA group (Mean 13.1±8.2days, range from 9 to 60 days). There was no significant difference for postoperative complications between the two groups (LA:37.5% vs OA:40.3% ). The rate of clinically significant postoperative-pancreatic-fistula (POPF) was 21.3 %, and there was only one case of C-degree-POPF. The average length of postoperative-gastrointestinal function recovery was 2.8 ± 0.9 days. And the average length of blood glucose fluctuation was 18±7.2 days. During the follow-up, 2 cases were found to be hypoglycemic again, and the rate of significant weight loss was 57.3% (51/89). Insulinoma was rare among patients who underwent surgical treatment at the Department. Their cases were benign, and their treatment was unproblematic. However, there was a small group of cases that could be associated with problematic clinical situations, and, therefore, treatment of patients with insulinoma should be conducted at specialist centers. Correct diagnostic and therapeutic management, involving close cooperation between multiple medical specialists, results in completely curing most patients.

Key words: insulinoma, pancreatic tumor, surgery
Background

Insulinoma is the most common functional neuroendocrine tumor of the pancreas [1], although its incidence in central China is rarely reported. Henan Province has a population greater than 130 million people, and more than 15,000 inpatients with various of health issues are cared for at The First Affiliated Hospital of Zhengzhou University each day. Here we aim to launch a retrospective analysis to study the characteristics of patients with insulinoma treated at the Department of Hepatobiliary and Pancreatic Surgery of The First Affiliated Hospital of Zhengzhou University between 2009 and 2019.

Materials and Methods

Subjects

617 patients were recruited into this retrospective study, including 89 cases of insulinoma and 528 cases of other tumors. The mean age was 54.7±12.1 years old, ranging from 13 to 78 years old. The ratio of males to females was 1/1.4. All data was obtained from the hospital’s medical records, surgical protocols and pathology reports. All surgical procedures were finished by the Department of Hepatobiliary and Pancreatic Surgery of the First Affiliated Hospital of Zhengzhou University from 2009 to 2019. Clinical characteristics are summarized in Table 1.

Methods

All insulinoma patients were admitted with typical symptoms, such as hypoglycemia or other nervous signs (Whipple’s triad). As a rule, the value of serum insulin and glucose were to be assayed, and other provocation tests, such as the hunger test and exercise test were performed before diagnosis. Notably, preoperative contrast enhanced CT scan and intra-operative ultrasound scan were regular in every case. According to the location of the tumor, several surgical procedures were selected whether by laparoscopic or open surgery, including tumor enucleation, radiofrequency ablation, spleen-preserving distal pancreatectomy, distal pancreatectomy, pancreaticoduodenectomy, and central pancreatectomy. All cases were confirmed by
pathological diagnosis after surgery. The different procedures are summarized in Table 2.

For other pancreatic tumor, all data were restricted from those who received radical resection. Palliative surgeries, such as choledochojejunostomy, were excluded. Of course, all cases were also confirmed by pathological diagnosis (Table 1). Patient follow-up was conducted for determination of survival and recurrence through review of our medical records, postal follow-up, and via telephone contact.

Quantitative data were summarized as means and standard deviations, analyzed using the t-test, χ2-test, and one-way ANOVA. All statistical analysis was performed with SPSS for MAC, version 21.0 (SPSS, Inc, Chicago, IL, USA). P<0.05 was considered statistically significant.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Human Research Committee of The First Affiliated Hospital of Zhengzhou University.

**Results**

Among all patients, there were 4 deaths in the perioperative period, 3 for adenocarcinoma and 1 for neuroendocrine carcinoma. No deaths occurred in the insulinoma group. The longest operation time (350 minutes) belonged to pancreaticoduodenectomy. The average size of the insulinoma tumor was 1.4±0.8 cm. The ratio of open surgical procedure (OA) vs. laparoscopic resection (LA) was 1.8/1 (57/32). The rate of conversion from LA to open surgery was 13.4%. The mean interoperation blood loss was significantly lower in the LA group (mean 35.2±17.4ml, range from 10 to 90 ml) than that in the OA group (mean 64.7±38.6ml, range from 25 to 400 ml). The greatest intraoperative blood loss (400ml) occurred in one case of distal pancreatectomy and, because of the splenic vein bleeding, ended in the conversion from laparoscopic to open operation. The mean postoperative hospital stay was lower in the LA group (mean 8.1 ± 3.2days, range from 5 to 20 days) than in the OA group (mean 13.1 ± 8.2days, range from 9 to 60 days). There were no significant differences for postoperative complications between the two groups (LA 37.5% vs. OA 40.3%). The rate of clinically significant postoperative-pancreatic-fistula (POPF) was 21.3 %. There was only 1 case of C-degree-POPF which developed into a pancreatic pseudocyst and
the patient underwent another operation six months later. The overall average length of postoperative oral intake time was 2.8 ± 0.9 days, with no significant difference between the two groups (LA 2.5 ± 0.8, OA 3.1 ± 0.7 days). Within one week after the operation, 60.1% (54/89) of patients had a peak level of blood glucose over 10mmol/L. The total average length of blood glucose fluctuation was 19.7 ± 5.6 days. During the follow-up, 2 cases were found to be hypoglycemic again, and the rate of significant weight loss was 57.3% (51/89).

The detailed data is shown in Table 2, which includes operative-related complications, overall morbidity, pancreatic fistula (PF), intra-abdominal abscess/ infection, postoperative hemorrhage, reoperation, length of postoperative gastrointestinal function recovery, length of mean hospital stay, weight lost, length of blood glucose fluctuation and recurrence of hypoglycemia.

Discussion

Insulinoma is the most common functional neuroendocrine tumor of the pancreas [2] and its incidence is 0.396 per 100,000 person-years [1,3-5], accounting for 1~2% of all pancreatic neoplasms [6]. Surgical resection is the only effective treatment for pancreatic insulinomas [7-11], and results in curing almost 95% of patients. However, some cases present problematic clinical situations, so clinical observation, monitoring and investigation are important aspects of the surgical treatment [12]. Each year, our center accepts 10 cases of insulinoma and more than 300 cases of other pancreatic tumors. Each of these patients presents a different situation, and it is most important to select suitable surgical procedures on a case by case basis.

Generally, the number and location of tumors are the most important factors to a treatment plan [9,11,13]. From multiphase dynamic CT enhanced scan to one stop perfusion enhanced scan, pre-operation image examination was routinely performed on every patient, and included MRI and ultrasonic examination. On occasion endoscopic ultrasonic was adopted [14], since EUS has been confirmed as the most sensitive preoperative technique for insulinomas [15,16]. Still, in a few patients, tumors were unable to be located exactly. Thus, in all cases, the whole pancreas should be evaluated with intraoperative ultrasonography because none of the current preoperative diagnostic methods are as sensitive as manual palpation of the pancreas and intraoperative ultrasonography [17,18]. In some insulinoma cases, the discovery in
pancreatic surgery and bimanual palpation of the whole pancreas are important [8]. We had 8 cases where new nodes were found during in exploratory surgery, which depended on palpation combined with ultrasonic investigation. Thus, we consider that palpation and ultrasonic scan in-operation is irreplaceable.

For tumors with a well-known location, enucleation is the most popular procedure. In this investigation, there were 41 patients who underwent tumor enucleation, 27 cases of open operation and 14 of laparoscopic operation. According to statistics, more than 80% of the insulinoma diameters were less than 2 cm [19], lending to the determination that these could be resected entirely laparoscopically. As instrumentation improved over time, we performed tumor enucleation increasingly through laparoscopy. Compared with open operation, there were no statistical differences in operation time or bleeding volume.

In addition to enucleation, we can perform distal pancreatectomy or spleen-preserving distal pancreatectomy by laparoscopic procedure, even for some tumors adjacent to spleen vessels which previously required resection by open operation. Considering the overall minimal disturbance to the gastrointestinal tract and faster recovery in function and postoperative oral intake, we consider the laparoscopic procedure as feasible, safe, and effective [20,21]. Furthermore, it can also reduce post-surgical pain and analgesic requirements [22]. However, some tumors remain difficult to address, especially some located in the head or sulcus of the pancreas. Of course, location in the neck is also difficult, especially when it invades the tubes or vessels. We had 3 cases of pancreaticoduodenectomy and 2 cases of central pancreatectomy.

We had 3 cases where the patient, due to advanced age or physical conditions, underwent laparoscopic-assisted radio-frequency ablation. None of these cases suffered hypoglycemic symptom relapse during the follow-up period, and we can suggest that RFA is a wise alternative compared with palliative treatment [23,24].

With the continuing development of technologies and instrumentation, procedures increasingly are being performed laparoscopically. Among our 89 cases of insulinoma, 32 cases were performed laparoscopically. The ratio of open surgical procedure vs. laparoscopic resection was 1.8/1 (57/32). Our data showed that there was no difference in the postoperative gastrointestinal function recovery time between the LA group and the OA group (2.5 ± 0.8 days versus 3.1±0.7 days, respectively; P < 0.001). However,
laparoscopic resection was distinctly superior to open procedure when considering intra-operation blood loss and length of mean hospital stay. However, laparoscopic operation is still a complicated procedure [25-28], requiring more study and improved techniques. We had 12 cases of LA converted to OA, similar to the conversion rates in the literature [27,22]. The most common (8 cases) reason was the inability to locate tumor successfully such as when the tumor was immersed in pancreatic head or due to lack of resolution in laparoscopic ultrasound. Other causes of conversion included excessive fatty tissue (1 case) a severe adhesion (1 case). Furthermore, the greatest danger was from intraoperation bleeding [11,10,29,30], and we had 2 cases with splenic vein bleeding, resulting in blood loss of 400 ml and procedure conversion.

Postoperative pancreatic fistula (POPF) is the most popular complication after pancreatic surgery [31]. Based on the criteria from the International Study Group of Pancreatic Fistula (ISGPF) [32], we defined a clinically significant POPF as grade B that required nonoperative intervention and grade C [33]. In our procedure, the clinically significant rate of POPF for insulinoma was 21.3%.

We had 3 patients who underwent pancreaticoduodenectomy and without POPF. But 2 cases underwent central pancreatectomy, resulting in 1 case of POPF. In addition, we had 3 cases involving radiofrequency ablation, finished by laparoscopically, resulting in 1 case of POPF. As for POPF, there were no difference between enucleation (24.3%; 10/41) and resection (17.8%; 8/45) (p = 0.45). Similarly, there were no difference between open operation (15.7%; 9/57) and laparoscopic operation (31.2%; 10/32) (p = 0.88). However, as shown in Table 2, for laparoscopic procedures, there existed a high rate for POPF with enucleation compared to resection (42.8% [6/14] vs. 20.0% [3/15]) (p = 0.18).

It has been reported that the rates of POPF for pancreatic neuroendocrine tumors (PNET) range from 17 to 39% [34,35,9]. In our procedure, the rate was obviously lower, possibly because the majority of cases were functional insulinomas. Comparatively, non-functional PNET and inherited diseases will have higher rates of POPF, such as VHL or MEN-1 [36,15], in part because they have increased abnormal pancreatic parenchyma [37-40]. Other reports suggest that PNET is a risk factor for developing POPF, when compared to procedures for pancreatic adenocarcinoma or chronic pancreatitis [41,40].
All patients had a closed suction intra-operative drain placed at the pancreatic anastomosis, resection margin, or enucleation bed. The data did not change our guidelines, although there were some investigations that found an increased risk for POPF with enucleation compared to resection [42,33]. In fact, we considered the character of the pancreatic gland, whether soft or tough, more related to POPF [43-45]. Among patients who underwent surgical procedures, only 2 cases were found to be hypoglycemic again after more than 6 months. One was found 20 months after operation, while the other was found 31 months later. Generally, we considered symptomatic hypoglycemia 6 months after removal as recurrence[1]. A limitation in our study was the follow-up period; we were unable to compare to other research with our cumulative incidence of recurrence over only ten years. Service et al. followed 169 cases for more than 60 years, and confirmed the cumulative incidence of recurrence was 6% at 10 years and 8% at 20 years[1]. They also confirmed that, if a recurrence has not appeared within 20 years, subsequent recurrence is extremely unlikely [1]. However, hyperglycemia with a need for insulin therapy occurring during the first postoperative week is a common phenomenon [46,47]. In our group, 60.1% (54/89) of patients had a peak level of blood glucose over than 10 mmol/L, and the average median time for blood glucose level to return under 6.9 mmol/L was 19.7 ± 5.6 days. which is much longer than the data reported by Yu [46].

During the follow-up period, we noticed that 57.3% (51/89) of patients had significant weight loss. 3 months after surgery, 51 patients had a body weight decrease of more than 5 kg, and the average percent of weight loss was greater than 8%. Many factors possibly contributed to the postoperative weight loss [48], such as decreased food intake, elimination of hyperinsulinemia and surgical trauma. Similar to our results, Hongmei et al. reported significant weight loss after surgery for a group of patients with insulinoma [49]. Their statistics showed that patients with high BMI (median BMI = 26.0 kg/m2) had a significant weight loss of 11.5 kg and %WL of 15.0% 3 months after surgery. Furthermore, they maintained a steady weight change from 3 months after surgery to 1-3 years after operation.

**Conclusion**

In conclusion, insulinoma is a very rare, but important disease. Accurate information about its natural history remains limited. Without doubt, surgical treatment is the most
important method in curing insulinoma, but due to the different body conditions and different tumor locations, exact surgical techniques should be selected on a case by case basis. Because of the retrospective character of this study, additional research is required.

Acknowledgments

All patients signed written informed consents and agreed to publish this report.

Funding:

No receiving funding

Authors' contributions

SQ, XH and YZ conceived and designed the experiments. SQ, MD, GZ, HL, and YG collected and analyzed the data. SQ and YZ interpreted the results and wrote the manuscript. All authors read and approved the manuscript and agree to be accountable for all aspects of the research and to guarantee for the accuracy and integrity of any part of the work.

Ethics approval and consent to participate

This study was performed in accordance with standard guidelines and was approved by the Ethics Committee of The First Affiliated Hospital, Zhengzhou University (Approval No: 2016004). All patients provided written informed consent prior to the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.
Table 1. Clinical data of 617 patients who underwent pancreatic surgery in The First Affiliated Hospital of Zhengzhou University

| HISTOPATHOLOGICAL | MEDIAN AGE (YEARS) ± S D | RANGE (YEARS) | MALE/ FEMALE RATIO | TUMOR LOCATION | TUMOR SIZE | PROCEDURE | DEATH |
|-------------------|--------------------------|---------------|---------------------|----------------|------------|-----------|-------|
|                   |                          |               |                     | UNCINATE | NECK | BODY / TAIL | LA | OA | CONVERT |
| PI                | 45±13.8                  | 13~74         | 1/1.8               | 6       | 14   | 69         | 1.4±0.8 | 32  | 57 | 13.4% | 0     |
| PDAC              | 56±14.6                  | 27~76         | 1/1.2               | 174     | 27   | 124        | 2.8±1.7 | 94  | 231 | 15.7% | 3     |
| IT                | 40±10.1                  | 25~60         | 1/0.4               | 2       | 2    | 6          | 3.5±3.2 | 1   | 9   | 20.0% | 0     |
| NET               | 48±11.2                  | 26~71         | 1/0.8               | 3       | 4    | 25         | 2.7±1.1 | 13  | 30  | 11.6% | 0     |
| NEC               | 39±10.7                  | 30~64         | 1/0.9               | 2       | 5    | 31         | 4.5±1.2 | 7   | 31  | 13.1% | 1     |
| IPMN              | 68±12.1                  | 50~78         | 1/0.6               | 22      | 3    | 7          | 1.5±2.2 | 14  | 18  | 6.2%  | 0     |
| MCN               | 48±5.4                   | 40~56         | 0/35                | 0       | 2    | 23         | 2.4±0.8 | 10  | 25  | 8.5%  | 0     |
| SCN               | 63±10.7                  | 48~74         | 1/4.0               | 0       | 2    | 8          | 8.4±5.6 | 4   | 6   | 0%    | 0     |
| GIST              | 61±14.6                  | 31~72         | 1/1.0               | 0       | 2    | 4          | 4.2±2.6 | 1   | 5   | 0%    | 0     |
| SPT               | 25±11.8                  | 18~45         | 1:3.4               | 4       | 3    | 15         | 9.34±2.7 | 8   | 14  | 4.5%  | 0     |
| SFT               | 35±8.9                   | 25~64         | 1/1.3               | 1       | 1    | 5          | 2.2±1.3 | 2   | 5   | 0%    | 0     |

PIs—pancreatic insulinoma, NEC—neuroendocrine carcinoma, NET—neuroendocrine tumor, GIST—gastrointestinal stroma tumor, PDAC—pancreatic ductal adenocarcinoma, IPMN—intraductal papillary mucinous neoplasm, SFT—solitary fibrous tumor, MCN—mucinous cystic neoplasms, SCN—serous cystic neoplasms, SPT—solid papillary tumor, IT—inflammatory
LA=Laparoscopic Operation; OA=Open Operation; RA=Radiofrequency Ablation; EN=enucleation; DP=distal pancreatectomy; PD=pancreaticoduodenectomy; CP=central pancreatectomy SPDP=spleen-preserving distal pancreatectomy;

POPF was defined analogous to the ISGPF criteria. Grade A POPF is defined as an asymptomatic elevation of pancreatic enzymes in the drainage without requiring a specific treatment. Grade B POPF is mostly associated with an abdominal infection. A specific treatment or persistent drainage over 3 weeks can be required. Grade C POPF a severe change of the clinical management or deviation from the normal clinical pathway occurs (e.g. reoperation, intensive care unit, death).

| Procedure                          | Open Operation | Laparoscopic Operation | Total |
|------------------------------------|----------------|------------------------|-------|
|                                    | EN  | DP  | SPDP | PD  | CP  | EN  | DP  | SPDP | RA  |
| Number                             | 27  | 16  | 9    | 3   | 2   | 14  | 11  | 4    | 3   | 89  |
| length of operation time (minutes) | Range          | 30~40~60~240~160~50~60~120~30~30~30~350 | 120 120 120 240 120 240 240 60 350 350 |
|                                    | SD  | 6.4±3.8 | 3.5±1.7 | 4.7±3.8 | 47.8±25.4 |
| Intra-operation blood lost (ml)    | Range          | 9~25~30~60~50~20~20~25~10~10~97 | 400 400 120 240 140 70 100 170 15 400 |
|                                    | SD  | 6.4±3.8 | 3.5±1.7 | 4.7±3.8 | 47.8±25.4 |
| length of mean hospital stay (days) | Range          | 9~15~8~12~10~6~7~7~5~5~15 | 15 60 24 24 20 14 20 18 20 60 |
|                                    | SD  | 6.4±3.8 | 3.5±1.7 | 4.7±3.8 | 47.8±25.4 |
| Gastrointestinal function recovery (days) | Range          | 1~5 | 2~4 | 2~5 | 2~5 | 2~4 | 1~4 | 2~5 | 2~5 | 1~3 | 1~5 |
|                                    | SD  | 3.1±0.7 | 2.5±0.8 | 3.1±0.7 | 2.8±0.9 |
| abdominal abscess/infection        | 3   | 2   | 1    | 1   | 1   | 0   | 0   | 0    | 0   | 0   | 8   |
| postoperative hemorrhage           | 0   | 1   | 1    | 1   | 0   | 0   | 0   | 0    | 0   | 0   | 3   |
| pancreatic fistula A+degree        | 4   | 2   | 1    | 0   | 1   | 6   | 2   | 1    | 1   | 21.3% |
| pancreatic fistula B+degree        | 0   | 1   | 0    | 0   | 0   | 0   | 0   | 0    | 0   | 0   | 3   |
| pancreatic fistula C-degree        | 0   | 1   | 0    | 0   | 0   | 0   | 0   | 0    | 0   | 0   | 3   |
| total postoperative complications   | 40.3% | 37.5% | 39.3% |
| weight lost >5kg in 3 month         | 11  | 9   | 5    | 3   | 2   | 10  | 7   | 3    | 1   | 57.3% |
| Blood glucose fluctuation (days)    | Range          | 12~21~13~21~13~13~10~11~13~21~25~21~25~21~28 | 20 25 21 28 27 20 19 16 19 21|
|                                    | SD  | 2.0±7.8 | 1.6±8.6 | 1.8±7.2 |
| symptom recurrence hypoglycemia     | 1   | 0   | 0    | 0   | 0   | 1   | 0   | 0    | 0   | 2   |

**Table 2. Clinical feature of patients with insulinoma**
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