Research Article
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Retrospective cohort analysis on perioperative adverse cardiac events in patients with Parkinson disease undergoing deep brain stimulation

Abstract

Advanced Parkinson disease presents unique perioperative considerations for the anesthesiologist primarily due to autonomic dysfunction. Postural hypotension, bradycardia, and supine hypertension are common manifestations of dysautonomia, which increase the incidence of perioperative adverse cardiovascular events. This retrospective study reveals that the incidence of adverse cardiovascular events in these patients during intraoperative period was 36% and the incidence in stage I DBS was 39% while the incidence in stage II DBS was 34%. Smoking, preoperative hypertension, renal failure, preoperative use of medications such as beta-blocker agents, calcium channel blockers and diuretics, as well as longer surgery duration are potential predictors for adverse cardiovascular events in this patient population.

Keywords: Bradycardia, Deep Brain Stimulation, Dysautonomia, Orthostatic Hypotension, Parkinson Disease

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Abbreviations: PD, Parkinson Disease; DBS, Deep Brain Stimulation; BP, Blood Pressure; MAC, Monitored Anesthesia Care; GA, General Anesthesia; ECG; Electrocardiogram; HR, Heart Rate; PACU, post anesthesia care unit; SBP, systolic blood pressure; DBP; diastolic blood pressure

Introduction

Parkinson disease (PD) is a multisystem neurodegenerative disorder, characterized by tremors, rigidity, bradykinesia, and impaired balance in addition to neuropsychiatric, and autonomic dysfunction.[1] PD presents unique peri-anesthetic challenges due to the underlying autonomic dysfunction. Orthostatic hypotension, associated with PD or anti-parkinsonian drugs, increases the risk of intraoperative hypotension. These patients are also prone to cardiac arrythmias in the perioperative period.[1]

Deep Brain Stimulation (DBS) is a surgical treatment for controlling motor symptoms in medically refractory PD. Stage I procedure involves stereotactic insertion of implantable electrodes within the subthalamic nucleus or globus pallidus interna in the brain. During stage II DBS, the electrodes are tunneled beneath the skin and connected to an implanted pulse generator beneath the clavicle. Monitored Anesthesia Care (MAC) is used during placement of the electrodes in the brain, with minimal sedation using propofol infusion. MAC is preferred during awake craniotomy for DBS stage I which allows a rapid awakening for neurological assessment during the procedure, while stage II DBS is usually performed under general anesthesia (GA) with a laryngeal mask airway or an endotracheal tube.

Patients with cardiac disease are more prone to cardiac arrhythmias and sudden cardiac death when the neuro cardiac axis is activated.[2] Electrical stimulation of midbrain reticular formation and posterior hypothalamus of cat brain has demonstrated increased blood pressure (BP) and electrocardiogram (ECG) changes including sinus tachycardia, ventricular premature contractions, bigeminal rhythm, atrio-ventricular dissociation and ventricular tachycardia.[3] Micro-stimulation of posterior insular cortex in rats resulted in escape rhythms, ventricular ectopics and death in asystole.[4,5] In patients with intraoperative insular stimulation prior to temporal lobectomy for seizure control, bradycardia and depressor responses were more frequently produced than tachycardia and pressor response on stimulation of the left cortex.[6] Although experimental models indicate insular lesions may be arrhythmogenic and insular cortex stimulation produces lethal cardiac arrhythmias, it is unknown whether stimulation of subthalamic nucleus can produce arrhythmias.[7]

There is scarce research exploring the incidence and causes of adverse cardiovascular events during DBS surgery in PD patients. We conducted a retrospective analysis with the primary aim of reporting the incidence of adverse cardiovascular events in these patients during intraoperative and postoperative periods. The secondary aim was to explore the preoperative factors associated with a composite outcome of intra/postoperative adverse events in a multivariate setting.

Material and methods

Patient selection

A single-center retrospective cohort study was performed on adults aged 20-100 years diagnosed with PD and received DBS at a major academic teaching hospital in the United States between 2009 and 2019. Institutional review board approved for waiver of informed consent, data was extracted from the electronic health records (EPIC) and the Perioperative Hemodynamic Database System (PHDS). The surgical stage was identified using CPT codes. 6420 DBS records screened, 394 were excluded since they had reoperation during the same visit (Figure 1).

Data processing

Screening for cardiac arrest and heart block was performed from the comments section of EPIC using keyword search and confirmed by documented medication use. Heart rate (HR) was recorded every minute in the operating room and every 15 minutes in post anesthesia care unit (PACU). Intraoperatively, bradycardia was defined as HR <40 BPM lasting for at least five minutes. Postoperative bradycardia was defined as at least one recording of HR <40 BPM in the PACU which was accompanied by use of atropine, glycopyrrolate or epinephrine.

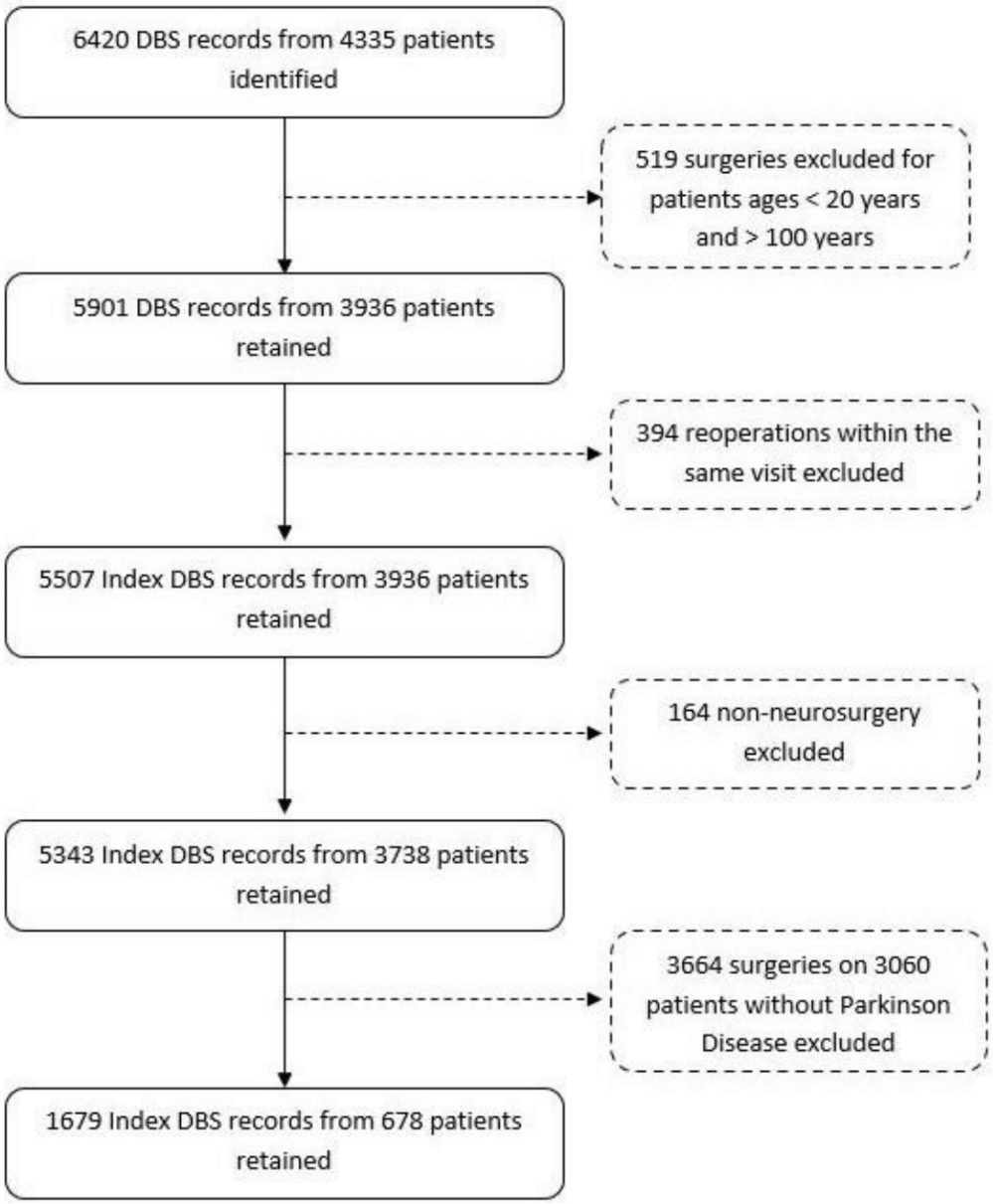

Figure 1 Flowchart on selection of study subjects based on inclusion and exclusion criteria.

Intraoperatively BP was recorded every minute in patients with arterial line and every five minutes in patients with non-invasive BP cuff. Intraoperative hypotension defined as systolic blood pressure (SBP) <90 mmHg or >35% below baseline (average SBP two weeks before the surgery) lasting >5 minutes. BP in PACU was recorded every 15 minutes; postoperative hypotension was defined as at least one reading of SBP >35% below baseline with documentation of vasopressor use or SBP <90 mmHg lasting for 5 minutes.

Statistical analysis

Patient profile was summarized with standard summary statistic as mean ± SD, median, or N (%), separately for both stages of DBS. For the primary analysis, we reported the incidence of adverse cardiovascular events including bradycardia, hypotension, heart block and cardiac arrest during the intraoperative and postoperative periods in both stages of DBS and compared the incidences between GA and MAC groups. We reported the incidence of the composite of the above-mentioned outcomes.

For the secondary analysis, we used logistic regression to explore the various preoperative factors associated with a composite outcome of intraoperative/PACU cardiac arrest, hypotension, bradycardia, and heart block in a multivariate setting (Table 1). Variables with univariable *p*-value <=0.20 were regarded as potential candidates and *p*-value based backward selection were performed to retain variables with adjusted *p*-value <0.05.

Sample size justification

Because of the low incidence of adverse events in the perioperative period, all cases of DBS were included from 2009 to 2020. Based on an estimated 1300 cases of DBS during the time period, and assuming an incidence of 20% for the composite outcome, 260 events were estimated, which allowed simultaneous consideration of 26 baseline predictors.

Results

1679 surgical records from 678 patients were included. 646 stage I surgeries were performed on 399 patients, and 1033 stage II surgeries on 622 patients. 34% (221/646) of stage I DBS were performed under GA, while 94% (975/1033) of stage II DBS were under GA. 343 patients received both stage I and stage II procedures.

The baseline demographic data is summarized in Table 1. Patients with a medical history of hypertension had a higher incidence of adverse cardiovascular events, while patients on beta-blocker, calcium channel blocker and diuretic medications preoperatively had lower incidence of adverse cardiovascular events during the perioperative period (p <0.05).

Table 1 Demographic characteristics categorized by stage of surgery

	Stage I (N = 646)			**Stage II (N = 1033)**		
	Intra/Postoperative cardiovascular events		**Univariable p-value**	**Intra/Postoperative cardiovascular events**		**Univariable p-value**
	Yes (250)	**No (396)**		**Yes (350)**	**No (683)**	
Age (years)	66±8	65±9	0.335	67±9	67±9	0.442
Female	70 (28)	110 (28)	1	84 (24)	196 (29)	0.125
Race			0.178			0.031
white	241 (96)	390 (98)		343 (98)	655 (96)	
black	3 (1)	1 (0.3)		5 (1)	7 (1)	
other	6 (2)	5 (1)		2 (1)	21 (3)	
BMI	28±52	29±131	0.178	29±51	28±6	0.004
Smoking status		4	0.382	4	1	0.202
Current smoker	8 (3)	22 (6)		8 (2)	31 (5)	
Former smoker	86 (34)	132 (33)		132 (38)	254 (37)	
Non-smoker	156 (62)	242 (61)		206 (60)	393 (58)	
Medical history						
Hypertension	123 (49)	157 (40)	0.021	159 (45)	250 (37)	0.007
Diabetes	28 (11)	40 (10)	0.755	48 (14)	91 (13)	0.938
Congestive heart failure	4 (2)	5 (1)	0.991	5 (1)	21 (3)	0.165
Chronic pulmonary disease	12 (5)	27 (7)	0.379	22 (6)	38 (6)	0.742
Kidney disease (Acute or Chronic)	3 (1)	10 (3)	0.378	5 (1)	23 (3)	0.107
Peripheral vascular disease	-	7 (2)	-	5 (1)	7 (1)	0.79
Arrhythmia	13 (5)	21 (5)	1	21 (6)	40 (6)	1
Orthostatic hypotension	1 (0.4)	3 (1)	0.961	4 (1)	12 (2)	0.624
Coronary artery disease	27 (11)	49 (12)	0.632	30 (9)	78 (11)	0.191
Hyperlipidemia	79 (32)	135 (34)	0.569	103 (29)	186 (27)	0.502
Atrial fibrillation	9 (4)	17 (4)	0.817	16 (5)	29 (4)	0.935
Acute cerebral vascular disease	1 (0.4)	6 (2)	0.346	1 (0.3)	-	-
Heart block	9 (4)	13 (3)	1	7 (2)	22 (3)	0.355
Preoperative ECG						
Myocardial infarction	-	2 (1)	0.69	4 (1)	6 (1)	0.94
ST or T Wave abnormality	4 (2)	5 (1)	0.991	7 (2)	9 (1)	0.566
Heart block	7 (3)	2 (1)	0.038	8 (2)	9 (1)	0.369
Preoperative medication						
Aspirin	41 (16)	58 (15)	0.624	31 (9)	88 (13)	0.069
Beta-blockers	198 (79)	316 (80)	0.934	137 (39)	344 (50)	0.001
Calcium channel blockers	149 (60)	283 (71)	0.002	87 (25)	228 (33)	0.006
ACE inhibitors/ARB	70 (28)	84 (21)	0.06	60 (17)	114 (17)	0.924
Diuretics	45 (18)	85 (21)	0.333	40 (11)	117 (17)	0.02
Insulin	40 (16)	49 (12)	0.236	40 (11)	64 (9)	0.352
Statin	84 (34)	148 (37)	0.374	87 (25)	171 (25)	1
Antiarrhythmics	85 (34)	94 (24)	0.006	45 (13)	116 (17)	0.101
Anticoagulant	57 (23)	112 (28)	0.146	60 (17)	117 (17)	1
Antiplatelet	36 (14)	54 (14)	0.876	26 (7)	85 (12)	0.018
Antidiabetic	41 (16)	51 (13)	0.258	49 (14)	77 (11)	0.243
Previous adverse anesthesia events	-	2 (1)	-	-	-	-
General anesthesia	98 (39)	123 (31)	0.041	336 (96)	639 (94)	0.141
Surgery duration (hours)	4.8±1.2	4.5±1.0	0.001	2.1±0.6	2.1±0.6	0.928

Variables were summarized as mean±SD or N (%).

ACE, Angiotensin Converting Enzyme; ARB, Angiotensin Receptor Blocker

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The overall incidence of adverse cardiovascular events during the intraoperative period was 36% (95% Confidence Interval, CI: 33% - 38%), and the incidence in stage I DBS was 39% (95% CI: 35% - 42%) while the incidence in stage II DBS was 34% (95% CI: 31% - 37%). Analysis by anesthesia type revealed that the incidence of any event was 44% (95% CI: 68% - 51%) in stage I DBS under GA, 36% (95% CI: 31% - 40%) in stage I DBS under MAC, 34% (95% CI: 31% - 37%) in stage II DBS under GA and 24% (95% CI: 15% - 37%) in stage II DBS under MAC (Table 2).

Table 2 Hemodynamic parameters categorized by adverse cardiac events and stage of surgery (N = 1679)

	Stage I DBS		**Stage II DBS**	
	Intraoperative/Postoperative cardiovascular events		**Intraoperative/Postoperative cardiovascular events**	
	Yes (N = 250)	**No (N = 396)**	**Yes (N = 646)**	**No (N = 1633)**
Intraoperative Hemodynamics				
TWA SBP	112±10	115±9	106±13	112±14
TWA DBP	61±6	63±5	59±6	67±7
TWA MAP	80±7	83±6	77±8	81±9
TWA SBP < 90	0.41±0.62	0.09±0.24	0.83±1.12	0.30±0.53
Percent time in hypotension	9 [4, 19]	-	15 [7, 33]	-
Hypotension episodes, treated	5 [2, 9]	-	3 [2, 5]	
PACU Hemodynamics				
TWA SBP	124±1412	125±1312	138±157	136±1511
TWA DBP	67±812	67±812	73±87	72±811
TWA MAP	86±912	86±912	95±97	93±911

Variables were summarized as mean±SD or N (%).

Superscript indicated number of missing data.

TWA, Time Weighted Average; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure.

A total of 589 cases of intraoperative hypotension had an incidence rate of 35% (95% CI: 33% - 37%). 284 patients were treated with medication, median [IQR] episodes of treated hypotension were 3 [2, 6]. 645 cases of stage I surgeries analyzed, 38% (95% CI: 25% - 42%) had intraoperative hypotension. 36% of them received vasopressors, median [IQR] episodes of treated hypotension were 5 [2, 9]. Forty percent of the cases had hypertension during the intraoperative period.

In stage I DBS, incidence of hypotension was 38% (95% CI: 25% - 42%), and 89 patients received vasopressors, median [IQR] episodes of treated hypotension of 5 [2, 9]. 247 cases of hypotension in stage I DBS, 97 were under GA (44%, 95% CI: 38% - 50%) and 150 were under MAC (35%, 95% CI: 31% - 40%).

33% (95% CI: 30% - 36%) of patients undergoing stage II surgery had intraoperative hypotension. 57% of them received vasopressors, median [IQR] episodes of treated hypotension were 3 [2, 5]. 331 cases were performed under GA (34%, 95% CI: 31% - 37%) and 11 cases were under MAC (19%, 95% CI: 11% - 31%).

There was one case of intraoperative cardiac arrest during stage II DBS. Intraoperatively, there was one case of heart block in stage I surgery as well as one case of heart block in stage II surgery. Intraoperative bradycardia occurred in 11 cases (0.7%, 95% CI: 0.4% - 1.2%). Amongst them, 3 cases were stage I DBS (0.5%, 95% CI: 0.2% - 1.4%) and 8 cases were stage II DBS (0.8%, 95% CI: 0.4% - 1.5%). Two of the 3 cases of bradycardia in stage I DBS were under GA (0.9%, 95% CI: 0.2% - 3.2%) and the third case was under MAC (0.2%, 95% CI: 0.04% - 3.2%). Five of the 8 cases of bradycardia in stage II DBS were under GA (0.5%, 95% CI: 0.02% - 1.2%), and the remaining 3 were under MAC (5.3%, 95% CI: 1.8% - 14.4%).

Postoperative data was available for 645 cases of stage I and 1030 cases of stage II surgery in PACU, which revealed one case of hypotension after stage I DBS and one case of bradycardia after stage II DBS. Both patients had an uneventful intraoperative period.

Table 3 summarizes the use of intraoperative medications. While antihypertensive drugs were more commonly administered in stage I surgery, vasopressors were more used in stage II surgery.

Table 3 Intraoperative medications categorized by the stage of surgery

	Stage I DBS		**Stage II DBS**	
	Intraoperative/ Postoperative cardiovascular events		**Intraoperative/ Postoperative cardiovascular events**	
	Yes (N = 250)	**No (N = 396)**	**Yes (N = 646)**	**No (N = 1633)**
Neostigmine	23 (9)	28 (7)	122 (35)	311 (46)
Sugammadex	3 (1)	3 (1)	5 (1)	12 (2)
Isofluorane	3 (1)	9 (2)	49 (14)	92 (13)
Sevofluorane	39 (16)	32 (8)	289 (83)	540 (79)
Ephedrine	61 (24)	46 (12)	197 (56)	279 (41)
Ephedrine (mg)	10 [5, 20]	10 [8, 20]	15 [10, 25]	15 [10, 20]
Propofol	248 (99)	384 (97)	344 (98)	676 (99)
Propofol (mg)	828 [450, 1187]	880 [515, 1230]	200 [150, 230]	170 [140, 220]
Labetalol	131 (52)	155 (39)	13 (4)	40 (6)

Table 3 Continued...

	Stage I DBS		Stage II DBS	
	Intraoperative/ Postoperative cardiovascular events		Intraoperative/ Postoperative cardiovascular events	
	Yes (N = 250)	No (N = 396)	Yes (N = 646)	No (N = 1633)
Labetalol (mg)	40 [15, 70]	25 [10, 45]	10 [5, 20]	10 [5, 15]
Succinylcholine	-	-	5 (1)	22 (3)
Nitroglycerin	96 (38)	147 (37)	11 (3)	32 (5)
Nitroglycerin (mg)	0.20 [0.10, 0.40]	0.20 [0.10, 0.35]	0.10 [0.08, 0.11]	0.10 [0.08, 0.16]
Phenylephrine	114 (46)	92 (23)	230 (66)	354 (52)
Phenylephrine (mg)	0.28 [0.15, 0.72]	0.20 [0.10, 0.40]	0.30 [0.11, 0.60]	0.25 [0.10, 0.58]
Metoprolol	14 (6)	21 (5)	2 (1)	5 (1)
Esmolol	34 (14)	61 (15)	12 (3)	52 (8)
Esmolol (mg)	40 [23, 60]	40 [20, 90]	30 [20, 43]	28 [20, 40]
Atropine	1 (0.4)	-	1 (0.2)	1 (0.1)
Epinephrine	1 (0.4)	1 (0.3)	9 (3)	4 (1)
Nicardipine	109 (44)	220 (56)	-	-
Norepinephrine	-	3 (1)	-	-
Group A medication	346 (87)	225 (90)	103 (15)	29 (8)
Group B medication	112 (28)	132 (53)	471 (69)	299 (85)

Group A Medication: Labetalol, Nitroglycerin, Metoprolol, Esmolol and Nicardipine.

Group B Medication: Ephedrine and Phenylephrine.

Variables were summarized as mean±SD or N (%).

Doses were summarized in those receiving medication.

Secondary analysis included 1,666 surgeries which had complete baseline variables. Using backward selection, current smoking, preoperative hypertension, renal failure, preoperative use of medications including beta-blocker, calcium channel blocker, diuretic and surgery duration were identified as potential predictors. Model coefficients are summarized in Table 4.

Table 4 Variables associated with intraoperative and postoperative cardiac events

	Odds ratio (95% CI)	P-value
DBS Stage (II vs. I)	0.81 (0.52, 1.25)	0.33
General anesthesia	1.48 (1.10, 2.00)	0.01
Smoking status		
Current smoker	0.50 (0.28, 0.90)	0.02
Former smoker	0.94 (0.75, 1.17)	0.56
Non-smoker	Reference	
Medical history		
Hypertension	1.95 (1.56, 2.45)	< 0.001
Kidney disease	0.33 (0.14, 0.76)	0.01
Preoperative medication		
Beta-blocker	0.69 (0.55, 0.88)	0.003
Calcium channel blocker	0.72 (0.55, 0.93)	0.01
Diuretic	0.58 (0.42, 0.79)	0.001
Surgery duration (hours)	1.22 (1.07, 1.40)	0.004
Year of surgery	0.97 (0.93, 1.01)	0.13

Discussion

This retrospective study analyzed the incidence of adverse cardiovascular events including bradycardia, hypotension, heart block and cardiac arrest during the intraoperative and postoperative period in both stage I and stage II DBS. Majority of stage I DBS was performed under MAC, while 34% cases had GA.

There was one case of intraoperative cardiac arrest in a 72-year-old male undergoing stage II DBS. The most common perioperative adverse cardiac event was hypotension, with incidence rate of 35% (95% CI: 33% - 37%).

Autonomic dysfunction in PD imposes hemodynamic instability during the perioperative period. Orthostatic hypotension is commonly detected, however supine hypertension is another manifestation of dysautonomia. Both hypotension and hypertension are deleterious. The target thresholds for blood pressure titration remain controversial as the individual patient conditions and surgical requirements dictate the need for most interventions. Brief duration of SBP <100 mm Hg and MAP <60-70 mm Hg are associated with organ injury.[8] Current literature is inconclusive about the treatment threshold for intraoperative hypertension. Monk et al. reported no association between SBP >180 mm Hg for >5 minutes or DBP >120 mm Hg for >5 minutes and increase in 30-day mortality in a cohort of 18756 adults. Furthermore, patients with neurological diseases who receive general anesthesia have worse neurological outcomes postoperatively.[9]

Vasovagal responses are associated with intraoperative hemodynamic changes. Intraoperative hypotension is associated with increased risk of perioperative myocardial injury and acute kidney injury.[10] Anesthetic agents blunt the baroreceptor reflex which could exaggerate intraoperative swings in blood pressure, this is more pronounced in patients with underlying severe dysautonomia. Furthermore, patients with autonomic dysfunction may respond unpredictably to sympathomimetic agents due to denervation hypersensitivity.[11] Anesthesiologists play a crucial role in preventing as well as promptly treating hypotension in the perioperative period. It is important to identify patients with orthostatic hypotension preoperatively so that measures can be taken to maintain blood pressure within target thresholds to minimize the deleterious effects of intraoperative hypotension.

Our secondary analysis explored the preoperative factors associated with composite outcome of intra/postoperative cardiac

arrest, hypotension, bradycardia, and heart block. Perioperative use of beta-blockers has been associated with increased risk of all-cause mortality and assuming there is benefit without substantial harm.[8,12,13] Our analysis reveals preoperative use of beta-blocker agents, calcium channel blockers and diuretics decreases the risk of perioperative cardiovascular events. We found that renal failure, current smoking, and surgery duration are potential predictors for cardiovascular complications in patients undergoing DBS procedures. Nicotine is a known arrhythmogenic since it stimulates the release of catecholamines which induces coronary spasm and sudden cardiac death.[14]

This study reveals that preoperative hypertension is a predictor of increased risk of adverse cardiovascular events. Patients with uncontrolled preoperative hypertension are prone to exaggerated sympathetic response with induction of anesthesia, as well as increased lability of BP during surgery. Although American Heart Association/American College of Cardiology (ACC/AHA) guidelines state that hypertension is not an independent predictor for increased perioperative cardiovascular risk, it is recommended that severe hypertension should be controlled prior to surgery.[15]

This is the first study of its kind to explore adverse cardiovascular events in PD during DBS. The retrospective design poses various challenges including missing data and inability to establish causality. This calls for the need for multi-center analysis with prospective cohort or interventional study design.

Conclusion

Advanced PD presents unique perioperative considerations for the anesthesiologist primarily due to autonomic dysfunction. Postural hypotension, bradycardia, and supine hypertension are common manifestations of dysautonomia, which increase the incidence of perioperative adverse cardiovascular events. This study identifies current smoking, preoperative hypertension, renal failure, preoperative use of medications such as beta-blocker agents, calcium channel blockers and diuretics, as well as longer surgery duration as potential predictors for adverse cardiovascular events in PD population.

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Conflicts of interest

None.

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