

Endocrinopathies: The current and changing perspectives in anesthesia practice

Sukhminder Jit Singh Bajwa, Gurpreet Kaur

Department of Anaesthesiology and Intensive Care, Gian Sagar Medical College and Hospital, Ram Nagar, Banur, Punjab, India

ABSTRACT

The gateways to advancements in medical fields have always been accessed through the coalition between various specialties. It is almost impossible for any specialty to make rapid strides of its own. However, the understanding of deeper perspectives of each specialty or super specialty is essential to take initiatives for the progress of the other specialty. Endocrinology and anesthesiology are two such examples which have made rapid progress in the last three decades. Somehow the interaction and relationship among these medical streams have been only scarcely studied. Diabetes and thyroid pathophysiology have been the most researched endocrine disorders so far in anesthesia practice but even their management strategies have undergone significant metamorphosis over the last three decades. As such, anesthesia practice has been influenced vastly by these advancements in endocrinology. However, a comprehensive understanding of the relationship between these two partially related specialties is considered to be an essential cornerstone for further progress in anesthesia and surgical sciences. The current review is an attempt to imbibe the current and the changing perspectives so as to make the understanding of the relationship between these two medical streams a little simple and clearer.

Key words: Acromegaly, anesthesia for endocrinopathies, craniopharyngioma, diabetes mellitus, endocrinology, pheochromocytoma, thyroid crisis

INTRODUCTION

Although anesthesia and Endocrinology are two different aspects of medical stream, but off late several breakthrough interventions in the literature have coalesced both the medical specialties especially related to surgical sciences and critical care. The practice of various traditional surgical techniques, nonavailability of newer and safer drugs, lack of monitoring tools, and scarcely available critical care services in the past, management of patients with various endocrinal disorders was always perceived more challenging by the practicing anesthesiologists.

Patients with various endocrinopathies pose varying challenges for anesthesiologist in the perioperative period. Newer literary breakthroughs in endocrine pharmacology involving three streams of medical field including medicine, pharmacology and anesthesia have definitely established a correlation in surgical sciences. As such, nowadays, a multidisciplinary approach involving endocrinologist, anesthesiologist, intensivist and surgeon is needed for better patient outcome in perioperative period. The impact of endocrine disorders on perioperative outcome cannot be ignored at all, however minor it may be.^[1-5] Thus, it becomes important to have a deeper knowledge of different anesthetic

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Corresponding Author: Dr. Sukhminder Jit Singh Bajwa, Department of Anaesthesiology and Intensive Care, Gian Sagar Medical College and Hospital, House No-27-A, Ratan Nagar, Tripuri, Patiala, Punjab, India. E-mail: sukhminder_bajwa2001@yahoo.com

and nonanesthetic drugs affecting neurotransmitter and hormonal secretion so as to reduce perioperative morbidity and mortality. Among major endocrinological disorders, those involving thyroid, parathyroid, pancreas, adrenal and pituitary glands significantly affect surgical outcome and anesthesia strategies.

Search strategies

The present review is compiled to highlight the basic and essential endocrine pharmacology influencing the current anesthesia practice. The measures adopted included extensive scrutiny of literary evidence from internet resources, journals and textbooks of endocrinology, medicine, pharmacology, anesthesiology, and intensive care. The strategies included exploration of full text articles and abstracts from various search engines such as PubMed, Medscape, Scopus, Science Direct, Medline, Yahoo, Google Scholar and many others. The search included key words like anesthesia for endocrinopathies, acromegaly, adrenal crisis, craniopharyngioma, diabetes mellitus, endocrinology, parathyroid, pheochromocytoma; thyroid crisis and endocrine disorders.

Basic understanding of endocrine disorders in anesthesia practice

Anesthesia administration for endocrine surgery is different from that of routine surgical procedures. Release of various hormones and neurotransmitters in the perioperative period can lead to unfavorable and unpredictable outcome. Hormonal secretion from various glands like pituitary, thyroid, parathyroid, pancreas and adrenal can affect surgical morbidity. Autonomic dysfunction associated with co-morbidities of these glands affect perioperative anesthesia management. Though slightly contentious, anesthetic agents such as use of nitrous oxide may be teratogenic and inhalational anesthetic agents can cause genetic modifications. Similarly, endocrine drugs like vasopressin antagonist for hyponatremia, insulin for hyperglycaemia, in parenteral nutrition and for hyperkalemia, testosterone for uterine bleeding, and vasopressin, Terlipressin etc. for control of gastrointestinal bleed have been proving extremely useful in anesthesia and critical care practice.^[6]

Hypothalamic-pituitary-adrenal axis: A crucial role

Activation of hypothalamic-pituitary-adrenal axis in response to surgical stimulus results in increased secretion of catabolic hormones. This pathway involves release of corticotrophin releasing hormone from hypothalamus, which stimulates anterior pituitary to release adreno-corticotrophin releasing hormone (ACTH), which further acts on adrenal cortex to release cortisol. Cortisol has got both mineralo-corticoid and glucocorticoid actions. It causes hyperglycaemia, as it promotes gluconeogenesis in liver, protein catabolism and by reducing peripheral

glucose utilization, apart from having an anti-inflammatory role also.

High doses of opioids in general anesthesia and extensive dermatomal blockade during regional anesthesia are needed to suppress release of cortisol to prevent surgical stimulus. Opioids, midazolam, dexmedetomidine and etomidate affect release of adrenocortical hormones. Daily cortisol secretion is approximately 25 mg in average healthy adult. In perioperative period, if patient develops hypotension which is not responsive to intravenous (IV) fluids, then a single dose of 25 mg IV hydrocortisone can be given after taking blood sample for cortisol estimation. As per recent guidelines, there is no need to administer steroids if patient is currently not on steroids for the last 3 months and also if daily prednisolone intake is <10 mg per day.^[7]

Various endocrine disorders along with their preoperative, intraoperative and postoperative issues have been discussed below and also in Table 1.

Anesthetic challenges of pituitary: Acromegaly

This endocrine disorder is due to excessive release of growth hormone from pituitary gland. Patients with acromegaly are usually posted for transsphenoidal excision of pituitary tumors and are invariably on multiple drug regimens, which should be continued according to the institutional protocols and laboratory values. Steroid replacement is usually needed in cases of panhypopituitarism. These patients pose difficulty particularly during airway management due to macroglossia, hypertrophy of soft tissues of oropharynx and enlargement of soft palate, epiglottis and ary-epiglottic fold.^[8] Therefore, before induction of anesthesia, difficult airway cart should always be made ready. If these patients are suffering from diabetes mellitus, oral hypoglycemic agents should be stopped 1-day prior to surgery to prevent development of refractory hypoglycemia and lactic acidosis. To provide hypotensive anesthesia, various drugs such as dexmedetomidine, beta blockers, inhalational and IV anesthetic agents can be used. Postoperatively, these patients usually need hydrocortisone replacement, which should ideally be done after measuring serum cortisol levels. However, the standard protocol is to administer 50 mg twice daily (BID) on postoperative day (POD) 1, 25 mg BID on POD 2 and 20 mg–10 mg in morning and evening on POD 3 and 15 mg BID after discharge, with blood sugar monitoring.^[9]

Other pituitary tumors like prolactin adenoma etc. are commonly seen in the females of child bearing age group and also interfere with hypothalamic-pituitary-ovarian axis. These tumors can also complicate the pregnancy as well as anesthesia procedure for any surgery during pregnancy.^[10,11]

Table 1: Anaesthetic management in endocrinopathies

Condition	Preoperative considerations and preparation	Intraoperative considerations	Postoperative issues
Acromegaly	Keep difficult airway cart ready Possibility of inadequate collateral circulation at wrist	Difficult mask ventilation, laryngoscopy and endotracheal intubation may be there Keep small sized endotracheal tube ready Careful placement of radial arterial line Neuromuscular monitoring Dexmedetomidine/beta blockers/ inhalational and intravenous anesthetic agents for hypotensive anesthesia	Hydrocortisone replacement
Craniopharyngioma	Raised intracranial pressure Hydrocortisone replacement before induction	Hypotensive anesthesia with intracranial pressure lowering measures Blood and blood products should always be kept ready	Urine output monitoring May need intranasal desmopressin
Phaeochromocytoma	Start alpha blockers Beta blockers for tachyarrhythmias Serial hematocrit monitoring for adequacy of intravascular fluid volume expansion and adequate alpha blockade Reduce anxiety Echocardiography for patients with suspected cardiomyopathy Evaluate for hyperglycemia and hypercalcemia	Avoid drugs that can stimulate sympathetic nervous system Supplement cortisol for bilateral adrenalectomy Invasive monitoring Laryngoscopy and intubation after adequate depth of anesthesia Short acting opioids, nitroprusside, phentolamine to avoid pressor response Clevidipine butyrate, also for hypertensive crisis Rapid infusion of crystalloids and colloids after ligation of adrenal vein with or without vasopressors support	Dopamine, phenylephrine, AVP for refractory hypotension Monitoring arterial blood gases, blood glucose levels and electrolytes is recommended in perioperative period Adequate pain relief
Parathyroid surgeries	Saline infusion along with diuretics for symptomatic hypercalcemia Bisphosphonates Hemodialysis may be needed to lower serum calcium levels	Maintenance of hydration and urine output Neuromuscular monitoring as response to muscle relaxants is unpredictable ECG monitoring	Treat hypocalcemia and hypomagnesemia Watch for hyperchloremic metabolic acidosis
Thyroid surgeries (hyperthyroidism)	Patient should be euthyroid Resting heart rate <100/min with beta blockers Relieve anxiety Continue with anti-thyroid drugs Evaluate for upper airway obstruction MEN syndromes may be associated	Careful positioning due to osteoporosis Barbiturates preferred for induction Avoids factors precipitating sympathetic nervous system stimulation Opioids, dexmedetomidine and propofol can be used Fiberoptic bronchoscope should be available Beta blockers should be kept ready Protect eyes Monitoring of neuromuscular blockade and temperature	Steroids may be useful for airway edema and postoperative nausea, vomiting
Diabetes mellitus	Should be the first case Intravascular fluid status, electrolytes should be normalized Adequate glycemic control End organ damage to be assessed Avoid metformin and ACE inhibitors Evaluate for autonomic neuropathy	Increased risk of aspiration Control glucose levels with insulin infusion Increased risk of silent myocardial infarction and arrhythmias Renal protective therapies Titrate neuromuscular monitoring Alpha adrenergic agonists prevent intubation stress response	Adequate glucose control Avoid hypoglycemia and hyperglycemia Adequate pain control Monitor urine output

AVP: Arginine vasopressin, ECG: Electrocardiography, MEN: Multiple endocrine neoplasia, ACE: Angiotensin-converting enzyme

Craniopharyngioma-the multiple impact tumor

These are benign tumors, commonly located in sellar or suprasellar regions and constitute about 2–6% of all primary intracranial tumors in childhood. Patients with these tumors can have both pressure symptoms and endocrine derangements in the form of deficiency of growth hormone, gonadotropin, thyroid stimulating hormone and adreno-corticotrophic hormone.^[12] An important aspect of anesthesia management is to provide hypotensive anesthesia, with the help of various intracranial pressure lowering measures. Injury to the adjacent major blood vessels can result in torrential bleeding, so blood and blood products should always be kept ready. Postoperatively, these patients can have anterior pituitary impairment and posterior pituitary dysfunction in 70-80% of cases.^[13,14] As such, these patients should be kept in high dependency units postoperatively.

Phaeochromocytoma-a perioperative dreadful tumor

Preoperative preparation, along with appropriate pharmacological management in these patients, is an important anesthetic consideration. Adequate alpha adrenergic blockade is very essential, which can be judged from adequate blood pressure control along with minimal fluctuations during period of perioperative stress. Restoration of intravascular volume with appropriate input/output monitoring, is also equally important.

Alpha adrenergic blockers should be given at least for 2 weeks during preoperative optimization of these patients, as their use along with correction of hypovolemia has been observed to cause significant reduction in perioperative mortality.^[15,16] These agents reduce incidence of myocardial infarction and intracranial bleed during time of stress, that is, at the time of laryngoscopy, intubation and tumor handling. Both nonselective and selective alpha blockers can be used in perioperative period. These drugs should be given at night time to avoid complications associated with postural hypotension. Tachycardia and dysarrhythmias should be managed with beta blockers which can be started after 2 weeks of initiation of alpha blockers. Calcium channel blockers (CCBs) including diltiazem, amlodipine, nicardipine, and nifedipine can also be used. These drugs cause relaxation of peripheral as well as coronary arteries and decrease cardiac morbidity.^[17]

A newer agent clevidipine butyrate, a third generation CCB is also being increasingly used to treat a hypertensive crisis. With an onset of action in 2–4 min, its initial rate is set at 1–2 mg/h and maximum rate can be adjusted to 32 mg/h. It acts by inhibiting calcium influx causing arterial vasodilatation.^[18,19]

These patients can possibly develop refractory hypotension during postoperative period as ligation of adrenal vein causes rapid fall in the levels of plasma catecholamines that may or may not respond to aggressive fluid management. In addition to dopamine and phenylephrine, arginine vasopressin is the preferred pharmacological agent, that can be used to treat refractory hypotension. Through its vasoconstriction properties and promotion of reabsorption of water in collecting ducts of kidneys, it restores the intravascular milieu.^[20]

Hormonal impact of parathyroid surgeries

Parathyroid surgeries are very delicate surgeries. Levels of parathyroid hormones are influenced by adrenergic stimulation and also by the current ionic calcium levels.^[21] Monitored anesthesia care leads to minimal stress response but excessive sedation can cause respiratory depression which can increase parathyroid hormone levels due to adrenergic stimulation. Total intravenous anesthesia (IV) anesthesia with propofol has been used for sedation, which is dose dependent. Although, it can be safely used but higher doses cause respiratory depression and thus can increase plasma catecholamine and parathyroid hormone levels.^[22,23] Recently, research oriented activities have been aimed at measurement of parathyroid hormone levels during administration of anesthesia which can influence and predict the various surgical decisions during perioperative period.^[24]

Thyroid surgeries-the never ending challenges

Thyroidectomy is one of the most common endocrine surgical procedures being performed in surgery. Along with euthyroid status, a great emphasis is also given to potential difficult airway. Presence of large sized goitre for long duration is a predisposing factor for tracheomalacia.^[25] Preoperative optimization of thyroid status is one of the main goals of anesthesia management. Propylthiouracil and methimazole can be used but carbimazole is the drug of choice in preparation of hyperthyroid patient. Its side effects include increased thyroid vascularity and fall in white blood cell count.^[26,27] Beta blockers are significantly useful in achieving perioperative cardiovascular stability.^[27] If hormonal imbalance is not corrected, then anesthetic drugs can potentiate risk of cardiovascular complications.^[28] Difficult airway equipment should always be ready before induction of anesthesia. Anticholinergic agents like atropine and glycopyrrolate are useful in premedication as these help in drying up of secretions and also test the adequacy of anti-thyroid treatment. Opioids, dexmedetomidine along with propofol can all be used in surgical cases with thyroid diseases. Availability of fiberoptic bronchoscope is essential as sometimes it is difficult to ventilate these patients after giving muscle relaxant. During intubation,

endotracheal tube should be advanced beyond the point of extrinsic compression. Neuromuscular blockade should be monitored and titrated as hyperthyroid patients may possibly be associated with myasthenia gravis. Dexmedetomidine is also important in preventing stress response during intubation as well as extubation.^[29] Corticosteroids have been observed to be very useful in view of airway edema and preventing postoperative nausea and vomiting. These patients may be associated with autonomic nervous system dysfunction as some of these may be associated with multiple endocrine neoplasia syndrome.

Diabetes mellitus-the most common endocrine challenge

Increasing prevalence of diabetes mellitus can significantly alter the anesthesia and surgical outcome. Almost every aspect of anesthesia management including analgesia, anesthesia and postoperative management in intensive care gets affected with this disorder.^[30] End organ damage is associated with several comorbidities and a significantly high mortality is associated with cardiovascular disease in these patients.^[31] Incidence of silent myocardial infarction, arrhythmias and sudden cardiac death is higher in these patients due to autonomic neuropathy.^[32-35] Autonomic neuropathy can be evaluated in these patients preoperatively with simple bed side tests like postural blood pressure fluctuations and valsalva maneuver.

Perioperative management of diabetes should be aimed at maintenance of euglycemia, euelectrolytemia and euvoolemia. Renal protective strategies should be adopted in patients with chronic renal failure.^[36] Gastroparesis due to autonomic neuropathy can result in pulmonary aspiration during induction of anesthesia.^[33] Therefore in such patient population, rapid sequence induction should be done preferably. However, succinylcholine should be avoided in patients with diabetes and hyperkalemia and rocuronium is a better alternative for rapid sequence induction and intubation. Midazolam decreases ACTH and cortisol levels but increases growth hormone levels and may possibly suppress hyperglycemic response to surgery.^[37] Among opioids, fentanyl is preferred analgesic over morphine in diabetic patients with renal compromise because morphine metabolites are excreted through kidneys.^[38] Alpha-2 agonists have become very popular in attenuating the stress response during intubation and have anesthesia sparing effect, thus preventing hyperglycemia along with maintenance of hemodynamic stability.^[26,39] Halogenated inhalational anesthetic agents inhibit insulin release and cause negative Inotropic effect.^[40]

Metformin and angiotensin converting enzyme inhibitors should be avoided in perioperative period.^[41,42] Perioperative IV insulin infusion is mandatory besides frequent glucose

monitoring in prolonged and major surgeries. These cases should be taken as first case in the morning to prevent metabolic complications due to starvation and hypoglycemia. Prevention of counter regulatory response is very important in such cases as fluctuation of blood glucose is more detrimental during perioperative period. Insulin should be administered slowly in patients with autonomic neuropathy as it can cause hypotension by decreasing systemic vascular resistance.^[43] Premixed and long acting insulins should not be given via IV route during perioperative period. Rapidly acting insulin such as Aspart and Lispro are compatible with all types of IV solutions. Glulisine is compatible only with 5% dextrose.^[44] Good glycemic control during perioperative period is associated with decreased morbidity and mortality and it should extend into postoperative period also. Adequate pain control is also essential as pain can increase counter regulatory hormone levels leading to hyperglycemia. Psychosocial counseling in critically ill diabetic patients also help in controlling the counter regulatory hormonal levels to a good extent.^[45]

Clinical challenges of endocrine emergencies

Endocrine emergencies include diabetic hyperglycemic states, adrenal insufficiency, myxedema coma, thyroid storm, and pituitary apoplexy which pose extreme clinical challenges during emergency surgery and critical care management, these will be discussed below and in Table 2. Their timely diagnosis and management is highly important as these can be associated with a very high mortality.^[46]

Diabetic ketoacidosis

This usually present as an acute metabolic complication in patients with type-1 diabetes, due to deficiency of insulin, mostly associated with an infection or co-morbidity. Deficiency of insulin results in decreased glucose uptake and its utilization by muscle, fat and liver with enhancement of glycogenolysis and gluconeogenesis. Increased lipolysis leads to production of ketone bodies with development of anion gap metabolic acidosis.^[47] Up to 5–7 liters (L) of fluid loss can occur with deficiency of sodium, potassium, magnesium, chloride, and phosphate. Therapeutic management goals mainly aim at replacement of total body water deficit of 10–12 L with 0.9% sodium chloride (NS). Two L of 0.9% NS can be given over first 2 h followed by 2 L 0.9% or 0.45% NS over next 4 h and 8 L of 0.9% or 0.45% NS over next 8 h with regular monitoring of central venous pressure. Insulin therapy is stated at rate of 0.1 units/kg/h with hourly blood glucose monitoring. Once blood glucose levels fall to 230–300 mg/dl, 5% dextrose infusion is started.^[48,49] Potassium deficit can go up to 300–1000 mEq and mainly occurs due to osmotic renal losses and shift of intracellular potassium to the extracellular space.^[48] Phosphate replacement is usually

Table 2: Management of Endocrine emergencies

Condition	Presentation	Management
Diabetic ketoacidosis	An acute metabolic complication. Increased lipolysis leads to anion gap metabolic acidosis	Aggressive fluid therapy Insulin therapy is started at rate of 0.1 units/kg/h with hourly blood glucose monitoring. For blood glucose levels=230–300 mg/dl, 5% dextrose infusion Potassium correction Phosphate replacement Bicarbonate replacement if pH is <7.0
Hypoglycemia	Signs and symptoms of sympathetic nervous system stimulation and neuroglycopenia	25 ml of 50% glucose Glucagon=1 mg IV/IM Careful use of long acting insulin preparations Should be taken up as first case for surgery
Thyroid storm	In hyperthyroidism and as complication of thyroid surgeries	Cooling mattress, cold crystalloids Propylthiouracil Esmolol Plasmapheresis, plasma exchange, peritoneal hemodialysis
Myxoedema coma	Severe form of hypothyroidism Altered mental status and hypothermia Cardiac conduction abnormalities, pericardial effusion, respiratory muscle weakness and adrenal insufficiency	Loading dose of thyroxine 300–500 mcg, followed by 50–100 mcg daily. Hydrocortisone replacement Treatment of precipitating cause Supportive therapy
Addisonian crisis	An acute adrenal insufficiency Usually presents with hypotension or shock	Hydrocortisone 75–100 mg given every 6–8 hourly or dexamethasone 3–4 mg every 6–8 hourly in case of hypotension along with fluid and electrolyte replacement
Diabetes insipidus	An acute complication seen with pituitary disorders	Desmopressin, intranasal and IV routes are preferred

IV: Intravenous, IM: Intramuscular

needed if initial serum phosphate concentration is 1.5 mg/dl. Presence of hypophosphatemia syndrome is characterized by decreased myocardial contractility, respiratory muscle weakness, hemolysis, and rhabdo-myolysis. These patients usually require 500–1000 mg of elemental phosphate over 12–24 h.^[48] Bicarbonate replacement is needed only if pH is <7.0 because acidosis usually gets resolved once insulin therapy is initiated.

Hypoglycemia

It is one of common endocrine emergencies in anesthesia practice among surgical patients. It is defined as blood glucose levels <3.5 mol/dl and target levels of glucose in critically ill surgical patients are 110 mg/dl. It is commonly encountered due to use of longer acting insulin preparations, especially if patient is fasting for a longer duration and decreased insulin resistance or clearance.^[48] This severity of this complication can be more in geriatric patients and as such these patients should be taken up for surgery as a first case in the morning.^[50,51]

Thyroid storm

It is a life-threatening complication seen with hyperthyroidism and is more dreaded and feared complication of thyroid surgery. Management includes supportive therapy and symptomatic treatment which include propylthiouracil 600–1000 mg loading dose, followed by 1200 mg/day divided into doses given every 4–6 h. Beta blockers like propranolol in 1 mg increments every 10–15 min or esmolol first as 250–500 mcg/kg followed by infusion of 50–100 mcg/

kg/min can be used. In refractory cases, plasmapheresis, plasma exchange and peritoneal hemodialysis can be used to remove circulating thyroid hormone.

Myxoedema coma

It is the severe form of hypothyroidism which can complicate the surgical outcome. Critically sick patients present with altered mental status and hypothermia (temperature as low as 21°C). Cardiac conduction abnormalities, pericardial effusion, respiratory muscle weakness and adrenal insufficiency are some of the presenting clinical features and should be managed aggressively during perioperative period. Management includes loading dose of thyroxine 300–500 mcg, followed by 50–100 mcg daily along with hydrocortisone replacement. Treatment of precipitating cause and supportive therapy are also important aspect of management.

Addisonian crisis

It is an acute adrenal insufficiency mainly caused by autoimmune disorders, infections, sudden withdrawal of adrenal replacement therapy, hemorrhage into adrenal gland etc. Adrenal crisis due to mineralo-corticoid deficiency usually presents with hypotension or shock. This may be associated with hyponatremia and hyperkalemia. Management strategies include administration of Hydrocortisone 75–100 mg given every 6–8 hourly or dexamethasone 3–4 mg every 6–8 hourly can be used in case of hypotension along with fluid and electrolyte replacement.^[52]

Diabetes insipidus

This is the most common acute complication seen with pituitary disorders. It may be seen in postpartum panhypopituitarism, severe head injury bleeding into pituitary tumor, patients operated for pituitary tumors and in stress induced hypopituitarism.^[53] Desmopressin is the main stay of treatment and is administered by careful titration of urine output, electrolyte and serum osmolarity. Intranasal and IV routes are preferred to avoid first pass hepatic metabolism.

CONCLUSION

The understanding of various endocrine pharmacological aspects influencing anesthesia practice can be further improved by undertaking various research and retrospective studies in surgical patients with endocrine disorders. At present, a significant progress has been made in Endocrine Anesthesia and a lot more is desired in the coming days for the advancements of these medical streams in general and betterment of mankind in particular. This can be achieved faster with a better coordination among anesthesiologists and endocrinologists while managing surgical patients with endocrine disorders.

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