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Role of salt tablets in the treatment of perioperative hypotension in patients with pheochromocytoma

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ABSTRACT
Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are rare and clinically important chromaffin cell tumors that typically arise, respectively, from the adrenal gland and from extra-adrenal paraganglia. Neuroendocrine tumors which have the potential to secrete catecholamines are either associated with sympathetic adrenal (pheochromocytoma) or nonadrenal (paraganglioma) tissue. Surgical removal of these tumors is always indicated to cure and prevent cardiovascular and other organ system complications associated with catecholamine excess.The clinical features and consequences of PHEO/PGL result from the release of catecholamines (norepinephrine and epinephrine). An undetected PHEO/PGL poses a hazard to patients undergoing surgery, childbirth, or general anesthesia, because of the potential for excess catecholamine secretion, which can result in significant, often catastrophic outcomes.Pheochromocytomas can be divided into two main categories: EPI secreting PPGLs that cause decreased cardiac contractility owing to downregulation of β-adrenoceptors and NE secreting PPGLs causing a decrease in circulating plasma volume secondary to α_1-adrenoceptor mediated vasoconstriction leading to postural hypotension.
Diagnosing and localizing a PHEO/PGL can be challenging. Plasma and urinary catecholamines as well as their metabolites and radio-iodinated metaiodobenzylguanidine (MIBG) scanning can yield false-positive/negative results in patients harboring the tumor, and computed tomography (CT) and magnetic resonance imaging (MRI) lack sufficient specificity. The molecular mechanisms by which genotypic changes predispose to the development of PHEO/PGL remain unknown, even in patients with identified mutations.

Keywords: perioperative, postoperative, pheochromocytoma, hypertension, hypotension, arrhythmia, pheochromocytoma, paraganglioma, catecholamines, metanephrines, dopamine.

Summary
Objective Pheochromocytoma treatment and fast knowledge of variables involving catecholamines release associated with changes in blood pressure helps, gets better results in the treatment of hypotension perioperatively. We evaluated if patients who have had hypotension perioperatively, obtain a good tolerance and prompt and adequate management of their hypotension to avoid intra and postoperative complications with the use of salt tablets.
We want to report three cases of hypotension being treated with salt tablets preoperatively with good tolerance and results in stabilizing blood pressure.

Objective and Methods
Observational study monitoring intake of salt tablets for the treatment of hypotension perioperatively in patients with pheochromocytoma and paragangliomas via a Database management system that allow us to verify patient compliance, patient intake, symptoms relief (hypotension) perioperatively, design an alarm system to provide acute care/management if required or if a salt tablet dose was missed. We will measure and document blood pressure readings 3 times a day for the following 3 months after surgery and 1 month before surgery, action will be taken if required by the alarm system, charge nurse will verify patient treatment compliance in-house.

Clinical and genetic aspects of pheochromocytoma and paraganglioma
Germline or somatic mutations of numerous genes have been implicated in the pathogenesis of pheochromocytomas/paragangliomas (PPGLs), including the isocitrate dehydrogenase 1 (IDH1) gene and alpha thalassemia/mental retardation syndrome X-linked (ATRX) gene. Although concurrent IDH1 and ATRX mutations are frequently seen in gliomas, they have never been reported together in PPGLs. The aim of this study was to characterize one paraganglioma with concurrent IDH1 and ATRX mutations identified by whole exome sequencing. We used leukocyte and tumor DNA for whole exome sequencing and Sanger sequencing. We measured the 2-hydroxyglurarate level and the global DNA methylation status in the

tumor and analyzed ATRX's cDNA transcripts. Tyrosine hydroxylase (TH), HIF1α and ATRX staining, as well as telomere-specific FISH were also performed. In this particular case, we confirmed the presence of a somatic IDH1 (c.394C→T, p.R132C) mutation and a concurrent somatic ATRX splicing mutation (c.4318-2A→G). Dramatic accumulation of 2-hydroxyglutarate was detected in the paraganglioma without the global DNA hypermethylation, and pseudohypoxia was also activated. Importantly, immunohistochemistry revealed negative TH staining in the tumor, and the first exon region of the TH gene was hypermethylated, resulting in normal plasma metanephrines. The splicing ATRX mutation resulted in two transcripts, causing frameshifts.
Immunohistochemistry revealed scarce ATRX staining in the tumor. Alternative lengthening of telomeres (ALT) was detected by FISH. The case represented the first concurrence of IDH1 and ATRX mutations in PPGLs. Although relatively rare, a somatic R132C mutation of IDH1 might play a role in a small subset of sporadic PPGLs.
Studies have also shown the first direct molecular-genetic evidence of an association between a somatic iron-regulatory protein 1 (IRP1) loss-of-function mutation and pheochromocytoma and secondary polycythemia. In patients diagnosed with PPGL and polycythemia with negative genetic testing for mutations in HIF2A (gene encoding hypoxia-inducible factor alpha), PHD1/2 (gene encoding hypoxia-inducible factor prolyl hydroxylase 1), and VHL (Von Hippel–Lindau disease tumor suppressor gene), IRP1 should be considered a candidate gene.

Role of salt tablets in the treatment of hypotension

Salt tablets have two important ingredients, sodium and chloride, electrolytes in charge of maintaining cellular stability via Na, Cl- and H2O transporters along the nephron mainly in the proximal tubule. Increased sodium chloride intake increases blood pressure. Consuming salt tablets and water will restore your sodium/chloride levels and help you retain more fluids in the process. On the other hand, studies have shown that salt sensitivity is more prevalent in hypertensive individuals (30–50 %) compared to normotensives, and the presence of salt sensitivity in normotensives is a risk factor for future development of hypertension.

Nephron physiology

1. Early proximal convoluted tubule (PCT): contains brush border. Reabsorbs all of the glucose and amino acids and most of the Na+, Cl-, H20, among other electrolytes such as HCO3-, PO4-3, K+. Isotonic absorption. Generates and secretes NH3, which acts as a buffer for secreted H+. PTH – Inhibits Na+/PO4-3 cotransport → PO4-3 excretion. AT II- stimulates Na+/H+ exchange → increases Na+, H2O, and HCO3- reabsorption (permitting contraction alkalosis). 65-80% Na+ reabsorbed.
2. Thin descending loop of Henle: passively reabsorbs H2O via medullary hypertonicity (impermeable to Na+).Concentrating segment. Makes urine hypertonic.
3. Thick descending loop of Henle: actively reabsorbs Na+, K+, and Cl-. Impermeable to H2O. Makes urine less concentrated as it ascends. 10-20% Na+ reabsorbed.
4. Early distal convoluted tubule (DCT) – actively reabsorbs Na+, Cl-. Makes urine hypotonic. PTH – increases Ca+2/ Na+ exchange → Ca2+ reabsorption. 5-10 % Na+ reabsorbed.
5. Collecting Tubule – reabsorbs Na+ in exchange for secreting K+ and H+ (regulated by aldosterone). Aldosterone – acts on mineralocorticoid receptor → insertion of Na+ channel on luminal side. ADH – acts at V2 receptor → insertion of aquaporin H20 channels on luminal side. 3-5% Na+ reabsorbed.

Hypertension is the most common sign and may be sustained or paroxysmal, with the latter more usual presentation occurring on a background of normal blood pressure or sustained hypertension. PPGL may also present with hypotension (excessive stimulation of beta adrenoreceptors by elevated levels of epinephrine), postural hypotension or alternating episodes of high and low blood pressure. On the other hand, Hypotension can also occur post-surgery.
Salt tablets have shown effectiveness in the treatment of hypotension perioperatively by allowing absorbing Na+ and Cl- electrolytes in the nephron primarily in the proximal tubule as mentioned previously.

The Bezold-Jarisch reflex

The Bezold-Jarisch reflex originates in cardiac sensory receptors with nonmyelinated vagal afferent pathways. These sensory receptors are located in the left ventricle, specifically in the inferoposterior wall. Stimulation of these inhibitory cardiac receptors by stretch, chemical substances or drugs increases parasympathetic activity (mainly seen in Norepinephrine-secreting PPGLs) and inhibits sympathetic activity. These effects promote reflex bradycardia, vasodilation and hypotension (Bezold-Jarisch reflex) and also modulate renin release and vasopressin secretion.

Clinical Correlation

Renin Angiotensin Aldosterone System

The renin-angiotensin-aldosterone (RAAS) system is a crucial mediator of cardiac, vascular, and renal physiology through the regulation of vascular tone and salt and water homeostasis. In addition to the main

physiological functions, the RAAS has a significant role in the pathophysiological conditions of hypertension, heart failure, other cardiovascular diseases, and renal diseases. Blockade of the overactivation of RAAS by various medications has been shown to improve outcomes in various cardiovascular and renal diseases.

Secondary Hypertension

During a study of a patient with pheochromocytoma, it is very important to obtain a very concise history and physical so we can rule out many differential diagnoses such as: Renal Artery Stenosis, Conn Syndrome, CushingSyndrome, Coarctiation of the Aorta, Congenital Adrenal Hyperplasia and Sleep Apnea as described in table below. It is necessary to investigate for secondary hypertension if you see the following: young (age<30) or old (>60) patient and failure to control pressure with 3 medications.

Table 1. Episodic hypertension: Unexplained symptomatic paroxysmal hypertension is considered the hallmark symptom of pheochromocytomas**.**

Specific findings in the history or physical	
Condition	**Finding**
Pheochromocytoma	Episodic hypertension
Closure of renal artery (stenosis)	Abdominal Bruit
Conn Syndrome	Hypokalemia
Cushing syndrome	Buffalo hump, truncal obesity, striae
Coarctation of the aorta	Upper extremity > lower extremity pressure
Congenital adrenal hyperplasia	Hirsutism
Sleep apnea	None

Renal Artery Stenosis

look for an abnormal sound (bruit) auscultated in the flanks or abdomen. Hypokalemia may be present. The best initial diagnostic test is renal ultrasound with Doppler. Doppler is specific, but not sensitive. If a small kidney is seen, its necessary to perform magnetic resonance angiography (MRA) or CT angiogram confirms renal artery stenosis, which it is the most accurate test.

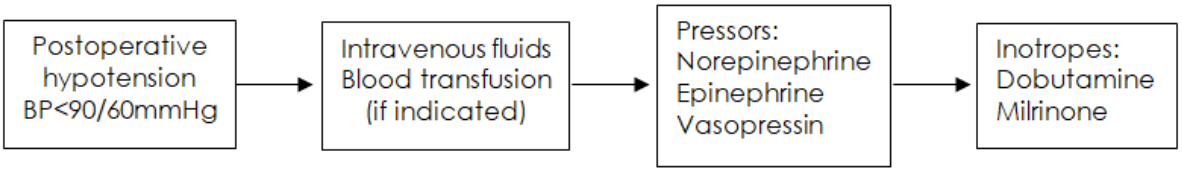
Salt Tablets Composition

Salt tablets or sodium chloride tablets are used in medicine for many purposes, such as an electrolyte replenisher for the prevention of heat cramps due to excessive perspiration, for the preparation of normal isotonic solution of sodium chloride in response to hemorrhagic shock from blood loss and finally for prevention of hypotension perioperatively in pheochromocytomas patients scheduled for adenectomy.

Role of salt tablets in the treatment of perioperative hypotension in Adenectomy

Hypotension is defined as blood pressure below 90/60 mmHg or any degree of low blood pressure leading to organ hypoperfusion or end-organ damage. Potential risk factors attributed to postoperative hypotension following PPGL resection include chronically low circulating plasma volume, an abrupt decrease in serum catecholamine levels, down-regulation of adrenoceptors, increased blood loss, and cardiogenic or septic shock. Independent tumor-related risk factors are open procedures, high preoperative plasma NE and EPI levels and increased urinary fractionated catecholamines excretion. EPI secreting PPGLs cause decreased cardiac contractility owing to downregulation of β-adrenoceptors on the heart, resulting in left heart failure, thus precipitating hypotensive state and collapse after resection. However, NE secreting PPGLs cause a decrease in circulating plasma volume secondary to α_1-adrenoceptor mediated vasoconstriction leading tohypotension due to extreme dilation of the capillary bed. Moreover, profound irreversible α-adrenoceptor blockade by phenoxybenzamine triggers recalcitrant postoperative hypotension by: (1) Prolonged half-life of the drug and (2) permanent covalent binding to adrenoceptors which are curtailed only after de novo synthesis. Nevertheless, this effect is comparatively less with selective α_1-adrenoceptor blockers.

First line management for postoperative hypotension following PPGL resection includes vigorous intravenous fluid administration. If fluid therapy fails, vasopressor use is justified to restore normal blood pressure. Vasopressors used to manage hypotension include NE, EPI (rarely), and vasopressin. However, pure α-adrenoceptor agonists such as phenylephrine are not used because of remnant effects of preoperative α-adrenoceptor blockade. Finally, the ultimate goal of managing hypotension is both restoration of adequate and prevention of inadequate tissue perfusion.



Graphic 1. Initial Management of postoperative hypotension.

As preoperative blood pressure management, we start with a combination of alpha and beta-adrenergic blockade medications.First, a non-selective alpha blocker is given : phenoxybenzamine blocks alpha-1 and alpha-2 adrenoceptors equally and irreversibly.After sufficient alpha-adrenergic blockade, a beta blocker may be started for additional blood pressure control and control of tachyarrhythmias.
Starting beta blockers before alpha blockade is contraindicated. Beta blockers cancel out the vasodilatory effect of peripheral beta-2 adrenoceptors, potentially leading to unopposed alpha-adrenoceptorstimulation, causing vasoconstriction and ultimately hypertensive crisis.

Perioperative hypotension risk Factors
-Preoperative: Use of nonselective alpha-blockers as phenoxybenzamine, anemia of chronic disease.
- Intraoperative: Hemorrhage secondary to lesion or rupture of large vessels, inadequate reposition of insensible loses**,** intraoperative hemorrhage and manipulation and dissection of the tumor tissue during surgery.Normotensive patients (in some series up to 30-40% so called low-risk patients) often become hypertensive during surgery, and demonstrate the unpredictable nature of blood pressure changes during an operation. Thus, Normotensive patients should also be given alpha-adrenoreceptor or calcium channel blockers preoperatively.
- Postoperative: adrenal insufficiency posterior to the total extraction of the adrenal tissue**,** residual alpha-adrenergic block effect secondary to preoperative alpha blockage medications.In an immediate postoperative period, hypotension is a common problem which is managed with intravenous fluids because vascular bed is effectively paralyzed by preoperative medications. Volumen replacement is quite large during initial 12-36 hours.

Beyond physiopathology and PPGLs studies
The normal adrenal medulla secretes about 85% epinephrine and 15% norepinephrine, but norepinephrine is the predominant catecholamine secreted by Pheochromocytomas.
Epinephrine Metabolism: it acts potently on b2-adrenergic receptors of the skeletal muscle vasculature causing vasodilation that results in hypotension. It has more potent alpha-adrenoceptor agonist than NE. Alpha effects predominate at high doses.Stimulates lipolysis, ketogenesis, thermogenesis and glycolysis and raises plasma glucose levels by stimulating glycogenolysis and gluconeogenesis. It has potent effects on pulmonary function, causing b2-adrenoceptor mediated dilation of airways. At low dose epinephrine has more beta2 effect than alpha 1 (beta 2 >alpha 1) while at high doses it has more alpha 2 effect than beta 1(alpha 2 >beta 1).

Norepinephrine Metabolism: It is a more potent b1-adrenoceptor agonist than Epinephrine.Norepinephrine is released locally from sympathetic nerve endings within the vasculaturecausing alpha1-adeceptor-mediated vasoconstriction resulting in hypertension. At any dose Norepinephrine has more effect on alpha 1 receptor, then alpha 2 and finally beta 1 receptors (NEPI: alpha1 >alpha2 >beta1).

Perioperative Management
Phenoxybenzamine is a non selective α-adrenergic receptor antagonist used in patients with pheochromocytoma or paraganglioma. One disadvantage of phenoxybenzamine include tachycardia, persistent postoperative hypotension in view of covalent, noncompetitive binding to the alpha-receptor, somnolence, stuff, stuffiness of nose, headache and postural hypotension requiring intravenous fluid replacement.Adequate alpha-blockade is indicated clinically by postural hypotension and then the patient is advised liberal salt and fluid intake for reexpansion of plasma volume. Diuretics should not be used. Target BP is less than 120/80 mm of Hg in sitting position and Systolic Blood Pressure not less than 90 mm of hg on standing.Once adequate alpha-blockade is achieved b-blockers are started to control tachycardia to achieve pulse rate of 60-80 per minute.During the intraoperative period patients are prone to accelerated hypertension, hypotension, arrhythmias and cardiovascular instability due to release of catecholamines during intraoperative handling of the tumor and effects of anesthetic agents. Thus, patients require a trained anesthetist team during surgery.

Dopamine-secreting PPGLs

Pheochromocytomas rarely produce dopamine as the only catecholamine. Two cases are reported here, and a review of the literature was conducted. Unlike norepinephrine-and epinephrine-secreting tumors, dopamine-secreting pheochromocytomas lack a classic clinical presentation and are often asymptomatic. Urinary and serum metabolites cannot be relied on to make the diagnosis, and serum or urine dopamine levels (or both) must be measured when dealing with a potential pheochromocytoma. Dopamine-secreting tumors are less likely to enhance with metaiodobenzylguanidine (MIBG) scanning and may benefit from the use of positron emission tomography. Treatment is en bloc surgical excision; but unlike other pheochromocytomas, alpha-blockade is not indicated as it may lead to hypotension and cardiovascular collapse. Metyrosine is a medication that can be useful for preoperative control of symptoms from these tumors. The function of metyrosine is to block dopamine synthesis; it has no alpha-blocking effect. This medication is an option for controlling symptoms but should not be used routinely in these patients. The prognosis for patients with these tumors is worse than for those with an epinephrine- and norepinephrine-secreting tumor. Because of their asymptomatic nature, dopamine-secreting pheochromocytomas tend to be detected later and are more likely to be malignant at the time of diagnosis. Decreased expression of dopamine β-hydroxylase, the enzyme that converts dopamine to norepinephrine, has been detected in these tumors. That's the reason why this is the type of tumor less likely to produce hypotensive peri operatory. Without dopamine β-hydroxylase, pheochromocytomas produce and predominantly secrete dopamine and not epinephrine or norepinephrine. Only eight cases have been described in the literature, and they have yet to be correlated with a specific syndrome. Elevated blood pressure is a classic sign associated with pheochromocytomas, which helps lead the clinician toward the diagnosis. Unfortunately, this does not apply to tumors that exclusively secrete dopamine. Neither of the cases reported here nor the ones in the literature described hypertension associated with dopamine-secreting tumors. In one case, in fact, the patient's blood pressure increased once the tumor had been removed. This is not surprising as dopamine acts through various mechanisms, influencing renal hemodynamics and aldosterone production, to decrease blood pressure; and abnormalities in dopamine receptor function can lead to hypertension. Unlike their adrenergic cousins, dopamine-secreting tumors lack a reliable constellation of signs and symptoms to aid in their diagnosis. Elevated plasma concentrations or urinary outputs of dopamine are more often associated with malignant than benign pheochromocytomas and the ones described in the literature are detected in a very late state, generally has already metastasized in other organs.In the meantime, the present data indicate that diagnosis of dopamine-producing tumors could benefit from alternatives to the currently widely used measurements of urinary dopamine. The combination of measurements of plasma-free methoxytyramine and dopamine offers such an alternative, which appears to provide an effective means to identify dopamine-producing paragangliomas. With increased use of these plasma markers, such tumors may prove to be not quite as rare as previously thought.

Results

Table 2. Management of perioperative hypotension with salt tablets.

Cases	WITH SALT TABLETS INTAKE					
	PREOPERATIVE		INTRAOPERATIVE	POSTOPERATIVE		
	Reflex tachycardia	Postural Hypotension	Hipertension	Postural Hypotension	Heart Failure	Hemorragic shock
A	-	-	-	-	-	-
B	-	-	-	-	-	-
C	+	+	+	-	-	-
D	-	-	+	-	-	-
E	-	-	-	-	-	-

Table 3. Management of perioperative hypotension without salt tablets.

Paste Cases	WITHOUT SALT TABLETS INTAKE								
	PREOPERATIVE				INTRAOPERATIVE			POSTOPERATIVE	
	Cathecolamine-induced CM	Myocardial Infarction	Acute Pulmonary Edema	Heart Failure	Hipertension	Hypertensive bleeding (Pericardial or intracraneal)	Heart Failure	Postural hypotension	Postoperative hypotension
F	-	-	-	-	-	-	-	-	+
G	+	-	+	+	-	-	+	+	+
H	-	-	-	-	-	-	-	-	-
I	-	-	-	-	-	-	-	-	-
J	-	-	-	-	-	-	-	-	+

Observational and prospective follow-up was performed on 10 patients with a recent diagnosis of pheochromocytoma. 5 of them were grouped in the patient team to be managed with daily dose sodium tablets and the remaining 5 were not managed with the latter one. We concluded that the use of sodium tablets is a

recommended practice for the management of perioperative hypotension in patients with a diagnosis of pheochromocytoma scheduled for adenectomy.
In the group of patients treated with sodium tablets, we concluded that the use of sodium tablets markedly decreased the development of perioperative hypotension, which was only evident in 1 of the 5 patients studied. On the other hand, it was seen that 1 of the 5 patients was very sensitive to the sympathomimetic activity of the salt tablets, generating intraoperative hypertension.
On the other hand, in the group of patients not treated with sodium tablets, it was seen that 60% of the patients studied presented postural hypotension, that 1 of them, who preoperatively presented catecholamine-induced cardiomyopathy, presented an episode of marked hypotension during the surgical procedure, causing heart failure and postural and postoperative hypotension. On the other hand, 80% of the patients studied presented postoperative hypotension.

CONCLUSION

Pheochromocytomas can be divided into three main categories: EPI secreting PPGLs that cause decreased cardiac contractility owing to downregulation of β-adrenoceptors, NE secreting PPGLs causing a decrease in circulating plasma volume secondary to α_1-adrenoceptor mediated vasoconstriction leading to postural hypotension and DOPA secreting PPGLs. Pheochromocytomas tend to secrete adrenaline (epinephrine), whereas paragangliomas overproduce noradrenaline (norepinephrine), that's the reason why NE-secreting PPGLs tend to cause more episodes of hypotension (especially in patients with greater metabolic sensitivity to norepinephrine), whereas pheochromocytomas more frequently have classic episodic symptoms ("spells") of adrenaline excess than paragangliomas. On the other hand, a paraganglioma is more frequently cancerous (malignant) than a pheochromocytoma.
The use of salt tablets definitely reduces the imminent risk of perioperative hypotension in patients undergoing adenectomy. However, the risk of hypotension in patients taking salt tablets will always exist, and the fact of taking salt tablets does not exclude that they will not present episodes of hypotension, so we conclude that the use of salt tablets reduces frequency, severity and recurrence rates of perioperative hypotensive episodes, but it does not eliminate the chance to have it. All this in turn, reduces multiple postoperative complications rates, including the most important ones, the ones in the cardiovascular system: congestive heart failure, cardiogenic shock and acute pulmonary edema and finally better postoperative recovery rates. Finally, as a management treatment before procedure, starting beta blockersbefore alpha blockade is contraindicated. Beta blockers cancel out the vasodilatory effect of peripheral beta-2 adrenoceptors, potentially leading to unopposed alpha-adrenoceptor stimulation, causing vasoconstriction and ultimately hypertensive crisis.
Hypertension alternating with hypotension is rare in patients with pheochromocytomas, and is believed to be associated with tumors that primarily secrete epinephrine. Prolonged exposure to high levels of epinephrine and norepinephrine could result in arterial and venous vasoconstriction, leading to a reduction in blood volume and cardiac output which would, in turn, stimulate excessive reflex catecholamine release, causing paroxysmal hypertension.The increase in BP would stimulate baroreceptors in the blood vessel walls and activate a negative feedback loop, mediated by the sympathetic and parasympathetic nervous systems, which would respond by decreasing peripheral vascular resistance and lowering cardiac output -- causing a subsequent reduction in BP. Baroreceptors are tonically active and can respond quickly to changes in BP, which could explain the rapid alternation between hypertension and hypotension seen in this patient.
A tumor that is primarily secreting norepinephrine usually produces sustained hypertension, whereas a tumor that is secreting large amounts of epinephrine may produce episodic hypertension. In contrast, tumors that secrete only epinephrine can produce hypotension. Common cardiac complications include congestive heart failure, myocardial infarction, and arrhythmias, all of which are due to a catecholamine-induced cardiomyopathy. Measurements of plasma free metanephrines not only provide information about the likely presence or absence of a pheochromocytoma, but when a tumor is present, can also help predict tumor size and location. This additional information may be useful for clinical decision-making during tumor localization procedures.

Ethical approval

No ethical approval was given since it is not applicable for a meta-analysis.

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Author contribution

Peer Review contribution related to peri and postoperative complications when performing adrenoceptor blockade.

Conflicts of interest disclosure
The author declare that he has no financial conflict of interest with regard to the content of this report.

Data availability statement
Data analysis is a product ofthe prevalence of the disease during the month of April, 2017.

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