Special Article

Insulinoma and anaesthetic implications

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ABSTRACT

Insulinoma is a rare neuroendocrine tumour of the pancreas, which is usually small, solitary and benign. It may be part of the multiple endocrine neoplasia type 1 syndrome. It is diagnosed by clinical, biochemical and imaging modalities. Hypoglycaemic symptoms can be medically controlled by diazoxide or somatostatin analogues. Localisation of the tumour is a challenge to clinicians. Surgical resection is the curative treatment with a high success rate. Intraoperatively, ultrasound and surgical palpation help to confirm the site of tumour. Intraoperatively, maintenance of optimum glucose levels is of main concern because there may be severe hypoglycemia while handling the tumour, symptoms of which remain masked under general anaesthesia. Glucose infusion and frequent plasma glucose monitoring to maintain plasma glucose level more than 60 mg/dL is found to be helpful. We performed a systematic search in PubMed, Cochrane Library and also in Google. We used the following text words for our search: Insulinoma, neuro-endocrine tumors, multiple endocrine neoplasia, hypoglycemia, anaesthetic management of insulinoma, glucose management. In this article, we review the incidence and epidemiology of insulinoma, its clinical features, diagnosis, localisation and treatment, with special emphasis on anaesthetic management.

Key words: Anaesthetic management of insulinoma and glucose management, insulinoma, multiple endocrine neoplasia, neuroendocrine tumours

INTRODUCTION

Neuroendocrine tumour of the pancreas comprises of a relatively rare group of tumour of which insulinoma is the most common functional variety. First described by Seale Harris in 1924,[1] insulinoma is usually small, solitary, benign and surgically curable. Whipple first described its pathognomonic triad of symptoms in 1938.[2,3] Fasting hypoglycaemia in a healthy, well-nourished adult should raise the suspicion of insulinoma and trigger further investigation. These hypoglycaemic episodes may be non-specific, remain unrecognized and occasionally misdiagnosed. There are reports of long-standing insulinoma with marked adaptation to extreme hypoglycaemia with near-normal plasma insulin levels.[4] Its small size often makes localisation difficult. Surgical excision of the tumour is the definitive treatment, and the major focus during excision is prevention and control of wide swings in blood glucose concentrations.

SEARCH STRATEGY

We conducted a systematic literature search in PubMed, Cochrane Library and also in Google. The PubMed search was done from 1968 till date. The search strategy was set up using the following single text words and combinations: Insulinoma, hyperinsulinism, neuroendocrine tumours, somatostatin analogues and anaesthetic management of insulinoma and glucose management. We also cross checked the reference list of relevant articles. We included studies and review articles that described the pathophysiology, diagnosis and surgical and anaesthetic management of insulinoma.

EPIDEMIOLOGY

Insulioma is an adenoma of beta (β) cells of islets of Langerhans, with an incidence of 1–4 per million population per year.[5] The median age of presentation is approximately 47 years, with a mild female

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preponderance (female:male 1.4:1).[6,7] Usually, they are small (90% less than 2 cm in size), solitary and benign. Only 10% can be malignant and 16% cases are associated with multiple endocrine neoplasia type 1 (MEN-1) syndrome. When associated with MEN-1 syndrome, they develop earlier, tend to be multifocal and occur throughout the pancreas.[5,7,8] Malignant insulinomas are seen more frequently in MEN-1 syndrome. Only histological features do not suffice to predict malignancy,[5,9] which can be diagnosed by intraoperative findings (metastasis in liver, regional lymph nodes or local invasion) as recommended by the World health organisation.[5,10] Some insulinomas also secrete additional hormones like gastrin, 5-hydroxy indole acetic acid (5-HIAA), adreno-corticotropic hormone, glucagon, human chorionic gonadotropin and somatostatin.[5,6] Combined medical and surgical modalities are used for the treatment of malignant lesions.[11]

AETIOLOGY

The gene causing MEN-1 is localized in band 11q13, and encodes a protein called menin, which is involved in transcriptional regulation, cell division and Deoxy ribo nuclic acid (DNA) repair. A study using the fluorescent microsatellite analysis technique showed that the DNA of insulinoma cells had lost heterozygosity in band 11q13. But, the mutations of the MEN1 gene do not play an important role in the pathogenesis of sporadic insulinomas.[5,6,12]

CLINICAL FEATURES

Inappropriate secretion of insulin from the adenoma results in hypoglycaemic episodes, which precipitate after fasting or exercise. To avoid the symptoms of hypoglycaemia, patients tend to overeat, resulting in weight gain. Sometimes, the presenting symptoms may be non-specific and bizarre, which physicians fail to recognize and cause delay in diagnosis.[13] Therefore, blood sampling for plasma glucose should be done during symptoms. Normal value in this symptomatic phase rules out diagnosis of insulinoma.[7,13] Hypoglycaemic symptoms appear when the plasma glucose falls below 50 mg/dL and neuroglycopenic symptoms appear at glucose levels below 45 mg/dL. These central nervous system symptoms occur due to neuronal deprivation of glucose. Therefore, symptoms can be divided into either adrenergic, resulting from the catecholaminergic response to hypoglycaemia (anxiety, tremor, nausea, hunger, sweating and palpitations) or neuroglycopenic (headache, lethargy, dizziness, diplopia, blurred vision, amnesia, seizures and, in more severe cases, confusion or coma).

Whipple's triad is pathognomonic of insulinoma, which includes (1) symptoms of neuroglycopenia, (2) documented hypoglycaemia (plasma glucose level less than 50 mg/dL) and (3) relief of symptoms (often within 5–10 min) following glucose administration.[2,5,14] Documented hyperinsulinism in presence of hypoglycaemia warrants further investigations to confirm insulinoma.

DIAGNOSTIC MODALITIES

In healthy individuals, the blood glucose level is maintained by a negative feedback mechanism. Decrease in blood glucose levels reduces insulin production. In β-cell adenomas, the production of insulin is not dependent on the blood glucose level.[5] Increased serum insulin level in the presence of hypoglycaemia is diagnostic of insulinoma.

72-h fasting test

The 72-h fasting test is a demonstration of Whipple's triad of symptoms, which is considered as the gold standard for the diagnosis. This test is conducted under supervised conditions, which requires hospitalisation of the patient. During the fasting period, the patient is allowed to drink calorie-free fluids and physical activity is encouraged. Blood glucose should be measured 6-hourly till it reduces to 60 mg/dL and then every 1 or 2 hours till it reduces to 40–45 mg/dL. When symptoms of hypoglycaemia appear, blood should be sampled for measurement of glucose, insulin, C-peptide, β-hydroxybutyrate and sulfonylurea.[5] Insulinoma is diagnosed when the following criteria are fulfilled[8]:

1. Blood glucose less than 50 mg/dL with hypoglycaemic symptoms
2. Relief of symptoms after meal
3. Elevated C-peptide (>200 pmol/L)
4. Absence of plasma sulfonylurea
5. Increased serum insulin level (>5–10 μU/mL)
6. Increased proinsulin level (≥25% or ≥22 pmol).

Recently, the Endocrine Society Clinical Practice Guidelines recommended the following criteria[15]:

1. Plasma concentrations of glucose less than 55 mg/dL (3.0 mmol/L)
2. Insulin of at least 3.0 μU/mL (18 pmol/L)
3. C-peptide of at least 0.6 ng/mL (0.2 nmol/L)
4. Proinsulin of at least 5.0 pmol/L.

Some authors described modified fasting test where duration of the fasting period is reduced to 48 h. In this test, at a plasma glucose level of 40–45 mg/dL, the patient is asked to undergo light exercise for 15–30 min even if there is no hypoglycaemic symptom.[5,16,17] Then, the plasma glucose measurement is repeated.

Other tests

Intravenous secretin test of insulinoma

Unlike in the normal population, beta cells of pancreas are insensitive to secretin in patients of insulinoma. In a normal individual, an intravenous injection of secretin 2 units/kg causes rise in plasma insulin more than 200%. However, in case of insulinoma, injection of secretin does not stimulate insulin secretion due to unresponsiveness of insulinoma cells to secretin.[5,18]

C-Peptide inhibition test with hog insulin

Infusion of hog insulin for 1 h leads to decrease in plasma C-peptide levels in healthy persons, whereas no such change was observed in patients of insulinoma.[5,19]

LOCALISATION

A variety of imaging modalities are used to locate the tumour. Because insulinoma is small, sporadic and intrapancreatic, the failure rate to localise it is almost 10–27%.[5,8] The success rate of non-invasive modalities is poor, as shown in different studies. In case of transabdominal ultrasound, it is 9–66%, computed tomography (CT) 50–80%, magnetic resonance imaging (MRI) 40–70% and somatostatin receptor scintigraphy 17%. The overall success rate of all these modalities together is around 80%.[8,10,20] CT and MRI are helpful to detect metastatic disease. The use of endoscopic ultrasound (EUS) has increased recently. The sensitivity of EUS is reported as 40–93%.[8]

Invasive modalities help to localise insulinoma when non-invasivetechniques fail. Pancreatic arteriography, which was considered as the "gold standard", is now not in much use.[5,7,8] Transhepatic portal venous sampling (THPVS) was also considered as one of the most accurate tools for localisation. In this test, step-up in the insulin level in the smaller draining veins reflects the location of the tumour. Because it is invasive, expensive and technically demanding, it is rarely used.[5,7,8,21] Intraarterial calcium stimulation test or arterial stimulation and venous sampling (ASVS) has almost replaced THPVS now. In ASVS, intra-arterial calcium is injected after catheterisation of gastroduodenal, superior mesenteric and splenic arteries. Then, blood is sampled from the right and the left hepatic veins for insulin level. A gradual rise in insulin concentration localises the tumour in a particular area.[8] A two-fold or greater step-up in right hepatic vein insulin concentration from baseline at 20, 40 and/or 60 s after arterial calcium injection is considered as a positive response.[20] This test was first used to localise Zollinger-Ellison syndrome.[22,23] Both hyper- and hypoglycaemia should be avoided during this test. Hyperglycaemia can stimulate insulin secretion from β cells of pancreas. This being a provocative test, has the potential risk of severe hypoglycaemia. Investigators maintained the blood glucose level at 100 mg/dL by adjusting the infusion of 10% dextrose and every 10-min monitoring of blood glucose.[23] Recently, different study groups recommended this ASVS test as superior to other localising tools.[20,24]

Lastly, intraoperative ultrasound (IOUS) is a very useful tool of localising the insulinoma, especially when it is small and not easily palpable. It also helps to define the proximity with the vessels and pancreatic or bile duct. Its use is mandatory in case of multiple lesions.[5,25,26] IOUS can localise insulinoma in almost 86-90% of the cases.[5,8,27]

MANAGEMENT

Medical management

Medical treatment is helpful to prevent or reduce symptoms in patients who are not surgical candidates or who are waiting for surgery. It includes dietary modification and pharmacological agents. Frequent small meals throughout the day and night help to avoid symptoms of hypoglycaemia.

Usually, diazoxide is used along with frequent feeds.[28,29] It is a benzothiadiazide that prevents hypoglycaemic episode by two different pathways. Firstly, it stimulates a-adrenergic receptors and thereby inhibits β-cells directly resulting in decreased release of insulin. Secondly, it stimulates glycogenolysis by inhibiting cyclic adenosine monophosphate phosphodiesterase. Dose is 150–200 mg in two to three divided doses and titrated to maximum 400 mg in 24 h. Sodium retention, oedema, nausea, vomiting and occasional hirsutism are frequent side-effects.[8]

Somatostatin analogues like octreotide and lantreotide are also used to prevent symptoms.[28,30-32] They bind with somatostatin receptors on insulinomas and decrease insulin secretion in 40–60% of the

patients.[8,31,32] The dose is 50 μg subcutaneously two to three times daily up to a maximum of 100 μg in 24 h. Side-effects include gastrointestinal bloating, abdominal cramp, malabsorption and cholelithiasis.

Phenytoin inhibits release of insulin from β-cells and hence may be helpful in the prevention of hypoglycaemia.

Glucocorticoids suppress insulin-mediated glucose uptake and augment glucose release. It increases insulin resistance, reduces glucose utilization, increases hepatic glucose production and impairs insulin secretion.

Prednisone therapy may be considered as a valid option to achieve symptomatic control in hormonally active therapeutically resistant insulinomas.[33] But, this therapy with cortisol may lead to post-operative hyperglycaemia, and there is an increased chance of infection.[34,35] Other drugs like calcium channel blocker (verapamil), β-blockers (propranolol) and glucagon have also been used.[5,8]

Perioperative management

Surgical excision of the tumour is the definitive treatment. Laparoscopic resection is the surgery of choice in recent days.[8] Although enucleation is the treatment of choice for all benign insulinomas, intraparenchymal insulinomas may be missed and may require distal or partial pancreatectomy. However, with the advance in diagnostic and localisation techniques, wider resection for small tumours is not recommended anymore.[36] Intraoperative US as well as careful surgical palpation have a success rate of 83–98% in identifying small insulinomas.[8,10]

The patient should get admitted 1 day prior to the scheduled surgery. Intravenous infusion of 10% dextrose should be started for the fasting period. Frequent glucose monitoring is important to prevent plasma glucose level to fall below 40–50 mg/dL at any time.[5] Diazoxide and somatostatin analogues are continued in the morning of surgery to reduce insulin secretion intraoperatively while handling of the tumour.[5,21,37]

Regarding anaesthetic agents, no specific recommendations are available. The anaesthetic technique should include drugs that decrease the cerebral metabolic rate for oxygen ($CMRO_2$).[38,39] Both thiopentone sodium and propofol reduce $CMRO_2$. Propofol has an advantage over thiopentone sodium as the latter can cause severe hypotension in patients receiving diazoxide therapy because both are protein-bound drugs.[37] Moreover, propofol has no effect on the release of insulin and glucose regulation.[38,39] For these reasons, some study groups recommended the use of propofol.[40,41] Investigators also commented that combination of general anaesthesia with propofol and epidural block is a useful choice of anaesthesia for removal of insulinoma.[41] Enflurane and halothane inhibit pancreatic insulin release, which results in hyperglycaemia. This inhibitory effect is higher with enflurane than with halothane.[42-44] Investigators advocated that halothane is not a suitable agent for patients of insulinoma as it increases sensitivity to insulin.[37,44,45] The main aim of anaesthetic management is to prevent hypoglycaemia until tumour resection and the control of rebound hyperglycaemia soon after resection. Various approaches have been described, including use of "artificial pancreas", which continuously monitors plasma glucose and delivers glucose or insulin to maintain a predetermined glucose level.[44] But, it is not much in use due to its cost and complexity. Another suggested approach is continuous infusion of 10% glucose and every 15-min monitoring of blood glucose levels to maintain plasma glucose in the range of 100–150 mg/dL.[45] This method helps to detect sudden hypo- or hyperglycaemia. Other groups recommended this frequency of sampling every 30 min.[35] Some surgical groups prefer to maintain moderate hypoglycaemia so that post-resection increase in plasma glucose concentration can be used as an indication of successful tumour removal. But, this technique can lead to severe hypoglycaemia intraoperatively and also hyperglycaemic rebound is not adequately reliable as there are reports of both false-positive and -negative responses.[46,47] Intraoperative glucose management is similar in paediatric patients with insulinoma. Recently, in a report, anaesthetic management of a 5 year-old child with insulinoma was described, where infusion of 10% glucose was continued till tumour resection. Then, infusion of insulin was continued to maintain blood glucose around 150 mg/dL. This glucose management was guided by continuous monitoring.[48] In another case study, a 13-year-old child diagnosed as insulinoma underwent laparoscopic enucleation of tumour.[49] The intraoperative blood glucose level was maintained at more than 100 mg/dL with administration of glucose solution.

Laparoscopic enucleation is the treatment of choice for all benign insulinomas. Pneumoperitoneum

during laparoscopy may lead to multiple physiological changes. Haemodynamic changes include decrease in cardiac output, rise in blood pressure and increase in systemic vascular resistance (SVR), which may result in release of catecholamines and vasopressin.[50] Pneumoperitoneum also causes release of cortisol. These factors stimulate glucose production. Intra abdominal pressure (IAP) of 15 mmHg results in a decrease in the cardiac output by 28%. IAP ≤12 mmHg has minimal effects on haemodynamic function.[51] Therefore, intraoperatively, regular monitoring of IAP is important. IAP maintained as low as possible and liberal perioperative fluid therapy help to minimise haemodynamic disturbances and disturbances in glucose homeostasis. Respiratory changes include alterations in compliance and resistance, which may require changes in ventilatory parameters to prevent hypercarbia or hypoxaemia.[51]

Usually, the blood glucose rapidly comes back to the normal level. But, it may take several hours to several days. That period of time should be supported by glucose infusion along with strict monitoring. In this process, the blood glucose level may rise up to 180–230 mg/dL,[5,29] which may require small doses of insulin. It is recommended to measure the blood glucose level frequently during hospitalisation and once daily after discharge.[5]

CONCLUSION

Insulinoma is a rare neuroendocrine tumour of the pancreas that produces symptoms due to hypersecretion of insulin from β-cells. A combination of clinical, biochemical and imaging tests is required to confirm the diagnosis. Surgical resection of the tumour is the treatment of choice. Intraoperative ultrasound is strongly recommended to localise the tumour. There may be a large swing in plasma glucose during handling of the tumour, which should be carefully monitored and maintained.

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