ISSN: 1607-8322, e-ISSN: 2220-5799 Anaesthesia, Pain & Intensive Care
Vol 26(4); August 2022 DOI: 10.35975/apic.v26i4.1967

CASE REPORT ANESTHESIA & CONCURRENT DISEASE

Anesthetic management of insulinoma; case report and review of literature

Omar Farooq[1], Fahad Rafiq Butt[2], Romana Shaida Durrani[3]

Authors affiliations:

1. Omar Farooq, Shaukat Khanum Hospital, Lahore, Pakistan; E-mail: omar_farooq1991@hotmai.com
2. Fahad Rafiq Butt, Shaukat Khanum Hospital, Lahore, Pakistan; E-mail: Fahadrafiqbutt@skm.org.pk
3. Romana Shaida Durrani, Shaukat Khanum Hospital, Lahore, Pakistan; E-mail: romanadurrani@gmail.com

Correspondence: Dr. Omar Farooq, E-mail: omarfarooq1991@hotmail.com; Phone: +92-3104115965

Abstract

Insulinoma is an insulin-producing tumor arising from the pancreas and secreting insulin in large quantities, which manifests itself as low blood sugar. It is a rare tumor with and incidence of only 4 cases per million developing every year. Other signs and symptoms include shakes, nervousness, vomiting, pulses, perspiration, and neuroglycopenic signs like migraine, vertigo, loss of vision, tiredness, loss of vision, amnesia, uncertainty, or convulsions. Anesthetic management aims to regulate irregular blood glucose levels as well as blood pressure. The authors present anesthetic management of two cases in this case report and discuss the consequences of insulinoma and the risks and their management during anesthesia.

Key words: Tumor, Insulin producing; Diagnostic Imaging / methods; Hepatectomy; Humans; Insulinoma / diagnosis; Insulinoma / therapy; Pancreatectomy; Pancreatic Neoplasms / diagnosis; Pancreatic Neoplasms / therapy; Treatment Outcome

Citation: Farooq O, Butt FR, Durrani RS. Anesthetic management of insulinoma; case report and review of literature. Anaesth. pain intensive care 2022;26(4):563-568; **DOI:** 10.35975/apic.v26i4.1967

Received: November 18, 2021; **Reviewed:** March 2022; **Accepted:** March 22, 2022

1. Introduction

Insulinoma is a rare tumor of the beta pancreatic cells producing insulin with an incidence of 4 cases per million. It has a slight female predominance (female to male ratio 1·4 : 1).[1] The median age at presentation is 47 (range 8–82) y, with a plethora of symptoms including hypoglycemic or adrenergic symptoms, such as body shakes, nervousness, vomiting, palpitations, perspiration; and neuroglycopenic signs like migraine, vertigo, loss of vision, tiredness, loss of vision, amnesia, uncertainty, or seizures etc.[1] Most of the insulinomas are solitary lesions but 10% are multiple.[2] The lesions are usually small with a diameter of less than 2 cm in 90%, and less than 1.3 cm in 50% of patients.[3] Most insulinomas are benign; only 10% have any evidence of malignancy. After successful surgical excision, the long-term survival is 88% at 10 y with a higher risk of recurrence in patients with multiple endocrine neoplasia, type 1 (MEN 1).[2]

In 1869, Paul Langerhans first described pancreatic islets and insulin was discovered by Banting and Best in 1922.[4] After five years, Wilder et al. reported an islet cell carcinoma in an orthopedic surgeon, who was suffering from hypoglycemic symptoms.[5] William Mayo performed an laparotomy on that surgeon and found a pancreatic tumor with multiple liver, lymph node and mesenteric metastases. An extract was prepared from the tumor which demonstrated insulin-like activity when injected to a rabbit. In 1929, Roscoe Graham performed the first curative operation for benign insulinoma in Toronto. Subsequently, Wermer reported disorders of one or more endocrine glands in five members of the same family in 1954. This familial syndrome, once called Wermer syndrome, was later known as multiple endocrine neoplasia type 1 (MEN-1).

We report the presentation and the anesthetic management of two cases of insulinoma with an aim to apprise our young anesthetist friends to always keep this possibility in mind if they come across

unexplained hypoglycemia, and be prepared well if they are called for anesthesia in such a patient.

2. Case Report-1

A 32-year-old gentleman with no known co-morbidities reported with episodes of irritation, fatigue, dizziness, recurrent hypoglycemia and loss of consciousness, which resolved following dextrose infusions. The family reported that his behavior altered during these episodes and he seemed impatient, restless and agitated. Extensive work-up had confirmed the presence of insulinoma and he was being treated with diazoxide 125 mg thrice a day for 3 months, but denies any other treatment. There was no significant surgical or medical history. The patient did not report use of alcohol or drugs.

His Laboratory investigations are given in Table 1.

Table 1: Blood chemistry of the patient No. 1

Factor	Patient Values	Normal Range
Cortisol	4.74 µg/Dl	AM 4.30-22.4 PM 3.09-16.6
Free T4	1.2 ng/dL	0.89-1.76
TSH	2.14 µIU/mL	0.35 - 5.5
Glucose (fasting)*	58 mg/dL	70 - 99
C-Peptide	4.42 ng/mL	0.9 - 7.1
Insulin	33.88 µIU/mL	Adult (fasting) 3-25

MRI scan of abdomen revealed an ill-defined, T2 high signal intensity focus in the body of the pancreas with delayed enhancement and no restricted diffusion. The features indicated atypical insulinoma, so endoscopic ultrasound (EUS) ± fine needle aspiration (FNA) biopsy correlation was suggested.

A multidisciplinary approach was adopted. involving the anesthetist, the surgeon, and the endocrinologist. A plan was proposed to surgically excise the tumor which was approved by the patient.

The patient was hospitalized for observation and optimisation prior to surgery. During his hospital stay he had episodes of restlessness, agitation and tremors as experienced at home. Consequently, blood sugar levels were checked on hourly basis which revealed a low blood sugar level (58 mg/dl). The symptoms subsided after intravenous glucose was administered. Despite being on a continuous dextrose 5% infusion, the patient experienced several bouts of hypoglycemia during the preoperative period, with the latest incident occurring just before the patient was transferred to the operating room.

After signing in as per WHO checklist in the operating room and attaching basic ASA monitoring, a thoracic epidural was sited at T8-T9 region to manage pain peri-operatively. Induction of general anesthesia was carried out with fentanyl 100 µg, propofol 150 mg and atracurium 50 mg. To compensate for the low cortisol, a bolus infusion of 100 mg cortisol was given after induction. An arterial line was placed to monitor blood gases periodically and evaluate the blood sugar level pattern. Blood sugar level was tested half hourly (Figure 2) and arterial blood gases were measured every hour. The right internal jugular vein was catheterized using ultrasound guidance. A continuous infusion of 10% dextrose at 100 ml/h was run until the tumor was removed. As a maintenance fluid, Ringer's lactate solution was infused. The surgery started laparoscopically, which was converted to open distal

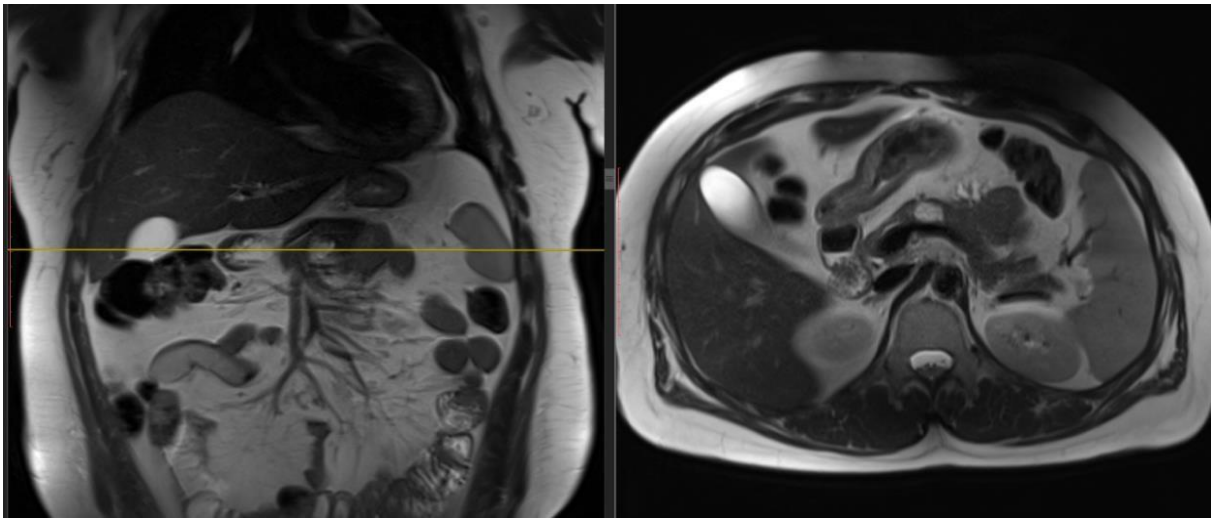

Figure 1: MRI scan showing atypical tumor in the body of pancreas

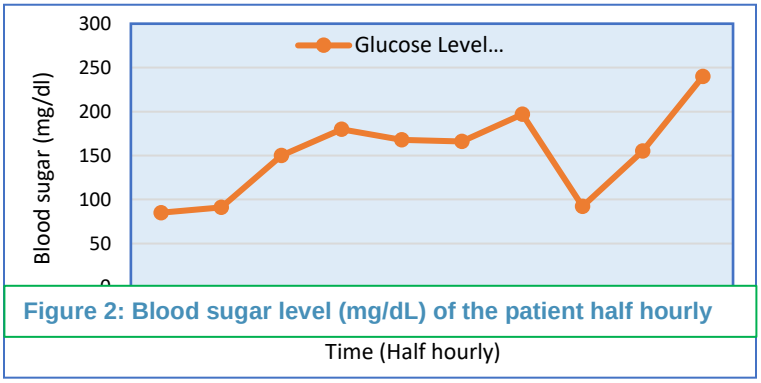

Figure 2: Blood sugar level (mg/dL) of the patient half hourly

pancreatectomy. The tumor was found in the pancreatic body and removed in its entirety. Total duration of surgery was 10 h, with minimal blood loss. Urine output remained adequate throughout. The course of anesthesia was smooth and the patient was extubated at the end of the surgery. Blood sugar levels were also monitored hourly in post-anesthesia care unit.

After surgery, the patient predictably developed diabetes, which was treated with metformin. The patient was discharged on the fourth post-operative day with no complaints during his postoperative stay.

Surveillance scan done after 8 months for follow up showed post-surgical changes without any evidence of local recurrence of the tumor or any distant metastasis.

3. Case Report-2

A 29-year-old female patient with no known co-morbidities presented with recurrent episodes of loss of consciousness since the past two and a half years, followed by spontaneous consciousness. Blood sugar levels were checked during a few episodes, and always found on the lower side. On taking a sweet drink or sweet dish, the symptoms subsided quickly.

She denied any significant medical or surgical history and did not report use of alcohol, drugs or any other medications. Physical examination did not reveal any abnormality.

After extensive workup and radiological imaging, she was diagnosed with insulinoma. CT triphasic scan of the abdomen (especially liver and pancreas) revealed a well-circumscribed, arterially enhancing, intra-pancreatic tumor at the junction of pancreatic neck and body with suggesting insulinoma. No peri-pancreatic infiltration or loco-regional nodal disease was seen. A small arterial feeder arising directly from the abdominal aorta just caudal to the coeliac trunk was the main arterial supply to this tumor.

Table 2: Blood chemistry of the patient No. 2

Factor	Patient Values	Normal Range
Cortisol	6.39 µg/dL	AM 4.30-22.4 PM 3.09-16.6
c-Peptide	5.69 ng/mL	0.9 - 7.1
Insulin	28.8 µIU/mL	Adult (Fasting) up to 29.1
Insulin like growth factor-1 (IGF-1)	107 ng/mL	84 - 259
Free T4	1.13 ng/dL	0.89 – 1.76
TSH	3.64 µIU/mL	0.35 - 5.5
Glucose (random)	50 mg/dL	70 - 140

In a multidisciplinary team conference, the results were examined, and surgical management in the form of laparoscopic removal of the tumor was planned. The patient was informed of the surgical plan and she consented to it.

The patient was hospitalized for observation and optimization prior to surgery. Her preoperative blood

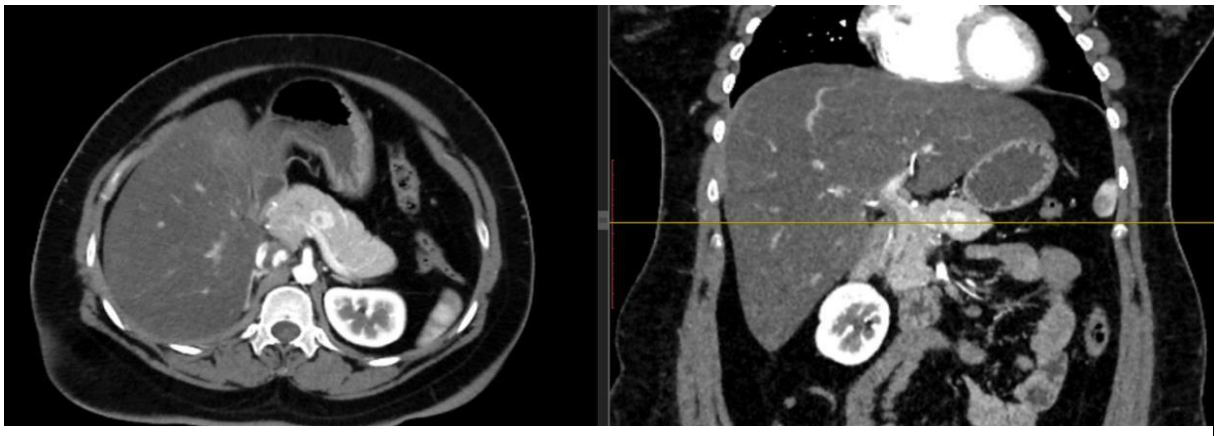

Figure 3: Abdominal CT scan showing presence of tumor at junction of neck and body of pancreas.

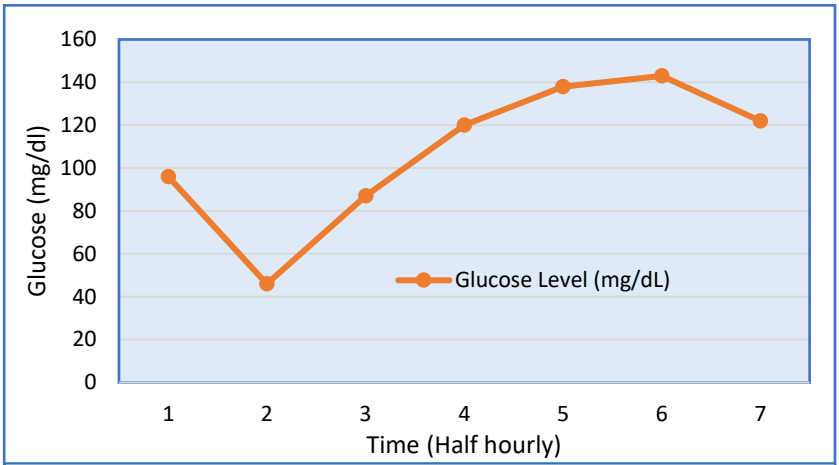

Figure 4: Blood sugar level checked half hourly

sugar levels were low; therefore, she was infused dextrose 5% solution at 80 ml/h continuously. Blood sugar was monitored hourly.

After signing in as per WHO checklist in the operating room and attaching basic ASA monitoring, a thoracic epidural was sited at T7-T8 region to manage peri-operative pain. General anesthesia was induced with inj. fentanyl 100 µg, inj. propofol 120 mg and inj. atracurium 50 mg. Due to her low cortisol, she was given a single dose of hydrocortisone 100 mg. Normothermia was maintained. An arterial line was inserted to monitor hemodynamics, blood sugar levels and blood gases. The right internal jugular vein was cannulated under ultrasound guidance. Sugar levels were monitored every 30 min during the surgery (Figure 4). A bolus of 25% dextrose was administered for low blood sugar, and a continuous infusion of 10% dextrose was used as a maintenance fluid.

The surgery involving tumor excision was performed and the course of anesthesia remained uneventful. At the end of the surgery the patient was extubated and transferred to PACU, where blood glucose was monitored hourly.

Continuous epidural infusion of bupivacaine 0.125% was used to treat post-operative pain. On the endocrinologist's recommendations the patient was put on insulin as per sliding scale. She was discharged on the fourth post-operative day in an adjusted diabetic dose. No significant concerns were found during the follow-up appointment.

Follow up with surgical and endocrinology team continued and started on glargine 6 units once a day. Six monthly follow up was unremarkable.

4. Discussion

Patients with an insulinoma usually present with symptoms of hypoglycemia that are secondary to excessive and uncontrolled secretion of insulin. These symptoms are often non-specific, episodic, vary among individuals and can differ from time to time in the same individual. The Whipple's triad is pathognomonic of Insulinoma, demonstrating the classical symptoms of hypoglycemia, a recorded level of low blood sugar and resolution of symptoms once blood glucose levels is normalized.

A shift in glycemic thresholds for responses to low plasma glucose occurs in a patient with an insulinoma resulting in tolerance of abnormally low plasma glucose levels without symptoms.[6]

In addition to insulin, tumors can secrete other hormones too, including serotonin, gastrin, glucagon, somatostatin, pancreatic polypeptide, corticotrophin and chorionic gonadotropin.[7]

Hypoglycemic symptoms can be non-specific, it is important to obtain a plasma glucose level during symptoms. Apart from the clinical features of the disease, biochemical testing is needed to confirm the diagnosis. Radio diagnostic help to determine the precise location of the tumors is imperative. Box 1 gives the diagnostic criteria on the basis of values of different biochemical substances in the plasma recorded after 72 h fasting.

Box 1: Diagnostic criteria for insulinoma after a 72 hour fast

Factor	Concentrate
Plasma glucose	≤ 2.5 mmol/l
Plasma insulin	≥ 6 µunits/ml (43 pmol/l)
Plasma C peptide	≥ 0.2 nmol/l
Plasma proinsulin	≥ 0.5 nmol/l
Plasma sulphonyl urea	Negative
Plasma β-hydroxybutyrate	< 2.7mm/l
Change in glucose with 1 mg glucagon	≥ 25 mg/dl at 30 min

The treatment of choice for insulinoma is surgical resection that offers the only chance of cure. Overall cure rates of 75–98% are reported after surgery, with prognosis dependent on the stage at presentation and whether complete resection was achieved.[8] Anesthetic management can be challenging to control the erratic blood glucose levels as the symptoms may be masked

under general anesthesia; fluctuations in blood sugar level should be anticipated during tumor handling and post operatively due to rebound hyperglycemia or even hypoglycemia due to extra pancreatic insulin secretion. Detailed discussion regarding anesthetic plan, post-operative pain control and blood sugar monitoring with patient should be done before surgery.

The 'triad of Whipple' is defined by pathognomonic signs (e.g., befuddlement, behavior) and autonomic signs (e.g., sweating), that occur in the presence of low blood glucose and disappear quickly following glucose delivery.[8]

Insulinoma may be difficult to diagnose. While insulinoma is usually recognized within 1.5 years of the start of the symptoms.[8] it might be mistaken as a seizure or mental condition in certain situations. With a positive history of recurrent hypoglycemia and the lack of sulfonylurea in the plasma, the 72-h supervised fasting test is the standard diagnostic test for insulinoma, demonstrating abnormal elevations in insulin ≥ 6 U/mL and C-peptide ≥ 0.2 nmol/L.[9]

Insulinoma is a benign, solitary tumor that affects the pancreas. Multiple endocrine neoplasia type 1 (MEN-1 syndrome), which comprises parathyroid hyperplasia, anterior pituitary adenoma, and neuroendocrine tumors of the pancreas or duodenum, may develop together in certain instances. A mutation in the MEN1 gene on chromosome 11 causes MEN-1 syndrome, an autosomal dominant illness. Insulinomas linked with the MEN-1 syndrome are often multicentric and manifest sooner than random insulinomas.[9]

Imaging modalities are utilized to pinpoint the tumor once it has been diagnosed. In order to plan the operation, an accurate diagnosis is required. CT scan, magnetic resonance imaging, transabdominal ultrasonography, penetrative scintigraphy, and positron emission tomography are some of the noninvasive imaging modalities, chosen based on the availability and the local radiologic expertise.[9] The CT scan is the recommended first scan at our facility. In circumstances when imaging scans are negative, invasive modalities such as endoscopic ultrasound and selective arterial calcium stimulation testing are used to locate the tumor.

Surgical excision is the preferred treatment for insulinoma. Because insulinoma is usually a single and benign tumor, complete enucleation is usually done. Distal pancreatectomy or the Whipple surgery are used if enucleation is not possible.[10] The popularity of laparoscopic resection is growing. The majority of individuals are cured of their condition after surgical therapy. Medical therapy (e.g. diazoxide and octreotide) may be employed for individuals who are not candidates for surgical resection.[11]

A history of hypoglycemic episode resulting in neurological impairment must be documented. Due to the likelihood of developing hypoglycemia it may be difficult to maintain a desirable period of NPO prior to surgery, so during the fasting period, an infusion of 5 or 10 percent dextrose should be begun. The goal is to keep blood glucose levels ≥ 50 mg/dL.[12]

Due to the difficulty in maintaining NPO because of recurrent bouts of low blood sugar the danger of aspiration must be anticipated, and proper precautions must be taken.

Signs of low blood sugar includes perspiration, palpitations, pressure, and pupil dilation. Similar signs can be observed in other situations such as hypovolemic shock, light plane of anesthesia, and use of certain medications that may result in masking hypoglycemia. As a result, identifying hypoglycemia when under anesthesia is challenging. Hypoglycemia during surgery may cause CNS damage in patients warranting post-operative ventilatory support.

Before induction, blood glucose levels should be tested, and every 15-30 min after that. It is particularly critical to monitor glucose levels during the recovery period, since there is a danger of rebound hyperglycemia after resection, and also hypoglycemia due to numerous adenomas being present which were not identified intra-operatively

An arterial line is required due to the need for regular blood samples for glucose measurement and blood gas evaluation. For insulinoma excision, general anesthesia with propofol and an epidural is the preferable method of anesthesia. Hypoglycemia after surgery indicates the possibility of a tumor not being identified or numerous additional insulinomas remaining.

5. Conclusion

Insulinoma is an extremely rare tumor. Due to insufficient fasting, prior neurologic impairment caused by recurrent hypoglycemic episodes, and erratic blood sugar levels during peri-operative period, these tumors provide a significant challenge to the anesthesiologists. Intraoperative blood sugar monitoring is crucial to counteract large fluctuations in sugar levels, thus leading to an improved treatment outcome.

6. Conflict of interest

None declared by the authors.

7. Consent of the patients

Signed consents were obtained from the patients to use the data and the pictures for educational purposes.

8. Authors' contribution

OF: Conduction of the study work and manuscript editing

FB: Conduction of the study work.

RSD: Concept, conduction of the study work and manuscript editing

9. References

1. Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma--incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc. 1991;66:771-779. [PubMed] DOI: 10.1016/s0025-6196(12)62083-7
2. Tucker ON, Crotty PL, Conlon KC. The management of insulinoma. Br J Surg. 2006 Mar;93(3):264-75. [PubMed] DOI: 10.1002/bjs.5280
3. Service FJ. Hypoglycemic disorders. N Engl J Med. 1995;332:1144-52. [PubMed] DOI: 10.1056/nejm199504273321707
4. Banting FG, Best CH. The internal secretion of the pancreas. Indian J Med Res. 2007 Mar;125(3):251-66. [PubMed]
5. Wilder RM, Allan FN, Power MH, Robertson HE. Carcinoma of the islands of the pancreas: hyperinsulinism and hypoglycemia. Journal of the American Medical Association. 1927 Jul 30;89(5):348-55. [PubMed]
6. Bartsch D, Kopp I, Bergenfelz A, Rieder H, Munch K, Jager K, Deiss Y, Schudy A, Barth P, Arnold R, Rothmund M. MEN1 gene mutations in 12 MEN1 families and their associated tumors. European journal of endocrinology. 1998 Oct 1;139(4):416-20. [PubMed] DOI: 10.1530/eje.0.1390416
7. Philippe J, Powers AC, Mojsov S, Drucker DJ, Comi R, Habener JF. Expression of peptide hormone genes in human islet cell tumors. Diabetes. 1988 Dec 1;37(12):1647-51. [PubMed] 10.2337/diab.37.12.1647
8. Doherty GM, Doppman JL, Shawker TH, Miller DL, Eastman RC, Gorden P, Norton JA. Results of a prospective strategy to diagnose, localize, and resect insulinomas. Surgery. 1991 Dec 1;110(6):989-97. [PubMed]
9. Okabayashi T, Shima Y, Sumiyoshi T, Kozuki A, Ito S, Ogawa Y, et al. Diagnosis and management of insulinoma. World J Gastroenterol. 2013;19:829-837. [PubMed] PMCID: PMC3574879 DOI: 10.3748/wjg.v19.i6.829
10. Grover AC, Skarulis M, Alexander HR, Pingpank JF, Javor ED, Chang R, et al. A prospective evaluation of laparoscopic exploration with intraoperative ultrasound as a technique for localizing sporadic insulinomas. Surgery. 2005;138:1003-1008. [PubMed] DOI: 10.1016/j.surg.2005.09.017
11. Hirshberg B, Cochran C, Skarulis MC, Libutti SK, Alexander HR, Wood BJ, et al. Malignant insulinoma: spectrum of unusual clinical features. Cancer. 2005;104:264-272. [PubMed] PMCID: PMC4136659 DOI: 10.1002/cncr.21179.
12. Goswami J, Somkuwar P, Naik Y. Insulinoma and anesthetic implications. Indian J Anaesth 2012;56(2):117-122. [PubMed] PMCID: PMC3371484 DOI: 10.4103/0019-5049.96301

