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Role of Dexmedetomidine in Perioperative Management of Pheochromocytoma

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Abstract:

The prevalence of Pheochromocytoma in patient with hypertension is 0.1-0.6%. These types of tumours are known for unpredictable perioperative course and hemodynamic instability. Various different drugs and anaesthesia techniques can be used to tackle these situations. Dexmedetomidine is emerged as newer agent with better hemodynamic stability, reducing requirement of other anaesthesia drugs, blunting of sympathoadrenal response in resection of Pheochromocytoma. We report four cases operated between January 2021 to June 2021.Preoperative preparation was done with α and β blockade. Dexmedetomidine was used during induction as 1 mcg/kg over 10 mins followed by 0.7mcg/kg/hr intraoperatively. Combination of Dexmedetomidine, Fentanyl, NTG, Isoflurane and Epidural analgesia was used. IF needed boluses of Esmolol and Labetalol were used during tumor manipulation. All the patients had an uneventful perioperative course. Dexmedetomidine with pre-operative α and β blockade reduce the need of other drugs intraoperatively and can be used as anaesthetic adjunct to maintain steady hemodynamic.

Key-words: Pheochromocytoma, Dexmedetomidine, Prazosin, Esmolol, Labetalol, NTG, SNP, Nor-adrenaline, Dopamine, Perioperative management, Epidural.

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Introduction:

Pheochromocytoma is a catecholamine secreting neuroendocrine tumor originating from adrenal medulla & extra adrenal tissue. Its incidence is 1-2/ 10,00,000 in Indian population[1]. Surgical resection carries high risk of perioperative hemodynamic complications.

Various drugs and anaesthesia techniques can be used in perioperative management of pheochromocytoma. As an anaesthesia adjunct Dexmedetomidine minimizes episodes of abrupt arterial hypertension during induction and manipulation of tumor[7].

Four cases performed during Jan2021 to June 2021 represents perioperative use of Dexmedetomidine.

Case History:

Case-1:

A 32year female with history of headache, sweating & palpitations since last 12 year was diagnosed to be pheochromocytoma. Patient was started on Tablet Telmisartan 40 mg OD, Tab. Metoprolol 25 mg OD. On admission her BP was 160/110 mm Hg. Diagnosis reconfirmed by MRI.

Table :1 Special Investigations done to confirm the diagnosis of pheochromocytoma& nature of tumor

	Investigations	Normal Range	Case-1	Case-2	Case-3	Case-4
1)	24 Hrs Urine Catecholamines: (µg/24 hr)					
	a) Epinephrine/ (µg/24 hr)	0- 20	13.94	16.79	23.14	18.27
	b) Nor-Epinephrine (µg/24 hr)	0- 90	1101.6	1176.8	1221.9	986.7
	c) Dopamine (µg/24 hr)	0-500	NA	NA	NA	NA
2)	24 Hr Urine VMA (mg/24 hr)	0-15	32.87	27.69	7.28	37.48
3) a)	Plasma Metanephrines (pg/ml)	0-65	75	54.2	69.7	78.5
b)	Nor- metanephrines (pg/ml)	0-196	1893	1126.6	1934.3	1756
4) a)	Urine Metanephrines (µg/24 hr)	0-400	326	460	389	214
b)	Nor-Metanephrines (µg/24 hr)	0-900	986	865	1022	761
5)	MRI Scan:					
	Size of tumor (mm)		56x43x41	43x38	50x43	86x86x100

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	Side of Adrenal Gland Affected		Right	Right	Left	Right

On admission patient started on Tab Labetalol 200 mg TDS and Tab Prazosin 5 mg BD with stoppage of previous antihypertensive drugs. After 3 weeks blood pressure was optimized (134/80 mm of hg). 2D-Echo and ECG was normal. HRCT was done to rule out Covid-19. CVP line and Arterial line inserted day before surgery. On day of surgery, patient preloaded with Ringer Lactate solution 500 ml. 18 G epidural catheter inserted at T9-T10 interspace. Dexmedetomidine 1 µg/kg i.v. over 10 minutes followed by infusion of 0.7 µg/kg/hr. Premedicated with inj. Midazolam 0.03mg/kg, Inj. Fentanyl 2 µg/kg.To attenuate intubation response Inj. Lignocaine 2% 1.5 mg/kg given. Anaesthesia induced with inj. Propofol 2mg /kg and inj. Vecuronium 0.1 mg/kg. Intra-operatively ECG, ABP, NIBP, CVP, SpO_2, $EtCO_2$, airway pressure, urine output and temperature monitored. Anaesthesia maintained with Isoflurane, $O_2$and N_2O, Vecuronium and IPPV. The highest arterial pressure during intubation was 126/80 mm of Hg. During pneumoperitoneum & tumor manipulation ABP was 150/94 &160/ 98mm Hg respectively. Inj. Labetalol 20mg was administered then. Intraoperative hemodynamic management as in

Table-2 .

All the drugs used, their total requirement in each case is as shown in the table. Boluses were given for Esmolol, Labetalol, Fentanyl & Epidural top-ups. Other drugs were given as infusions. Total requirement of each drug in bolus & infusion is mentioned in the table below.

Sr. No.	Drugs Used	Concentration that we made	Case-1	Case-2	Case-3	Case-4
1.	Esmolol (ml)	10 mg/cc	4	4	5	6
2.	Labetalol(ml)	10 mg/cc	2	1	2	1
3.	Fentanyl(ml)	50 µg/cc	4	4	4	4
4.	NTG (mg)	50 mg/50 cc	23.2	19.6	29.7	17.2
5.	SNP (mg)	50 mg/50 cc	7.8	8.4	5.6	NA
6.	Nor-Adrenaline (mg)	16 mg/50 cc	0.768	0.608	0.736	2.9696
7.	Dopamine (mg)	400 mg/50cc	-	-	-	76.8
8.	Epidural Top Ups	3cc Lignocaine+ Adrenaline (Test Dose)	3cc	3cc	3cc	3cc
		5 cc 0.5% Bupivacaine	4	3	4	2

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Upon ligation of vein ABP dropped to 80/40 mm of Hg. ABP returned to 110/60 mmHg with immediate discontinuation of Dexmedetomidine, fluid boluses and Noradrenaline infusion. Noradrenaline infusion stopped at the end of the surgery.

Surgery lasted for 4hrs and 35 mins and the patient extubated uneventfully. PCA with Epidural top ups & Paracetamol. Postoperative hypokalaemia (2.4 mEq) was corrected with KCl infusion. The patient made an uneventful recovery.

Case 2:

A 36year male with palpitations and sweating since 3 months & hypertension since 6 months & was on Tab. Telmisartan+ Hydrochlorothiazide 40/12.5 mg OD & Tab. Amlodipine 5mg OD. Patient was diagnosed as Rt. Adrenal tumor. Preoperative evaluation and optimization were similar to the first case. Perioperative course was uneventful except minimal Noradrenaline infusion till second postoperative day.

Case-3:

A 22year male patient had headache since 4 months. Since last month headache worsened along with palpitations, tremors, sweating. Patient diagnosed with pheochromocytoma. Patient started on Tab. Prazosin 5mg OD & Tab. Metoprolol 25 mg OD. Peri-operative management was similar to first two cases. Patient extubated. Noradrenaline infusion which was tapered gradually & stopped. On postoperative day -0, patient complained of bilateral chest pain. ECG- s/o mild ST-T changes in V2-V4. Cardiac markers report negative. No active cardiac treatment required. Further post-operative recovery was uneventful.

Case-4:

A 40year male complaining of pain in abdomen with sudden hypertensive episode 3 months ago diagnosed as pheochromocytoma. Patient was posted for open rt. adrenalectomy.

Figure-1: Depicts intraoperative tumor size, MRI report showing the tumour &its invasion in renal hilum &IVC& Preoperative ECG showing Complete RBBB

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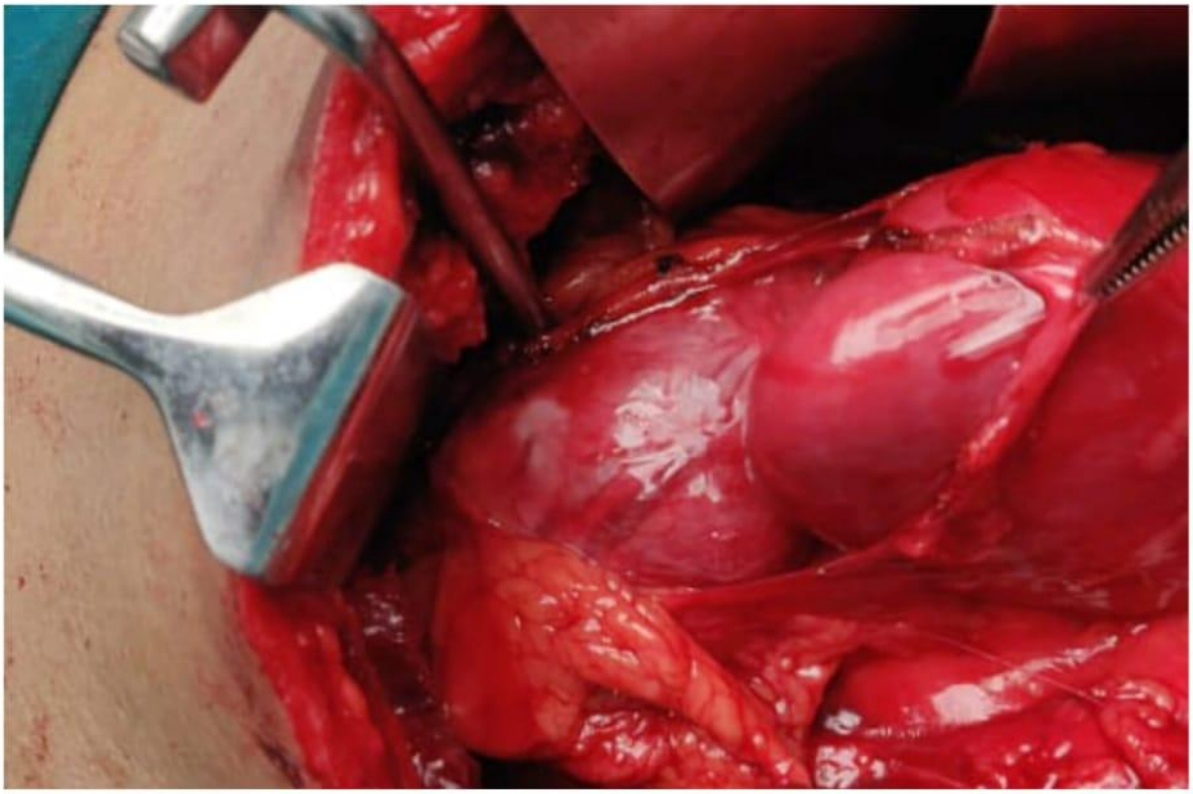

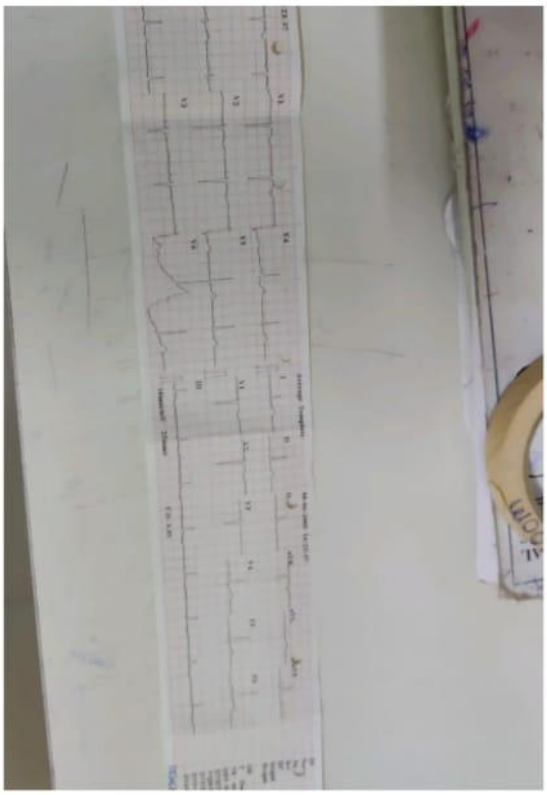

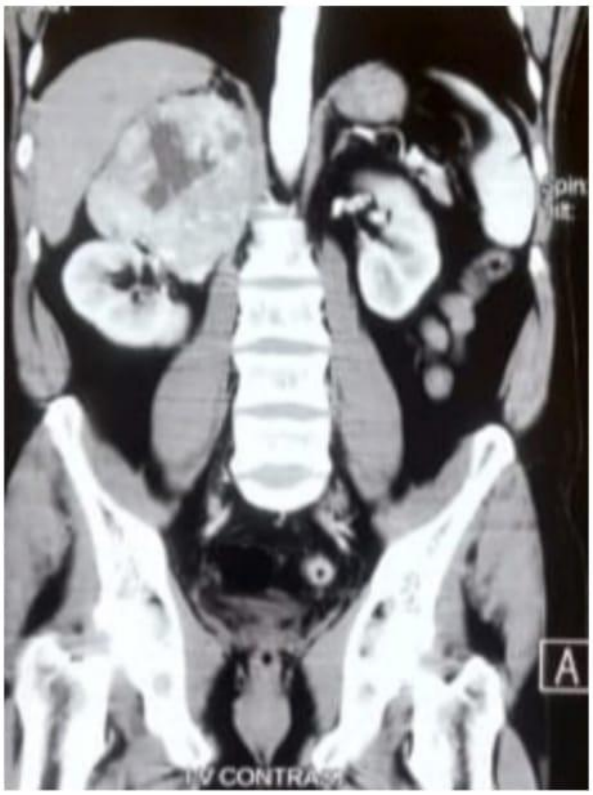

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Patient optimized with Tab. Prazosin 5 mg OD & Tab. Propranolol 10 mg OD. ECG s/o Complete RBBB, 2D-Echo & cardiac evaluation done. Due to h/o COVID-19 infection 1 month back HRCT Thorax was advised, report Corads-1 and CT severity index -0. Peri-operative preparation done similarly as above.

On table, patients ABP was 150/92 mm Hg & HR-98 bpm, Sinus rhythm. During dissection, accidental IVC rent noted with sudden blood loss. ABP dropped to 60/30 mm Hg. HR- 140/min. Immediately started resuscitation with Colloid, Nor-adrenaline and NTG stopped. After about 3 minutes, patient developed ventricular tachycardia, HR-180/min. Treated with Inj. Lignocaine 2% 1.5 mg/kg, Inj. Amiodarone 150 mg iv. Patient responded to blood & blood products along with inotropic support & fluid resuscitation. IVC rent repaired and rt nephrectomy was done along with adrenalectomy. Surgery lasted about 5 hours & 40 minutes with total blood loss of about 4 lit. Patient was electively ventilated overnight & extubated coming morning. Patient re-developed RBBB on post-op day-3 but was hemodynamically stable. Recovered & discharged.

All the drugs used, their total requirement in each case is as shown in the table. Boluses were given for Esmolol, Labetalol, Fentanyl & Epidural top-ups. Other drugs were given as infusions. Total requirement of each drug in bolus & infusion is mentioned in the table below.

Table-3: Line Diagrams showing Intraoperative Hemodynamic in various steps of surgery

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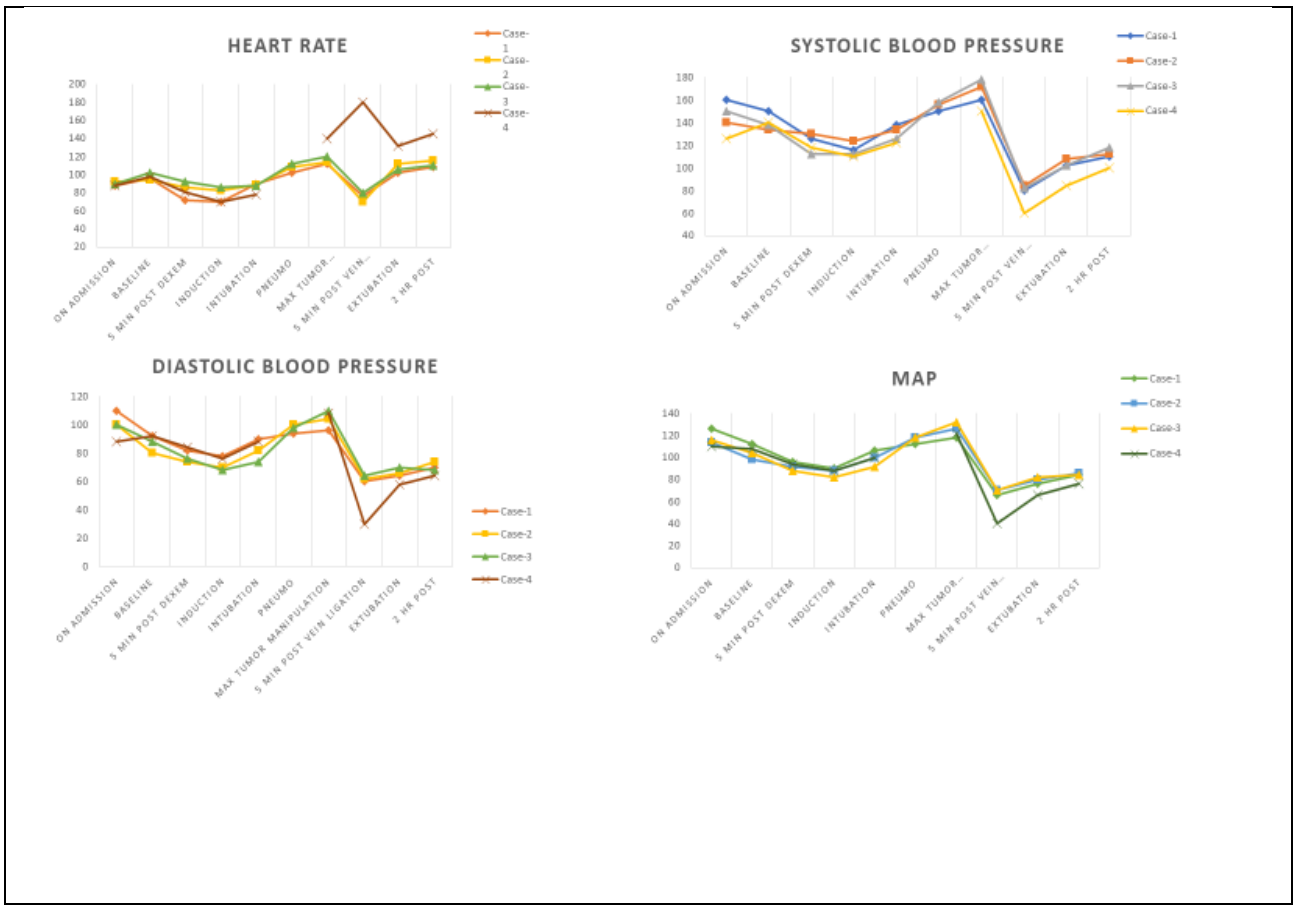

Discussion:

Pheochromocytomas is known as the 10% tumours, 10% of tumours are inherited,10% are Extra adrenal, 10% are Malignant,10% are Bilateral and 10% occur in children. Sporadic pheochromocytomas occur around the fourth decade, whereas hereditary forms are diagnosed earlier.[3]

These may be associated with other tumours like MEN 2A and 2B, Von Hippel–Lindau disease, succinate dehydrogenase enzyme mutations, and neurofibromatosis.[3]

The first step in the diagnosis of Pheochromocytoma is confirmation of excessive catecholamine level in the patient[3].Metanephrines are constantly produced and hence they are better for screening purposes[4]. MRI is preferred because contrast media used for CT scans can provoke paroxysm.[3]

Roizen *et al.* in 1982proposed a set of criteria to objectively gauge the efficacy of adequate preoperative alpha blockade.[14]

The alpha-adrenergic blockade is typically administered 10-14 days preoperatively.[5] In general, the high risk associated with these conditions was reduced by achieving SBP of 140 mm Hg[6].

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Most experienced centres perform minimally-invasive adrenalectomy via laparoscopic and retroperitoneoscopic approaches as the gold standard particularly for adrenal masses <6 cm diameter and weight <100 g.[15]

Prazosin used is 2 to 5 mg in two to three divided doses. Gradually increased to 15 to 20 mg. Beta-blockers should never be used before initiation of alpha-blockade in patients with functional tumors.[6] Propranolol and Metoprolol are the preferred drugs.[4] Other antihypertensive drugs like ACE inhibitors can be added to control hypertension preoperatively.

Another modern option is dexmedetomidine as it attenuates the sympathetic response.[7]

Attenuation of the pressor response to laryngoscopy is a crucial aspect of anaesthetic induction and adjuncts commonly used include Fentanyl, IV Lignocaine, Esmolol & infusions of NTG/SNP as needed.[5]

SNP causes predominantly arteriolar dilatation while NTG is principally a venodilator. SNP infusions should be started at 0.5–1.5 μg/kg/min and increased up to 4 μg/kg/min as required.[8]

Tumor manipulation generates more dramatic pressor response that can be managed with deepening the depth of anaesthesia and rapidly administering direct arterial vasodilators.[5]

Sudden hypotension may occur following ligation of the tumor. Mainly Norepinephrine and seldom Epinephrine have been recommended to control hypotension following tumor withdrawl.[9]

We decided that the combination of Dexmedetomidine, Fentanyl, NTG/SNP, Isoflurane and Epidural analgesia might make additional hypotensive agents unnecessary.

Plan A was to use these agents and manage the post-resection hypotension with Norepinephrine infusion as it was a primarily Norepinephrine secreting tumor.

Plan B included the addition of Esmolol and if necessary Labetalol during tumor manipulation in case of failure of above agents.

For control of post-resection hypotension, we proposed to use Phenylephrine bolus injections and Dopamine infusion in case of non-response to Norepinephrine.

The combination of Dexmedetomidine, NTG/SNP, Isoflurane, Fentanyl and Epidural analgesia was used in our patient. Short lived BP surges during tumor manipulation were controlled by Dexmedetomidine infusion along with few Esmolol and Labetalolboluses. There was no event of dangerous bradycardia. After vein ligation, hypotension was a concern in spite of terminating NTG and Dexmedetomidine infusions. Norepinephrine infusion had to be started.

Similar results have been published by few studies.

A.Y.C Wong in 2004 used Dexmedetomidine for resection of large pheochromocytoma with invading inferior vena cava he found that Dexmedetomidine was useful for preventionof abrupt hypertensive crisis.[2]

Bryskin and Weldon in 2010 used Dexmedetomidine and Magnesium sulphate for the perioperative management of a child undergoing laparoscopic resection of bilateral pheochromocytoma.[10]

Dexmedetomidine and Remifentanil has been used for an adolescent undergoing resection of pheochromocytoma Jung *et al*. in 2012.[11]

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Khetarpal *et al*.in 2014 used Dexmedetomidine and Sevofluranein an adult undergoing resection of pheochromocytoma in 2014. [12]

Raylene Dias et al. in 2015 reportedanaesthetic management of Pheochromocytoma in a child with Von Hippel Lindau type 2 syndrome. They found that Dexmedetomidine based anaesthesia along with pre-operative receptor blockade reducerequirement of vasoactive drugs in the intraoperative period.[13]

In our patients there were very few spikes in BP which were short lived and controlled by above measures only in case 4 because of IVC rent MAP dropped below 60 mm Hg and that responded to blood and blood products along with inotrope support.

CONCLUSION

Adequate preoperative α andβ receptor blockade and Dexmedetomidine as anaesthetic adjunct helps inmaintain steady hemodynamicand preventing abrupt hypertensive crisis.

The endpoint hemodynamic stability has no absolute definition that's why such studies will have to include a large number sample. Correct solution for this will be to conduct Randomized, clinical trial which is very difficult to conduct considering the very low incidence of the disease. Hence this case series encourages to study use of Dexmedetomidine in view of collection and publishing the required data before providing further recommendation.

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