Review Article

Implications and considerations during pheochromocytoma resection: A challenge to the anesthesiologist

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ABSTRACT

Pheochromocytoma is a rare catecholamine secreting tumor arising commonly from adrenal medulla. It has got multidimensional challenging aspects in spite of our improved understanding of its physiological and clinical behavior during surgical resection. This neuroendocrine tumor is associated with a most unpredictable and fluctuating clinical course during anesthesia and surgical intervention. The clinical difficulties and challenges increase manifold in patients with undiagnosed or accidental diagnosis of pheochromocytoma who present to the hospital for the treatment of some other disease or emergency. The most common manifestations of this clinical spectrum include hypertension, headache, palpitations, episodic sweating, and feeling of doom. The definite and only treatment for this rare tumor is surgical resection which itself is very challenging for an anesthesiologist. This article reviews the pre-operative evaluation, pharmacological preparation, intraoperative and post-operative management of patients with pheochromocytoma especially from anesthesiologist's perspectives.

Key words: Beta-blockers, catecholamines, epinephrine, hypertension, magnesium sulphate, nor-epinephrine, phenoxybenzamine, pheochromocytoma

Introduction

Technological advancements and development of new therapeutic and diagnostic modalities have taken the medical services to a much higher level, thus improving the provision of overall quality healthcare services to the patients. Despite these progressive breakthrough achievements, few diseases still acquire a threatening clinical course during various surgical interventions. Pheochromocytoma is one such pathological entity which has got multidimensional challenging aspects in spite of our improved understanding of its physiological and clinical behavior during surgical resection. This neuroendocrine tumor is associated with a most unpredictable and fluctuating clinical course during anesthesia and surgical intervention. Equally distressing is the management of such patients in the intensive care unit. The clinical difficulties and challenges increase manifold in patients with undiagnosed or accidental diagnosis of pheochromocytoma who present to the hospital for the treatment of some other disease or emergency. Management of such patients requires good clinical knowledge and skills, intensive pre-operative preparation, adequate diagnostic facilities, set-up for advanced surgical and anesthetic interventions, and post-operative resuscitation facilities backed up by a dedicated intensive care unit.

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Clinical and Patho-physiological Profile

Pheochromocytoma is a rare catecholamine secreting tumor arising commonly from adrenal medulla and to some extent

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from other paraganglia of the sympathetic chain but can arise from any part of the body with an incidence of 1.55-2.1 per million populations per year.[1,2] The term "dusky-color tumor" is commonly applied to this pathological entity. A remarkable feature associated with this tumor is the "rule of 10" as 10% of the tumors are bilateral, 10% are extra-adrenal, 10% of the tumors undergo malignant change and in about 10% of the patients, pheochromocytoma exist with various familial disorders such as multiple endocrine neoplasia (MEN) syndromes [MEN 2A and 2B], von Recklinghausen disease, and von Hippel Landau syndrome.[3-5] The incidence of this tumor shows a slightly higher female preponderance in a ratio of 60:40 as compared to the prevalence in males.[6] The classical symptomatology arising as a result of the patho-physiologic actions of this tumor is mainly attributable to the excessive secretions of the catecholamines mainly nor-epinephrine, epinephrine, and dopamine and to a smaller extent to some other hormones and peptides including somatatostatin, calcitonin, oxytocin, vasopressin, enkephalins, insulin, adreno-corticotrophic hormones, etc.[7-9] The most common manifestations of this clinical spectrum include hypertension, headache, palpitations, episodic sweating, and feeling of doom [Table 1]. Hypertension is usually paroxysmal in 65% of the patients and sustained in 35%. Among the organ systems, cardiovascular manifestations include arrhythmias, dilated cardiomyopathy, and peripheral vasoconstriction which ultimately lead to cardiac failure. Central nervous system involvement is exhibited by excessive anxiety, psychosis, and nervousness, while hyper metabolic state leads to weight loss. All these clinical signs and symptoms lead to the development of various complications such as cardiac failure, acute pulmonary edema, systemic arterial shutdown leading to severe metabolic acidosis or presenting as fulminant toxemia during pregnancy.[10,11]

Table 1: Clinical signs and symptoms in patients with pheochromocytoma

Signs	Symptoms
Hypertension++++	Headache++++
-Paroxysmal+++	Palpitations++++
-Sustained++	Anxiety+++
Tachycardia+++	Nervousness+++
Reflex Bradycardia+++	Tremulousness++
Sweating++++	Weakness++
Hyperglycemia++	Fatigue++
Postural Hypotension+	Nausea and vomiting+
Pallor++	Faintness+
Flushing+	Visual disturbances+
Weight loss+	Paraesthesias+
Decreased peristalsis+	Bowel disturbances+
Tachypnea+	Pain abdomen+

The signs (++++) – (+) depicts the occurrence of signs and symptoms in decreasing frequencies in patients with pheochromocytoma

Diagnosis

Measurement of free catecholamines in a 24 hour period urine collection is the best confirmatory test for the existence of pheochromocytoma.[9,12] The accurate measurement of free epinephrine, nor-epinephrine, and dopamine is carried out by high performance liquid chromatography.[13] The older methodology measuring urinary catecholamine metabolites like metanephrine, nor-metanephrine, and vanillylmandelic acid (VMA) has been reduced to just supplementary diagnostic importance although in our setting VMA is easily available as diagnostic modality. The role of CT scanning and MRI is very critical not just for identification but also for accurately determining a tumor of size as small as of 1 cm which assumes a huge significance for planning the surgical intervention. Tumor at extra-adrenal site and metastasis can best be diagnosed with meta-iodobenzyl guanidine (MIBG) scintigraphy.[8,14,15]

Pre-anesthetic Evaluation

The challenges for anesthesiologist begin during the pre-anesthetic evaluation stage. Apart from routine history taking and screening for associated abnormalities, developing an intimate rapport with these patients is extremely essential as these patients are invariably over-anxious and nervous during physical examination besides having other organ dysfunctions. The appropriate psychological counseling and meticulous examination goes a long way in optimal planning of anesthetic intervention. Also, a close co-ordination and co-operation between an anesthesiologist, a surgeon, a cardiologist, and an endocrinologist is an essential pre-requisite for a successful outcome.

The assessment during this stage should include examining the severity of hypertension, cardiac manifestations, and end-organ damage especially the catecholamine-induced cardiomyopathy with failure which is associated with a high mortality.[16] Blood pressure measurement should be carried out in a pre-operative or recovery room as these places projects a very stressful scenario for the patients as well as such an examination provides a good assessment of the effectiveness of various pharmacological interventions employed to inhibit the responses to sympathetic stimulation.

Since, the only definitive and curative treatment for pheochromocytoma is surgical resection; therefore baseline investigations pertaining to individual organ system functions should be sought. ECG may be supplementary in diagnosing arrhythmias, ischemia, cardiomyopathy, but echocardiography is a must to evaluate the status of cardiac

tissue. Chest X-ray and spirometry are valuable adjuncts to determine the structural and dynamics aspects of lungs especially in the patients in whom parenchyma of lungs and right sided involvement of heart is anticipated. Hematocrit estimation provides an approximate assessment of pre-operative blood volume which can be extremely helpful in the initiation of alpha adrenergic blockade therapy. Serum electrolytes, blood urea, and serum creatinine provides a useful insight into the metabolic and renal function status. Blood sugar estimation can determine the dose of insulin requirement as few patients have uncontrolled hyperglycaemia pre-operatively.

Preparation for Surgery and Anesthesia

Scientific literature is abundant with various case series and reports citing peri-operative mortality and morbidity statistics associated with pheochromocytoma resection but not a single study has come out with definite conclusions enumerating the factors affecting the mortality statistics.[17-21] The pre-operative preparation, pharmacological interventions, and cardiovascular optimization are the most important aspects before surgical resection of pheochromocytoma. The mortality can however reach up to almost 50% in unprepared patients.[21]

The induction of anesthesia, laryngoscopy, intubation, and peri-operative stress during tumor manipulation can lead to a hazardous situation due to adrenergic crisis. The main objectives during this phase are as follows:

- Adequate control of blood pressure
- Adequate control of heart rate and arrhythmias
- Restoration of normal blood volume

The adequacy of alpha adrenergic blockade pre-operatively is assessed by the fulfillment of the above criteria especially the minimum fluctuations of these parameters to any nonsurgical stress and situation.

Alpha adrenergic blocking drugs

Although no randomized clinically controlled prospective research has been carried for the effectiveness of alpha adrenergic blocking drugs but nevertheless their pre-op use definitely reduces the incidence of peri-op complications like hypertensive crisis, wide fluctuation of BP during intra-op handling of the tumor and peri-op myocardial dysfunction.[17-21] In spite of existence of different schools of thought for the pre-op pharmacological management of pheochromocytoma, the most common denominator is the pre-op pharmacological optimization with alpha adrenergic blockade for at least 2 weeks. Once the patient is adequately prepared by the administration of alpha blockers, beta blockade can be instituted to treat any associated tachyarrhythmias [Table 2].

Notable observations in a few case series was the reduction of peri-op mortality from 13-45% to 0-3% when alpha adrenergic blocking drugs were meticulously used pre-operatively along with correction of pre-op hypovolemia.[21,22] Myocardial failure, myocardial infarction, or hypertensive bleed into the myocardium or brain are mainly responsible for the higher mortality rates during surgical resection of the tumor and incidence of all these catastrophic situations appears to get reduced with alpha adrenergic blockade.[21,22]

Numerous pharmacological preparations are available but

Table 2: Pharmacological agents used in the pre-operative preparation of patients with pheochromocytoma

Drugs	Dose	Side effects
Alpha adrenergic blockers		
Phenoxybenzamine	Initial (O) 10/30 mg/d Max. 80-250 mg	Postural hypotension, sedation, nasal stuffiness, dry mouth
Phentolamine	Bolus 1 mg IV Infusion of 20 mg in 500 ml of 5% dextrose	Hypotension, tachycardia, arrhythmias, myocardial ischemia
Beta adrenergic blockers		
Propranolol	Initial (O) 80-120 mg Max. 480 mg/d IV 1-10 mg	Cardiac failure, bronchospasm, fatigue
Atenolol	Initial (O)50-100 mg/d Max. 300 mg/d IV 2.5-10 mg/d	Severe bradycardia
Esmolol	Bolus (IV) 500 μg/kg/min Infusion 50-200 μg/kg/min	Bradycardia
Labetolol	Initial (O) 50-100 mg/d Max. 1200 mg/d IV slowly 0.25 mg/kg	Hypotension
Arterio-veno Dilator		
Sodium nitroprusside	Initial 0.5-1.5 μg/kg/min Max 3-5 μg/kg/min	Hypotension, cyanide toxicity, methemglobinemia
Calcium channel blockers		
Diltiazem	Initial (O) 60-120 mg/d Max. 360 mg/d	Bradycardia, cardiac failure
Nifedipine	Initial (O) 30 mg/d Max. 180 mg/d	Hypotension, peripheral edema
False transmitters		
Alpha methyl-p-tyrosine	Initial(O) 1 g/d Max. 4 g/d	Crystaluria, extra-pyramidal and psychic disturbances

the most commonly used is oral phenoxybenzamine in the doses of 20 mg three times daily with a maximum dose of 250 mg. Phenoxybenzamine's potential in providing a long duration of alpha blockade and non-competitive blockade as a result of covalent binding to drug receptors prevents the frequent surges of catecholamine releases during pre-op period. On the flip side, it blocks alpha-2 receptors also thereby inhibiting the feedback loop for release of nor-epinephrine and as a result huge amount of nor-epinephrine is released causing undesirable chronotropic and ionotropic effects.[23] Increased post-op somnolence, headache, stuffy nose, and postural hypotension are some of the major side effects of phenoxybenzamine. The intra-op α-2 receptor blockade by phentolamine is hardly required in these patients.

Selective α-1 antagonist

The selective α-1 antagonist drugs offer several advantages as these drugs do not elicit reflex tachycardia. In the absence of α-2 receptor affinity, the action of these drugs last for a short duration which helps in the smoother titration of the drug dose and as a result the risk of postural hypotension is minimized. Prazosin, Doxazosin, and Terazosin are commonly used selective α-1 antagonist to achieve a good pre-op control of the pheochromocytoma induced hypertension. Compared to phenoxybenzamine, these drugs require a higher use of phentolamine intra-operatively for α-2 receptor blockade.[24]

Currently, there is no universal consensus on the pharmacological preferences among α- adrenergic blockers. Although selective α-1 adrenergic blockers like doxazosin, terazosin, etc are specific, competitive and short acting but all these selective α-1 antagonists have the potential to cause severe postural hypotension after the administration of the first dose and therefore preferably be given during night just before sleep. The added advantage as compared to non-selective α-adrenergic blocker phenoxybenzamine includes easy titration of the dose, less expensive, and lower incidence of reflex tachycardia, and post-operative hypotension.

In volume-depleted patients, the hypotensive effects of selective α-1 antagonist are more marked as compared to phenoxybenzamine. Not a single study has established with definite evidence that selective α-1 antagonist can effectively control blood pressure during pre-op, peri-op, and post-op periods as compared to phenoxybenzamine. Furthermore, no study has been conclusive enough about the intra-op phentolamine or labetolol requirement in doxazosin- and phenoxybenzamine-treated patients especially relating to the control of blood pressure during tumor handling. To summate, it is an individual and institutional practice regarding the choice of α-adrenergic blockade for optimal pre-op pharmacological control of pheochromocytoma. Few other factors such as easy availability, ease of pharmacological administration of drugs and individual acumen also determine to some extent the pattern of usage of these pharmacological agents.

Beta-antagonist

The pathophysiologic considerations during the pre-op control of tachycardia mandate the use of β-blockers as also the persistent dysarrhythmias resulting from the administration of phenoxybenzamine in this subset of patients. Administration of β-blockers like propranolol, atenolol, and metoprolol is highly contraindicated in the absence of effective α-1 receptor blockade as the vasoconstrictor effects of the latter go unopposed and the loss of β-receptor-mediated vasodilatation may produce dangerous hypertension. Special precautions have to be observed in patients with catecholamine-induced cardiomyopathy as the lack of β-stimulation can lead to the development of pulmonary edema.

Calcium channel blockers

Calcium channel blockers like diltiazem and nifedipine relaxes smooth muscles of coronary and peripheral arteries and reduces the catecholamine induced spasm of these vessels.[25] The mechanism involved is the inhibition of epinephrine stimulated calcium influx. However, these drugs should be used cautiously in patients with left ventricular dysfunction.

False transmitters

Drugs like α-methyl-p-tyrosine act as false neurotransmitters and block the synthesis of catecholamines by inhibiting the enzyme tyrosine hydroxylase. This pharmacological intervention is just supplementary to the adrenergic blockade and it may not be completely effective in controlling the symptomatology. However, the significance of their usefulness cannot be denied in patients with inoperable malignant stage and in patients who are resistant to α-1 blockade.[26,27]

Magnesium sulfate

The role of magnesium sulfate has gained significant importance recently as its role is well established now in decreasing the plasma levels of catecholamines by inhibiting their release.[28] It also abolishes the arrhythmias induced by epinephrine and effectively acts as α-adrenergic antagonist.[29] The beneficial effects are more pronounced during the peri-op period as it profoundly dilates the arterioles, reduce the peripheral vascular resistance, and exert minimal effect on venous return or pulmonary capillary wedge pressure.[30] The role of magnesium sulfate

acquires significant proportions during the management of pheochromocytoma crisis. However, its use is not completely free from side effects as it is associated with increased sedation, muscular weakness, and occasional respiratory paralysis requiring prolonged mechanical ventilation.[31,32]

Recently, the role of other drugs has also been explored for the adequate control of pheochromocytoma pre-operatively. These drugs include amlodipine (10-20 mg/d), nicardipine (60-90 mg/d), nifedipine (30-90 mg/d), verapamil (180-540 mg/d), and urapidil. A skillful psychologic counseling, rapport with the patient and administration of benzodiazepines as premedicant, helps in achieving pre-op objective of adequate sedation and anxiolysis. This is extremely helpful in preventing the surges and fluctuations in arterial blood pressure as these patients invariably have a decreased blood volume and high hematocrit from a chronic vasoconstricted state. The best pharmacological practices mandate the administration of both α and β-adrenergic blockers even on the day of surgery.

Peri-op Anesthetic Management

Despite the deeper understanding of the patho-physiologic aspects of pheochromocytoma and the principles of its pharmacological management, it still remains a very challenging surgery for the concerned anesthesiologist. The fundamental objective during this stage include the prevention of hypertensive episodes especially during the procedures provoking a stress response such as laryngoscopy, intubation, and during surgical handling of the tumor.

Numerous anesthetic techniques have been used from time to time but among these the use of a combined epidural and general anesthesia is considered to be the most suitable and the preferred technique.[33,34] The bottom line is that changing an anesthetic technique does not cause a major impact on the surgical outcome. The total intravenous anesthesia technique using propofol and opioids such as fentanyl, sufentanyl, and remi-fentanyl is a good alternative to the traditional inhalational anesthetic technique but the scarce availability of drugs like sufentanyl and remi-fentanyl in our country has pushed this technique to a slight oblivion. The regional anesthetic technique though suppresses the stress response of surgical incision but cannot control the quantum of catecholamines released during the tumor handling.[19]

Among the inhalational agents, isoflurane and sevoflurane are the preferable agents as they do not sensitize the myocardium to catecholamines as compared to halothane and enflurane which are potentially arrhythmogenic in the presence of catecholamines. Fentanyl is the drug of choice for providing analgesia though sufentanil is a much better option in this regards but its scarce availability in our country is a big administrative issue.[35,36] Neuroleptanaesthesia (combination of droperidol and fentanyl) appears to offer some advantage as it preserves a good cardiovascular stability during pheochromocytoma resection.[37] Droperidol has got antiarrhythmic effects and acts as antiemetic by blocking α-2 receptors and inhibiting catecholamine re-uptake.

The attention of an anesthesiologist should not be restricted only to technique employed. Rather his responsibilities start right from planning a smoother transportation of the patient from the pre-op room to the operation theatre. Besides ensuring a smoother pre-op period nothing can replace a good communication pattern between the surgeon and the anesthesiologist which go a long way in relieving the stress associated with these pre-op events thus causing sudden catecholamine release and its associated hazardous effects.

Thiopentone and propofol are the commonly used drugs during induction of anesthesia. However, propofol is preferred as it produces vasodilatation and blunts to some extent the hypertensive response to laryngoscopy and intubation. During induction, succinylcholine can be hazardous as it produces sympathetic activation and the raised pressure due to abdominal muscles contraction can be transmitted to the tumor mass that causes release of catecholamines. Vecuronium should be preferred as a muscle relaxant due to its cardiovascular stability. Tubocurarine, atracurium, and mivacurium releases histamine, while pancuronium is not preferred because of its indirect sympathetic stimulation profile. All these anesthetic agents may exhibit pharmacological merits in theoretical practice but their clinical efficacy and advantages have not been established by any clinically controlled study in this subset of population.

Though, the established practices favor insertion of arterial and venous lines before induction, some prefer to perform these procedures after stabilizing the patient post-induction as these patients are very anxious pre-operatively. The pain and anxiety associated with these procedures can lead to sudden hypertensive response and will defeat the goals of good premedication and pre-operative preparation as these patients are very sensitive to pain. Epidural catheter placement should be carried out after liberal use of local anesthetics at the lumbar puncture site to avoid any pain and a preservative free lignocaine should be employed. The test dose should be administered as usual as the amount of

adrenaline in the small volume of LA will not only help in the identification of the position of epidural catheter but will also be almost harmless to the effects of small amount of adrenaline in the solution.

The baseline hemodynamic parameters should be recorded in the pre-op room, on immediately shifting in the operation theatre and 5 mins after that before induction of anesthesia. This gives a good picture of the overall hemodynamic picture and the effectiveness of the pre-operative interventions. During the entire surgical procedure, the main aim will be to keep these vitals as close as possible to the baseline values. Peri-operatively the wide fluctuations in blood pressure are best managed by either dopamine or phenylephrine (for hypotension), whereas nitroprusside is the drug of choice to control hypertensive episodes.

At the end of surgical procedure it will be solely the anesthesiologist's decision whether to extubate the patient on table or later in the intensive care unit. The immediate post-operative course and recovery depends upon many intra-operative factors such as peri-op clinical status of the patient, peri-op eventful hemodynamic episodes, duration of surgery and anticipated stormy post-op period. Neuromuscular blockade should be reversed by a combination of neostigmine and glycopyrrolate as the antimuscarinic effects of the latter coincide with the onset of cholinergic effects of the former thus producing minimal tachycardia.

Post-operative Management

Patients should be closely monitored either in the ICU or post-anesthesia care unit (PACU) as these patients are highly vulnerable to hypertensive, hypotensive, or hypoglycemic episodes.[12] The higher incidence of post-op hypotension can be explained on the basis that after ligation of the adrenal vein there is a rapid fall of plasma catecholamine levels and the persistent hypotension is invariably refractory to intravascular volume replacement and adrenergic agonists. Persistent hypotension can also be due to residual effects of pre-op adrenergic blockade or rarely there can be intra-abdominal bleed.[27]

Immediate post-op hypertension can be due to recovery from anesthetic drugs or pain. The incidence of hypertension can be as high as 50% for few days in these patients as elevated catecholamine levels are present for 7-10 days after pheochromocytoma resection and sometimes a residual tumor may be responsible for the hypertension.[38] The insulin levels rises dramatically after surgical resection as the suppression of the beta cells of pancreas ceases to be effective. This results in development of hypoglycemia which can also be ascribed to reduced lipolysis and glycogenolysis due to removal of tumor and alpha blockade. It is mandatory to check the blood glucose levels regularly during the entire surgical period as well as into the post-op period. The post-op intravascular status optimization can be instituted with dextrose containing fluids.[39]

Special situations

Rarely, an undiagnosed case of pheochromocytoma presents to the hospital with some other type of pathological state or may come with pregnancy. This situation is extremely challenging for the attending anesthesiologist and the concerned specialist as the mortality rate is very high in such a subset of untreated patients.

Emergency surgery

In our country, a majority of the emergency surgical procedures are handled by young and not so experienced anesthesiologists and this can create an extremely stressful situation for these anesthesiologists. Majority of times many fatal cases go undiagnosed and its only post-mortality analysis which reveals the retrospective diagnosis of pheochromocytoma. Any unusual abdominal symptom or unexplained pulmonary edema or cardiac failure peri-operatively should raise suspicion of pheochromocytoma.[40,41] During an exploratory laparotomy for abdominal mass, any hypertensive event occurring should be assumed due to the presence of pheochromocytoma unless proven otherwise. Similarly, such hypertensive episodes are usually followed by hypotensive episodes but that should not deter one from excluding the possibility of myocardial infarction. These pheochromocytoma crises are best managed with IV bolus of $MgSO_4$ which can be titrated to achieve the hemodynamic control.[42] Beta-blockers should never be considered as first option in spite of excessive tachycardia as these agents can worsen the clinical scenario further and therefore should be administered only after achieving peripheral vasodilatation with $MgSO_4$.[43,44] The management of emergency surgery for pheochromocytoma warrants an extremely close co-ordination among the endocrinologist, surgeon, anesthesiologist, and obstetrician. Although nowadays laparoscopic surgical procedures are in vogue but the type of surgical intervention does not significantly alter the prognosis of such patients. However, laparoscopic procedure itself has its own inherent disadvantages, especially due to raised intra-abdominal pressures due to pneumoperitoneum which can deteriorate the clinical condition especially in the background of chronic

vasoconstricted state and reduced venous return resulting in accentuation of the decompensated cardiac status.

Pregnancy

Pheochromocytoma diagnosed for the first time during term pregnancy can raise the maternal mortality to 40% and fetal mortality to 56%. The notoriety of this tumor in a pregnant state is difficult to diagnose as it can mimic many other clinical conditions such as pre-eclampsia, cardiomyopathy, etc.[45-48] The onset of cardiac failure in pregnant female with pheochromocytoma carries an extremely grave prognosis and majority of these deaths occur due to catecholamine-induced cardiomyopathy. Drug of choice for managing clinical situation during late pregnancy is $MgSO_4$ as it reverses the depressed myocardium with great efficacy and efficiency. During early pregnancy, if pheochromocytoma is accidentally diagnosed, therapeutic options include doxazosin and phenoxybenzamine to provide hemodynamic stability and ultimately tumor removal.[45-48] Early caesarean section should be undertaken as soon as possible, provided the fetus should also remain viable.

With better understanding and knowledge of the pathophysiology of pheochromocytoma and advent of new drugs, the mortality statistics have come down drastically over a period of time. Surgical resection, pre-operative and peri-operative control of blood pressure and volume optimization are the mainstay in improving the outcome of surgery.

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