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Original Article / Özgün Araştırma

Long-term Outcomes of Surgical Management of Insulinoma: Single Center Experience

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Abstract

Objective: Limited data are available in regards to the surgical management and outcomes of insulinoma. This study aimed to assess the outcomes associated with surgical treatment of insulinoma, as the most common pancreatic endocrine tumor.

Methods: Medical records of patients who diagnosed as insulinoma from 2000 to 2010 at General Surgery Department of Cukurova University Hospital were retrospectively reviewed. Surgical treatment (resection vs. enucleation) was based on preoperative radiological investigations (abdominal spiral contrast tomography, ultrasound, selective angiography for selected cases) and intra-operative ultrasound imaging once indicated.

Results: Surgically treated thirteen patients (F/M:9/4) who diagnosed with insulinoma were assessed with a mean follow-up of 5.3 (0.5-10) years. Enucleation and distal pancreatectomywere performed for 11 and 2 (one of those is spleen-preserving) patients, respectively. No mortality was recorded. All patients became normoglycemic after surgery without re-operation and with acceptable complication rates (n=3 pancreatic fistula, n=1 pancreatitis).

Conclusion: Surgical treatment of insulinoma is associated with favorable outcomes.Intra-operative ultrasound with manual palpation is still the gold standard for localizing insulinoma. Location, size and relationship with main pancreatic duct of the lesions are key components for the selection of optimal surgical procedure.

Keywords: insulinoma; surgical treatment; enucleation; pancreatic endocrine tumor.

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İnsülinomanin Cerrahi Yönetiminde Uzun Dönem Sonuçlar: Tek Merkez Deneyimi

Öz

Giriş: İnsülinomanin cerrahi yönetimi ve sonuçlarıyla ilişkili olarak sınırlı miktarda bilgiler mevcuttur.Bu çalısma en sık pankreatik endokrin tümör olan insülinomaların cerrahi tedavisiyle ilgili sonuçları değerlendirmeyi amaçlamıştır.

Yöntemler: Çukurova Üniverstitesi Genel Cerrahi Departmanında 2000 ile 2010 yılları arasında insulinoma tanısıyla ameliyat edilen hastalar geriye dönük olarak değerlendirildi. Rezeksiyon yada enükleasyondan oluşan cerrahi tedavi kararı preoperatif radyolojik değerlendirme (abdominalkontrastlı tomografi, ultrason ve endikasyou olan hastaraselektifanjiografi) ve intraoperatifultrasonografik görüntülemeye göre yapıldı.

Bulgular: Cerrahi olarak tedavi edilen, insulinoma tanısı alan ve ortalama takip süresi 5.3 yıl (0.5-10) olan 13 hasta (K/E:9/4) calışmayadahil edildi. Enükleasyon 11 hastaya uygulanırken 2 hastaya distalpankreatektomi (biri dalak koruycu) uygulandı. Mortalite izlenmedi. Cerrahi sonrası tüm hastalar tekrar ameliyat gereksinimi olmaksızın kabul edilebilir komplikasyon oranları (panreatik fistül, n=3; pankreatit, n=1) ile normoglisemik hale geldi.

Sonuç: İnsülinomanin cerrahi tedavisi olumlu klinik sonuçlarla ilişkilidir. İnsulinomanin lokalizasyonunu saptamada intraoperatifultrasonla birlikte palpasyonla yapılan değerlendirme altın standarda sahiptir. Uygun cerrahi prosedürü belirlemede lezyonun lokalizasyonu, boyutu ve ana pankreatik kanal ile ilişkisi kritik öneme sahiptir.

Anahtar kelimeler: İnsülinoma; cerrahi tedavi; enükleasyon; pankreatik endokrin tümör.

INTRODUCTION

Insulinoma is the most common pancreatic endocrine tumor, with an incidence of 2-4 cases per million people per year[1,2]. These tumors are usually small (less than 2 cm), single and only 5-8% of those are malignant[3,4]. The typical symptoms of insulinoma include tiredness, weakness, faintness, trembling, awareness of the heartbeat, nervousness and hungerand have been attributed to low blood sugar concentrations secondary to excessive insulin release. Other symptoms include headache, confusion, vision abnormalities, unsteadiness, and marked changes in personality (glycopenic and sympathoadrenal)[4,5]. Loss of consciousness, seizures and coma may also occur[6]. Insulinoma presents many problems associated with diagnosis and localization[7]; fortunately, new imaging modalities such as endoscopic ultrasound and intraoperative ultrasonography have improved identification and localization[7-11].

Insulinoma should immediately be treated surgically to prevent the risk of malignancy and development of life threatening symptoms associated with hormonal affects. This report reviews our experience with the diagnosis, localization and treatment of thirteen cases of insulinoma.

METHODOLOGY

The This retrospective study was carried out at the Department of General Surgery of Cukurova University Hospital over a period of ten years from 2000 to 2010. The Institute's Ethics Committee approved the study (number:66/47; date: 07/07/2017) and written informed consent was obtained from each participant. Thirteen patients had clinical and laboratory findings giving rise to suspicion of insulinoma. We recorded the following data: patient demographics, clinical presentation, surgical procedure, hospitalization, morbidity, clinical outcome, and long-term follow-up. We also analyzed preoperative and postoperative serum glucose, insulin, proinsulin and C-

peptide levels. Preoperative radiological investigations, such as abdominal spiral contrast tomography, ultrasound and, in selected cases, angiography, were used to localize the lesion and assess the prospects for surgery.

During surgery, the pancreas was inspected and palpated. If the tumor could not be localized, we performed intra-operative ultrasound imaging with manual palpation. Once the tumor was located, enucleation or resection was performed according to tumor size, localization and suspicion of malignancy. Intra-operative frozen sections were also taken routinely but in all patients the specimens were sent for formal histopathological confirmation.

Patients were postoperatively followed up at 1, 6, 12, 18, 24 months, and yearly thereafter in the outpatient clinic. Clinical presentation and serum insulin, proinsulin and C-peptide were recorded at intervals of six months. Descriptive statistic is used to evaluate study outcomes.

RESULTS

Thirteen patients were diagnosed with insulinoma and were surgically treated between 2000 and 2010.There were 9 female and 4 male with median age of 56 (range 27-72 years). Neuroglycopenic and sympathoadrenal symptoms had occurred in all patients and the mean duration was 17.3 months (range 11-27 months). No abnormality was found on physical examination. Table-1 shows the demographic and preoperative laboratory data.

Three insulinomas were detected by transabdominal ultrasonography and seven by computed tomography (Figure-1). Insulinoma was detected by angiography in one particular patient (Figure-2). Intra-operative ultrasound was used in six patients as a part of surgical exploration and the tumor was detected in five. Twelve tumors were detected with the aid of intra-operative ultrasound and manual palpation together. Tumor size, preoperative radiologically detected tumors, palpated tumors, tumors detected with the aid of intra-operative ultrasound, and surgery performed are shown in table 2.

Five insulinomas were located in the head of the pancreas, six in the body and one in the tail.Eleven patients underwent enucleation and one had distal pancreatectomy (Figure3). One tumor was not localized after extensive exploration and intra-operative ultrasonography, and a spleen-preserving distal pancreatectomy was performed. This patient also became normoglycemic after surgery. In all cases, histopathology confirmed the presence of a neuroendocrine tumor, all benign. Tumor size was ranged from 1 to 4 cm (mean 1.85 cm). The overall mortality was zero. The most common complication was pancreatic fistula which was observed in three cases(flow rate: 150 cc/day for all) and treated conservatively.Pancreatititis was seen in one case; no re-operation was required.The mean follow-up was 5.3 (0.5-10) years. At present, all patients are alive and normoglycemic.

DISCUSSION

Insulinoma is the most common pancreatic neuroendocrine tumor. Non-specific adrenergic symptoms include anxiety, sweating, and palpitations, but true organic endogenous hyperinsulinism is characterized by neuroglycopenic symptoms such as confusion, amnesia, visual disturbances, seizures and coma[1-6].Surgery is the treatment of choice and has an extremely high success rate (75-98%) in experienced hands[8,12,13].

Table 1: Preoperative demographic characteristics and laboratory data

Patient No	Sex	Age	Blood Sugar (mg/dl)	Insulin (U)	C-peptide (U)
1	F	70	48	18.02	1.20
2	F	62	54	21.56	2.50
3	F	31	60	14.21	3.31
4	M	28	55	17.23	2.41
5	F	27	52	46.88	0.145
6	F	30	62	31.02	3.71
7	F	49	50	14.03	1.35
8	M	46	49	25.00	3.41
9	M	42	61	20.79	2.89
10	F	64	53	27.31	3.82
11	F	50	57	25.01	2.01
12	F	72	55	24.02	3.52
13	M	70	50	34.20	3.65

F: female; M: male

Table 2: Tumor size, detection method and surgical procedure

NO	Tumor diameter (mm)	Preoperative Detection	Palpation	Intraoperative Ultrasound	Surgical Procedure
1	10	**-**	**+**	+	Enucleation
2	15	**+**	**+**	NA	Enucleation
3	15	**-**	**+**	+	Enucleation
4	10	**+**	**+**	NA	Enucleation
5	-	**-**	**-**	-	Spleen preserving distal pancreatectomy
6	40	**+**	**+**	NA	Distal pancreatectomy
7	25	**+**	**+**	NA	Enucleation
8	15	**+**	**+**	NA	Enucleation
9	15	**+**	**+**	NA	Enucleation
10	20	**+**	**+**	NA	Enucleation
11	20	**-**	**-**	+	Enucleation
12	15	**-**	**+**	+	Enucleation
13	30	**+**	**+**	+	Enucleation

Figure 1: CT appearance of aninsulinoma at the head of pancreas

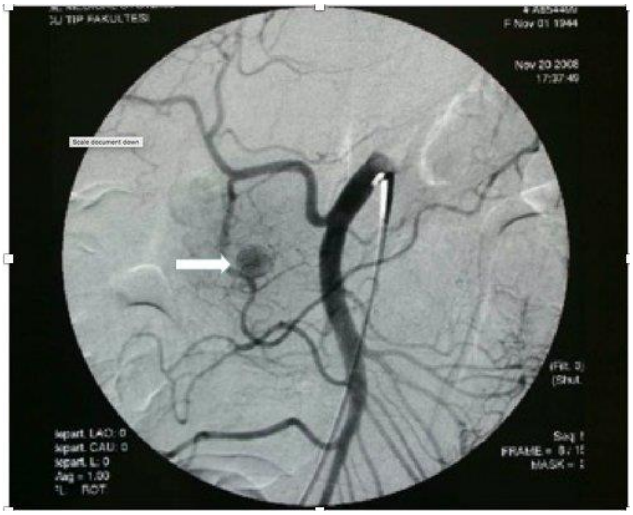

Figure 2: Angiographic appearance of an insulinoma

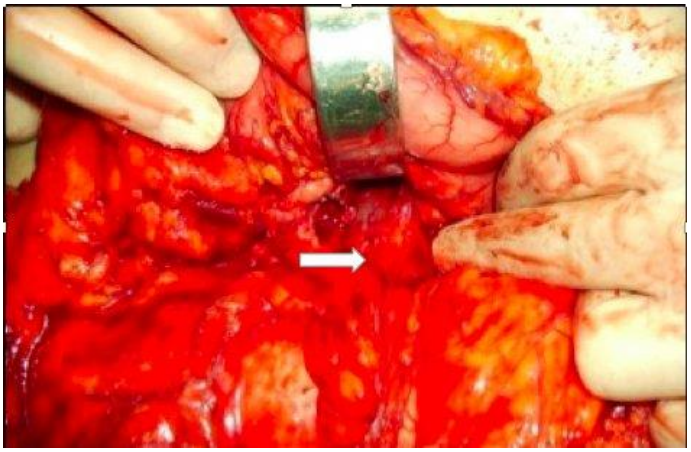

Figure 3: Tumor mass is seen at the anterolateral side of portal vein

After the diagnosis has been made from the symptoms and laboratory findings, it is essential to localize the tumor, which can be problematic[1,11,12]. Preoperative localization of the insulinoma is of utmost importance in the management of these neoplasms, since their location in the pancreas, their number and their relationship to important anatomical structures are the most important determinants of the surgical procedure selected[7] Trans-abdominal ultrasonography, abdominal computed tomography, magnetic resonance imaging, arteriography, endoscopic ultrasonography, transhepatic portal venous sampling, selective arterial calcium with hepatic venous sampling, in-labeled octreotide scans with single photon emission CT, intraoperative ultrasonography and intra operative palpation have all been used[8-11,13].

The sensitivity of transabdominal ultrasonography in the localization of pancreatic insulinoma is 9 – 64%[8-11,14]. Endoscopic ultrasound has a sensitivity of 54-94%[9-11], but is invasive, expensive, operator-dependent and the detection rate for distally localized tumors and malignancy is poor[8-11,13,14]. The sensitivity of CT in insulinoma detection has been improved recently; 60-65% of all insulinomas can be detected by transabdominal ultrasonography and computed tomography[13-17]. CT is the most commonly used non-invasive preoperative localization test. Contrast enhancement is routinely used and insulinomas are usually visualized as rounded, well-defined lesions based on CT imaging. However, developments in CT technology have drastically changed its usefulness as a first-line option in preoperative detection and previous modest results are probably not indicative of the current state of the technology. Dynamic CT has supplantedconventional CT scanning as the modality of choice due its ability to better detect small lesions thus increasing sensitivity to over 80%[17,18,19,20].In our clinic, ultrasound and/or dynamic CT imaging could detect the lesion in majority of insulinoma patients.

If radiological imaging techniques fail to show tumor localization, transhepatic portal venous sampling and selective arterial calcium with hepatic venous sampling may be used[15-21]. However, these techniques were unavailable in our center. At the time of surgical exploration, the entire gland should be inspected and palpated with the aid of intraoperative ultrasonography[5,8,9,11,13-15]; we detected eleven of the tumors thus.Intraoperative ultrasound was used in six patients as a part of surgical exploration and the tumor was detected in five of those.

Pancreatic insulinoma may occur in any part of the gland[8-10,13,22]; five of ours were located in the head of the pancreas, six in the body and one in the tail. Only in one case did we failed to detect the tumor after extensive exploration and intraoperative ultrasonography. The patient became normoglycemic after spleen-preserving distal pancreatectomy. In another case, distal pancreatectomy and splenectomy were performed because of uncontrolled bleeding from the splenic hilum. Enucleation was performed in the remaining eleven cases. Recent guidelines suggest that the blind distal pancreatectomy should not be performed when localization has failed[4,7,12,15].Traditional resections and parenchyma-sparing resections or a combination of both can be employed depending on indications. Factors that dictate the choice of procedure and should be addressed preoperatively are a diagnosis of multiple endocrine neoplasia syndrome type 1 (MEN 1), the number of insulinomas, the tumor's size, location in the pancreas and anatomical proximity to the major pancreatic duct and major blood vessels, and the likelihood of malignancy. As previously stated, the majority of insulinomas are sporadic and in turn most sporadic insulinomas are solitary and benign. Therefore, parenchyma-sparing procedures such asenucleation and central

pancreatectomy are frequently performed in the management of sporadic insulinoma. Conversely, in MEN1 patients, due to the fact that the disease is regularly multifocal, a different strategy is employed and a distal pancreatectomy is the standard of care with or without enucleation of masses in the head of the pancreas[3-7]. Current treatment guidelines strongly recommend enucleation in sporadic solitary insulinoma with a diameter <2cm on intraoperative ultrasound and if structural integrity of the pancreatic duct can be maintained[20-23].

In regards to the complications, three patients undergoing enucleation suffered pancreatic leakage with low flow; which were managed conservative treatment. There was no fistula in two cases of distal pancreatectomy in which the pancreatic stump was closed by hand.

In conclusion, surgery is the treatment of choice and has an extremely high good outcome in management of insulinoma. Success is correlated with good tumor localization; we believe that intra-operative ultrasound with manual palpation is still the gold standard for localizing insulinoma once a biochemical diagnosis has been confirmed.

Declaration of Conflicting Interests: The authors declare that they have no conflict of interest.

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