Perioperative glycemia regulation for insulinoma surgery – challenges faced by the anaesthesiologist. A case report.

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SUMMARY

Insulinoma represents a benign, insulin-secreting neuroendocrine tumor of the beta cells of islets of Langerhans in the pancreas, which leads to frequent episodes of hypoglycemia. Surgery is the definite treatment. However, the perioperative treatment of patients with insulinoma is highly challenging. We present the perioperative management of a 46-year-old obese male patient with insulinoma. As the patient reported frequent severe hypoglycemia episodes, the main priority of the perioperative treatment was to prevent hypoglycemia before tumor resection and to control rebound hyperglycemia after tumor removal. Maintaining normoglycemia was challenging during the regular fasting period before abdominal surgery, as well as during the intervention, as general anaesthesia masks the symptoms of hypoglycemia. Obesity further complicated the anaesthetic management, due to expected difficult airway management and central venous access. Glycemia was monitored in 15-minute intervals during surgery and in 30-minute intervals postoperatively, and dysglycemia was corrected according to the trend of variations. As insulinoma is a rare phenomenon with an unpredictable clinical course, current reportings regarding the anaesthetic management of patients with this pathology are relatively lacking. Therefore, our case report could contribute to expanding the limited data about the perioperative treatment of patients with this condition.

Keywords: *insulinoma; glycemia; anaesthetic management; case report*

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INTRODUCTION

Insulinoma represents a benign, insulin-secreting neuroendocrine tumor of the beta cells of islets of Langerhans in the pancreas, which leads to frequent episodes of hypoglycemia. Surgery is the definite treatment. However, the anaesthetic management of patients with insulinoma is highly challenging (1). First of all, wide swings in blood glucose concentrations are expected, as well as some difficulties regarding airway management and peripheral venous access, due to severe obesity induced by neuroendocrine dysregulation (2).

The clinical features of patients with insulinoma are often nonspecific. Nevertheless, Whipple's triad is well known to be pathognomonic of this condition and includes symptoms of neuroglycopenia (e.g. headache, lethargy, dip lopia, dizziness, etc.), documented hypoglycemia (plasma glucose concentration below 2.775 mmol/L) and relief of symptoms after glucose intake.

To avoid the symptoms of hypoglycemia patients often tend to overeat, which leads to significant weight gain (1, 3).

Proper perioperative management is essential for successful surgery of insulinoma. However, the perioperative clinical course is mostly unpredictable. Laparoscopic resection is the treatment of choice, but in some cases, distal or partial pancreatectomy may be required. Disregarding the applied surgical method, the main concerns in anaesthetic management are related to the prevention of severe hypoglycemia until tumor resection and the control of extreme hyperglycemia after resection. Moreover, pneumoperitoneum, due to the laparoscopic approach may induce hemodynamic changes, which require further corrections. In the postoperative period, glycemia should be strictly monitored and supported until glucoregulation returns to its physiological patterns (1, 4).

In this case report we present the perioperative management of a successfully treated patient with insulinoma. Taking into consideration the low incidence of this condition and the highly unpredictable clinical course, we suppose that this case presentation could contribute to expanding the relatively limited clinical data about the perioperative management of patients with insulinoma.

CASE PRESENTATION

A 46-year-old male patient with radiologically and histologically diagnosed insulinoma was admitted to the surgical department one day prior to the planned abdominal surgery. The preoperative physical examination and medical record review revealed some co-existing conditions of the patient: obesity (body weight – 102 kg, body height – 186 cm, BMI – 29.5), hyperlipidemia, and mild anxious disorder (coped with clonazepam). Since the appearance of severe hypoglycemia episodes with blood glucose levels as low as 1-2 mmol/L, the patient has regularly consumed diazoxide. MR imaging of the abdomen verified a tumor in the tail of the pancreas. Therefore, the laparoscopic resection of the tail of the pancreas was performed.

The day prior to surgery the patient was taking small amounts of food in short time intervals, but from the evening prior to surgery peroral food administration was interrupted and only water intake was allowed. Therapy with diazoxide was not interrupted until the morning of the intervention. Regardless of the thorough preoperative psychological and pharmacological

preparation, the patient had frequent periods of sweating and was objectively anxious.

Beside crystalloid infusions, a continuous infusion of a 10% glucose solution, with a flow rate of 20 mL/h, was administered during the day prior to surgery and glycemia was monitored in three-hour intervals. Normoglycemia (3.5 – 6.5 mmol/L) was obtained during the entire day, until late evening. At 9 PM glycemia was 2.1 mmol/L. Therefore, the infusion rate of the 10% glucose solution was set to 30 mL/h and a 10 mL bolus of 50% glucose solution was administered. After monitoring glycemia in one-hour intervals and administering two more 10 mL boluses of 50% glucose solution, the continuous infusion rate of the 10% glucose solution was elevated to 50 mL/h. On the morning of the operative day at 6 AM, glycemia was 4.2 mmol/L.

On the day of surgical intervention at 7.30 AM the patient was transferred to the operating room,where he received premedication and glycemia was measured. The blood glucose concentration was3.4 mmol/L, thus 40 mg methylprednisolone was administered intravenously in order to maintainnormoglycemia, according to the recommendation of the endocrinologist. Balanced general anaesthesia with propofol induction (1.5-2.5 mg/kg intravenously (IV)) and sevoflurane maintenance (1.2-1.4% end-Tidal; 1-1.2 Minimum Alveolar Concentration (MAC)) was administered. Due to obesity, short neck constitution, dental status, and an estimated Mallampati class 3 difficult airway management was expected. Thus, depolarizing muscle relaxant succinylcholine was administered at an induction dose of 100 mg IV and intubation was performed using videolaryngoscopy and bougie.

Intubation was performed for the first attempt, without any complications, and pressure-regulated volume-controlled ventilation was provided. Prior to the surgical procedure, two peripheral venous accesses were obtained and a central venous catheter was placed in the right internal jugular vein, using the Seldinger technique, without any complications. An arterial line was inserted into the left radial artery and invasive hemodynamic monitoring was performed during the intervention. Bispectral Index (BIS) monitoring was performed during the entire time of anaesthesia and their values ranged between 40 and 60 intraoperatively. Muscle relaxation maintenance was provided by administering rocuronium-bromide boluses of 0.1-0.3 mg/kg IV (total dose of 210 mg IV), according to Train Of Four (TOF) neuromuscular monitoring (stimulation of the ulnar nerve, using a stimulus of 50 mA in two-minute intervals, obtaining a TOF count of 0/4 – ¼). Intraoperative analgesia was provided with boluses of fentanyl (50-100 mcg IV, a total dose of 300 mcg IV) and alfentanyl (250 mcg IV, a total dose of 750 mcg IV). The total operation time was 4 hours and 5 minutes, and the anaesthesia time (with central venous catheter placement, arterial line insertion, and patient positioning) was 5 hours and 5 minutes. The patient was intraoperatively hemodynamically stable, with adequate respiratory parameters, gas exchange, and satisfactory diuresis. The reversal of anaesthesia and extubation were performed immediately after surgery, in the operating room, without any complications.

Glycemia was monitored in 15-minute intervals during surgery. Normoglycemia was obtained by administering a 10% glucose solution, with a basal flow rate of 10 mL/h, which was gradually increased up to 50 mL/h, according to blood glucose concentrations. The results of blood glucose level monitoring during the intervention are provided in Table 1. Hypoglycemia was treated with boluses of a 50% glucose solution, initially in the volume of 10 mL, followed by two 3 mL boluses. The continuous infusion of the glucose solution was interrupted after tumor removal. Octreotide in a single dose of 0.05 mg subcutaneous (SC) was administered at the beginning of surgery in order to suppress pancreatic enzyme excretion and a potential pancreatic fistula formation. In the Table 1, intraoperative glycemia values are reported, with the undertaken response to glycemia variations. Postoperatively the patient was transferred to the intensive care unit. Glycemia was monitored in 30-minute intervals and corrections were undertaken according to glycemia variations, administering small doses of human insulin and 5% glucose solution with a maximal flow rate of 20 mL/h. In the Table 2, glycemia values and required corrections immediately after surgery are reported, until the morning of the first postoperative day. On the first postoperative day glycemia was monitored in 2-hour intervals, the second postoperative day in 4-hour intervals, and on the third and fourth days in 6-hour intervals. Glycemia corrections were undertaken by administering 5% glucose solution or 10% glucose solution, with boluses of human insulin, according to the trend of variations.

Octreotide 0.1 mg/8h SC was administered five days long in the postoperative period, according to the request of the surgeon. Boluses of morphine-hydrochloride, metamizole-sodium, and paracetamol were administered to achieve sufficient analgesia. Minimal drainage was observed on the three abdominal drains and the nasogastric tube was removed on the first postoperative day.

The patient was transferred to the surgical ward on the fourth postoperative day and discharged from the hospital on the twentieth postoperative day. Although the postoperative course was without any complications, the patient was kept longer in the intensive care unit to promptly and adequately manage the expected hyperglycemia. Beside crystalloid infusions, a 500 mL 10% glucose infusion was administered daily to the patient, and glycemia monitoring was continued in 6-hour intervals until hospital discharge. No or minimal glycemia corrections with human insulin were required after the fourth postoperative day.

Table 1. Intraoperative glycemia values in 15-minute intervals and sequentially undertaken corrections.

GLYCEMIA	CORRECTION	GLYCEMIA	CORRECTION
3.6 mmol/L	10% glucose solution cont. 10 mL/h	4.1 mmol/L	→ +3 mL 50% glucose solution
3.8 mmol/L	10% glucose solution cont. 20 mL/h	4.2 mmol/L	→
3.2 mmol/L	10% glucose solution cont. 30 mL/h	7.9 mmol/L	10% glucose solution cont. 40 mL/h
3.0 mmol/L	10% glucose solution cont. 40 mL/h + 10 mL 50% glucose solution	8.1 mmol/L	→
4.3 mmol/L	10% glucose solution cont. 50 mL/h	9.0 mmol/L	10% glucose solution cont. 20 mL/h
6.0 mmol/L	→	8.3 mmol/L	→
5.6 mmol/L	→	7.8 mmol/L	→
3.9 mmol/L	→ + 3 mL 50% glucose solution	9.0 mmol/L	STOP
7.6 mmol/L	10% glucose solution cont. 40 mL/h	9.4 mmol/L	
5.3 mmol/L	10% glucose solution cont. 50 mL/h	9.2 mmol/L	

Legend: → indicates that the continuous infusion of glucose solution is administered with the same flow rate as previously.

Table 2. Postoperative glycemia values in 30-minute intervals and sequentially undertaken corrections.

GLYCEMIA	CORRECTION	GLYCEMIA	CORRECTION
9.9 mmol/L		10.3 mmol/L	
15.3 mmol/L	human insulin 6 i.u. SC	5.3 mmol/L	5% glucose solution cont. 20 mL/h
13.9 mmol/L		11.8 mmol/L	STOP
15.0 mmol/L		11.0 mmol/L	
12.9 mmol/L		7.9 mmol/L	5% glucose solution cont. 10 mL/h
14.8 mmol/L		10.1 mmol/L	5% glucose solution cont. 5 mL/h
13.5 mmol/L		12.3 mmol/L	→
13.6 mmol/L		11.7 mmol/L	→
12.0 mmol/L		12.5 mmol/L	→
13.9 mmol/L		12.9 mmol/L	STOP
14.2 mmol/L		13.4 mmol/L	
15.4 mmol/L	human insulin 6 i.u. SC	11.0 mmol/L	
14.6 mmol/L		12.0 mmol/L	
14.7 mmol/L		12.4 mmol/L	
14.0 mmol/L		11.9 mmol/L	
13.7 mmol/L		11.9 mmol/L	
13.1 mmol/L		11.8 mmol/L	
13.3 mmol/L		10.5 mmol/L	

Legend: → indicates that the continuous infusion of glucose solution is administered with the same flow rate as previously.

DISCUSSION

Insulinoma is a rare phenomenon, with an incidence of 1-3 cases per million in the world population per year (5). Therefore, current reportings or clinical trials regarding the anaesthetic management of patients with this pathology are relatively lacking.

Several challenges can be faced during the perioperative treatment of patients undergoing insulinoma removal. Firstly, in the case of our patient, peroral food administration was reduced after admission to the hospital and completely interrupted the evening before surgery, according to the standard preoperative protocol for laparoscopic abdominal surgery. Reduced food intake was well tolerated during the afternoon prior to surgery. However, during the fasting period in the late evening hours, the glycemia values showed a sharp decrease, which was coped with boluses of the 50% glucose solution and increased flow rate of the continuous 10% glucose solution. Later, the patient reported that since the appearance of glycemia dysregulation, he had taken large amounts of food in the late evening hours, before sleeping, in order to compensate the overnight hypoglycemia. Therefore, it could be possible to predict the hypoglycemic response, as a consequence of fasting in the usually overeating period. Second, as a result of regular overeating before night, the patient experienced a significant weight gain. It is well known that airway management, as well as peripheral and central venous access can be challenging in obese patients, thus our team was prepared for difficult intubation and central venous line insertion. However, all the procedures were performed for the first attempt, without any complication.

Maintaining adequate blood glucose levels was the main priority in the perioperative period. However, it can be highly challenging, as general anaesthesia masks the symptoms of hypoglycemia. The first warning signs are hypertension, tachycardia, or sweating, which are vastly nonspecific symptoms (4). Moreover, the optimal time interval for glycemia monitoring during surgery is still not well defined. Some authors (6) suggest 30-minute intervals for blood glucose monitoring, but others recommend shorter periods, especially when glycemia is hardly balanced (1).

According to some authors, the administration of somatostatin analogs in patients undergoing surgical treatment of insulinoma is not only useful for the prevention of pancreatic fistula formation, but they also decrease insulin secretion in more than half of the patients, by binding to the somatostatin receptors on insulinomas (2). In the modern clinical setting of the "artificial pancreas" – a device for continuous blood glucose monitoring and computer-operated target-controlled glucose and insulin infusion – may be applied for intraoperative and postoperative blood glucose control. However, the current experiences are highly controversial (7, 8). According to some recent case presentations, glycemia regulation is challenging using an "artificial pancreas" and this device cannot be used if glycemia is under 3.885 mmol/L (7). Moreover, the routine application of the "artificial pancreas" is currently not affordable in most of the centers, due to its high cost.

Our case report provides insight into to challenging perioperative treatment of a patient undergoing surgical treatment of insulinoma. The anaesthetic management aims to prevent hypoglycemia prior to tumor resection and to control rebound hyperglycemia after tumor removal. The limited available literature about the perioperative treatment of insulinoma patients highlights the need for further investigations in this topic, as well as the importance of developing guidelines for the anaesthetic management of patients undergoing insulinoma removal.

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