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Clinical Study

Factors predicting incremental administration of antihypertensive boluses during deep brain stimulator placement for Parkinson's disease

Shobana Rajan [a], Milind Deogaonkar [b], Roop Kaw [c], Eman MS Nada [d], Adrian V. Hernandez [e], Zeyd Ebrahim [a], Rafi Avitsian [a,*]

[a] Department of General Anesthesiology, Anesthesiology Institute, Cleveland Clinic, 9500 Euclid Avenue, E-31, Cleveland, OH 44195, USA
[b] Department of Neurosurgery, Center for Neuromodulation, Ohio State University Medical Center, Columbus, OH, USA
[c] Department of Hospital Medicine and Outcomes Research, Cleveland Clinic, Cleveland, OH, USA
[d] Department of General Anesthesiology, University of Arkansas for Medical Sciences, Little Rock, AR, USA
[e] Postgraduate School, Universidad Peruana de Ciencias Aplicadas (UPC), Lima, Peru

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ABSTRACT

Hypertension is common in deep brain stimulator (DBS) placement predisposing to intracranial hemorrhage. This retrospective review evaluates factors predicting incremental antihypertensive use intraoperatively. Medical records of Parkinson's disease (PD) patients undergoing DBS procedure between 2008–2011 were reviewed after Institutional Review Board approval. Anesthesia medication, preoperative levodopa dose, age, preoperative use of antihypertensive medications, diabetes mellitus, anxiety, motor part of the Unified Parkinson's Disease Rating Scale score and PD duration were collected. Univariate and multivariate analysis was done between each patient characteristic and the number of antihypertensive boluses. From the 136 patients included 60 were hypertensive, of whom 32 were on angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB), told to hold on the morning of surgery. Antihypertensive medications were given to 130 patients intraoperatively. Age (relative risk [RR] 1.01; 95% confidence interval [CI] 1.00–1.02; $p = 0.005$), high Joint National Committee (JNC) class ($p < 0.0001$), diabetes mellitus (RR 1.4; 95%CI 1.2–17; $p < 0.0001$) and duration of PD >10 years (RR 1.2; 95%CI 1.1–1.3; $p = 0.001$) were independent predictors for antihypertensive use. No difference was noted in the mean dose of levodopa ($p = 0.1$) and levodopa equivalent dose ($p = 0.4$) between the low (I/II) and high severity (III/IV) JNC groups. Addition of dexmedetomidine to propofol did not influence antihypertensive boluses required ($p = 0.38$). Intraoperative hypertension during DBS surgery is associated with higher age group, hypertensive, diabetic patients and longer duration of PD. Withholding ACEI or ARB is an independent predictor of hypertension requiring more aggressive therapy. Levodopa withdrawal and choice of anesthetic agent is not associated with higher intraoperative antihypertensive medications.

1. Introduction

Deep brain stimulation (DBS) by implantation of electrodes has now become a clinical alternative in the treatment of advanced Parkinson's disease (PD) [1,2]. The procedure is performed in a staged manner, the first stage consisting of placement of the stimulating electrode in the subthalamic nucleus (STN) accompanied by microelectrode recording (MER), followed by a second stage to implant a programmable generator. The second stage may be done as a separate procedure or during the same setting as the first stage.

The initial part of the first stage involves providing moderate sedation accompanied by scalp infiltration with local anesthetic for the placement of the head frame (asleep phase). Subsequently, the sedation is discontinued and the DBS is placed followed by MER. A pre-requisite for adequate MER is an awake patient with a stable blood pressure (awake phase) [3]. Upon completion of mapping, sedation and analgesia may be restarted (asleep phase).

MER has been reported as the standard procedure in many leading centers [3,4], however it could be associated with an increased risk of brain hemorrhage due to either multiple passes of the microelectrode through the brain parenchyma or secondary to acute hypertension intraoperatively [4,5].

In this retrospective study we sought to evaluate the preoperative factors which could predict the incremental use of

* Corresponding author. Tel.: +1 216 444 9735; fax: +1 216 444 2294.
E-mail address: avitsir@ccf.org (R. Avitsian).

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antihypertensive boluses during the testing period. Identifying patients who are most likely to need sustained management of their hypertension during the awake part of the DBS procedure can help us plan strategies to achieve more stable control of their intraoperative blood pressure.

2. Methods

Institutional Review Board approval was obtained to conduct this retrospective review of medical records. We retrospectively reviewed medical records of patients with PD who underwent MER placement between 2008 and 2011 and identified 136 patients. Preoperative data collection included age, sex, levodopa equivalent dose (LED), levodopa dose, comorbidities such as presence of preoperative hypertension according to Joint National Committee (JNC) 7 classification (Table 1) [6], baseline preoperative blood pressure collected during an office visit, type of medications used for hypertension, presence of diabetes mellitus (DM), a medical diagnosis of anxiety disorder documented on the medical records, the motor component of the Unified Parkinson's Disease Rating Scale (mUDPRS) score in off state (mUPDRS off) when the patient is off anti-parkinson medications and duration of PD in years. LED was calculated using standardized LED formulae based on dose intensities of different anti-parkinson medication described in the literature [7].

2.1. Surgical technique

The surgical technique in all these patients consisted of a stereotactic frame placement, MRI and CT scan acquisition, use of stereotactic navigation system for anatomic targeting and trajectory planning and MER for physiological targeting as previously described. The target of DBS placement was either STN or globus pallidus internus (GPi). The commercially available DBS electrode (either 3389 or 3387; Medtronic, Minneapolis, MN, USA) was placed at the final target. The second stage of the DBS procedure was implantation of the pulse generator which was performed under general anesthesia either on the same day as DBS placement or in a staged fashion on a different day.

2.2. Anesthetic management

All patients underwent a routine preoperative evaluation. Antiplatelets, anticoagulants and anti-parkinson medications were withheld prior to surgery. Anti-parkinson medications were withheld the night before the surgery to render the patients in an "off" drug state for intraoperative neurological testing. According to institutional policy all patients who were on beta blockers or calcium channel blockers for hypertension were told not to withhold medication on the morning of surgery. Those who were on angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) were told to hold their medication on the morning of surgery. American Society of Anesthesiologists (ASA) monitors, non-invasive blood pressure or invasive blood pressure as deemed necessary and two peripheral intravenous catheters were placed in all patients upon arrival to the operating room. The anesthetic regimen during the asleep phase included infusion of propofol and/or dexmedetomidine. For statistical analysis however the four patients who received only dexmedetomidine were removed. Patients were breathing spontaneously with supplemental oxygen (2 to 8 L/minute) through a nasal cannula with the ability to monitor end tidal CO_2 and a nasal airway in most patients.

A forced-air warming device was used to maintain normothermia and axillary temperature was measured with a skin temperature probe. During the awake stage of the procedure, all sedation was stopped in order to be able to perform motor and cognitive assessment and MER. Based on published evidence of an association of intraoperative systolic blood pressure of >140 mmHg with cerebral hemorrhage, our institutional protocol mandates to maintain the systolic blood pressure at $\leqslant$130 mmHg during MER placement and during neurophysiologic monitoring [8].

Our primary outcome is the number of boluses of antihypertensive medication given during the period of testing. Systolic blood pressure during testing was not taken as an outcome in our study because the blood pressure was being aggressively managed whenever it was above 130 mmHg. The standard practice in our institute is to administer labetalol in increments of 5–10 mg, nitroglycerin 80–160 mcg, esmolol 20–30 mg, and hydralazine 5 mg, each of which is considered as one bolus in this study. Propofol and/or dexmedetomidine were restarted after completion of testing. Whether or not the programmable pulse generator was placed in the same setting, the antihypertensive boluses given during the testing period alone were taken into consideration for the purposes of the study.

Table 1
Reference card from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure

Category	SBP, mmHg		DBP, mmHg
Normal	<120	and	<80
Pre-hypertension	120–139	or	80–89
Hypertension stage 1	140–159	or	90–99
Hypertension stage 2	$\geqslant$160	or	$\geqslant$100

DBP = diastolic blood pressure, SBP = systolic blood pressure.

2.3. Statistical analysis

Categorical variables are shown as number and proportions, continuous variables as mean ± standard deviation or median (interquartile range [IQR]). Differences in proportions between categorical variables were tested with the chi-squared test. Associations between patient characteristics and the number of intraoperative antihypertensive boluses were evaluated with Poisson regression models, and the associations were expressed as relative risks (RR) and their 95% confidence intervals (CI). The RR expressed the risk associated to the increase in one antihypertensive bolus. Univariate analysis was done between each patient characteristic and the number of antihypertensive boluses, and those characteristics with a $p < 0.2$ were chosen for multivariate analysis. In multivariate analysis, characteristics with a $p < 0.05$ were considered significant. SAS 9.2 (SAS Institute, Cary, NC, USA) was used for all statistical analysis. Multivariable analysis was adjusted for the duration of the total procedure.

3. Results

3.1. Demographic data

Retrospective analysis was carried out in 136 PD patients who underwent DBS placement using intraoperative MER. Collected data included baseline demographics, age, sex, weight and ASA class. There were 90 men and 46 women. Median age was 63 years with a range from 38 to 85 years. Average duration of PD was 10.5 years with a range from 3 to 25 years. Average off state mUPDRS score was 35.5 with a range of 11 to 67. Average levodopa dose was 950 mg/day with a range from 225 mg/day to 2350 mg/day. Average LED in this patient group was 1030 mg/day and maximum was 2600 mg/day. Total number of patients with a history of hypertension was 60 and the average JNC class was II. ACEI or ARB were used in 32 hypertensive patients, all of whom were

told to hold their medication on the morning of surgery. Twenty three patients had DM and 32 patients had a preoperative medical diagnosis of anxiety and were being treated for anxiety preoperatively. Average ASA class was 2.5.

3.2. Anesthesia management

In 62 patients only propofol (dose range 45–125 mcg/kg/minute) was used, and four patients received only dexmedetomidine (0.2–0.65 mcg/kg/hour). In the remaining 70 patients a combination of propofol (35–90 mcg/kg/minute) and dexmedetomidine (0.1–0.4 mcg/kg/hour) was used during frame placement. Additional bolus doses of fentanyl (25–100 mcg) were given in only 17 patients during this initial stage of frame placement. For statistical analysis the four patients in whom dexmedetomidine was the only sedative used were removed and the remaining 132 patients were analyzed, and it was found that the addition of dexmedetomidine to the propofol infusion did not make any difference in the number of antihypertensive boluses administered.

Infusions were stopped during MER and a rise in systolic blood pressure to more than the cut off value was treated with intermittent bolus doses of labetalol, usually 5–10 mg (94% of patients). Additional doses of nitroglycerin (80–160 mcg), hydralazine (usually 5 mg) or esmolol (20–40 mg boluses) were given if deemed necessary depending on the anesthesiologist.

3.3. Intraoperative use of antihypertensive medications

Invasive arterial blood pressure was monitored in 17 patients and noninvasive blood pressure was monitored in the remaining 119 patients. Antihypertensive medications were given to 130 patients intraoperatively. No anesthetics or any other medication other than antihypertensive medications were given during the testing period. The most common antihypertensives used were labetalol (average dose per patient 59.50 ± 43.8 mg), hydralazine (average dose 10.98 ± 9.76 mg), nitroglycerin (average dose 88.08 ± 233 mcg) and esmolol (average dose 5.92 ± 21.17 mg). Four patients received continuous infusion (two with nicardipine, one with nitroglycerin and one with nitroprusside) and for statistical analysis this was taken as 10 boluses (average number of boluses) and any additional boluses given were added to this number. Patients with JNC class III and IV hypertension received a higher number of intraoperative antihypertensive boluses. The median number of boluses was nine (IQR 5–14; range 0–30; average 10.66) per patient.

3.4. Systolic blood pressure

Each 5 minute time period that the systolic blood pressure was above 130 mmHg was taken as one epoch. The median amount of time the systolic blood pressure was above 130 mmHg per patient was 25 minutes (range 10.0 to 46.4 minutes).

3.5. Predictors of incremental requirement of antihypertensive boluses in the intraoperative period

The following patient characteristics predicted the incremental increase in one bolus each of the number of intraoperative antihypertensive medications on univariate analysis: higher age ($p = 0.003$), presence of preoperative hypertension ($p < 0.0001$), high JNC class (class III/IV; $p < 0.0001$), use of ACEI or ARB preoperatively ($p < 0.0001$), DM ($p < 0.0001$); duration of PD >10 years ($p = 0.002$), and mUDPRS >35 ($p = 0.02$) (Table 2). Upon multivariate analysis mUDPRS was not significant anymore perhaps because of its collinearity with duration of PD >10 years (Table 3, 4). There is very slight change in existing multivariable RR after adjustment for duration of the total procedure. Duration of the total procedure was independently associated with the number of boluses. In the 32 patients who were taking ACEI or ARB as an antihypertensive preoperatively, 21 needed more than nine boluses. The preoperative use of ACEI or ARB predicted the incremental increase requirement of each antihypertensive bolus although this effect was lost in the multivariate analysis (RR 1.1; 95%CI 0.9–12; $p = 0.5$). Higher age (RR 1.01; 95%CI 1.00–1.02; $p < 0.005$); high JNC class ($p < 0.0001$); DM (RR 1.4; 95%CI 1.2–17; $p < 0.0001$) and duration of PD >10 years (RR 1.2; 95%CI 1.1–1.3; $p = 0.001$) were independent predictors of the incremental use of single bolus of antihypertensive medication intraoperatively. No difference was noted in the mean dose of levodopa ($p = 0.1$) and LED ($p = 0.4$) between the low (I/II) and high (III/IV) JNC groups.

3.6. Incidence of hemorrhage

Immediate post-procedure head CT scan showed two incidents of intracranial hemorrhage. One patient had intraparenchymal hemorrhage (target nucleus was GPi) and one patient had subdural hemorrhage (target STN); a total of two out of 136 patients (1.47%). The maximum blood pressure in the first patient was 140 mmHg for 15 minutes and the maximum blood pressure in the second patient was 180 mmHg for 20 minutes.

All patients were followed up with a head CT scan 3–4 weeks after surgery as per surgeon's protocol. Any intracranial hemorrhage (five cases) which was discovered during the first 4 weeks postoperatively per this protocol but was not present in the immediate post-procedure CT scan was counted as not related to the intraoperative event or hypertension.

4. Discussion

To the best of our knowledge this is the first study to have analyzed the preoperative predictors of intraoperative hypertension during MER guided DBS placement in patients with PD. There are studies that refer to intraoperative hypertension being responsible for increased hemorrhagic complications during DBS surgery [9,10] but no studies have looked at the predictors of intraoperative hypertension. The most significant predictors of the incremental use of one bolus each of the number of intraoperative antihypertensive medications found in our study were higher age, high JNC class, DM and duration of PD >10 years.

In this retrospective study we collected the dosage, type of antihypertensive medication and number of boluses from the electronic anesthesia chart. Since different patients received different antihypertensive medications depending on the anesthesiologist's choice it was not possible to have an equivalent measurement. Hence number of boluses was used as the primary outcome. Since blood pressure was being aggressively and actively managed intraoperatively, we could not use mean arterial pressure as the primary outcome for intraoperative hypertension and the number of boluses was taken as a surrogate.

Age is an independent predictor of perioperative complications in numerous studies [11,12]. Aging results in a shift of autonomic balance toward sympathetic predominance in higher age groups, limiting the reactiveness of the cardiovascular system to adjust to different demands [13]. Aging is also associated with poor autonomic balance mechanisms [14].

Autonomic imbalance, cardiac dysautonomias and autonomic failure are also seen in advanced PD [15,16]. Advanced PD as reflected by higher mUPDRS score and a prolonged duration can be a frequent cause of primary autonomic failure with an involvement of the peripheral autonomic system as shown by reduced iobenguane (metaiodobenzylguanidine) cardiac uptake [15–17].

Table 2
Poisson regression model evaluating the association between predictors and antihypertensive medication boluses (expressed as the increase in one bolus) on univariate analysis

	Univariable RR (95%CI) for increase of one bolus	*p* value
Age[a]	1.01 (1.00–1.01)	0.003
Preoperative LED dose[b]	1.0 (0.98–1.01)	0.4
Preoperative levodopa dose[b]	1.0 (0.99–1.01)	0.7
Preoperative hypertension	1.2 (1.1–1.4)	<0.0001
JNC class		
I	1	<0.0001
II	1.0 (0.9–1.1)	
III+IV	1.4 (1.2–1.6)	
Preoperative antihypertensive medication		
ACEI or ARB	1.4 (1.3–1.6)	<0.0001
Other	1	
Diabetes mellitus	1.6 (1.4–1.8)	<0.0001
PD duration >10 years	1.2 (1.1–1.3)	0.002
mUPDRS >35	1.1 (1.0–1.3)	0.02
Preoperative anxiety	1.1 (0.9–1.2)	0.3
Anesthesia medication dexmedetomidine or propofol and dexmedetomidine	1.0 (0.9–1.1)	0.5

ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CI = confidence interval, LED = levodopa equivalent dose, mUDPRS = motor component of the Unified Parkinson's Disease Rating Scale, PD = Parkinson's disease, RR = relative risk, SD = standard deviation.
[a] One year increments.
[b] 100 mg increments.

Table 3
Association between the predictors and the antihypertensive medication boluses on multivariable analysis

	RR (95% CI) for increase of one bolus	*p* value
Age[a]	1.01 (1.00–1.02)	0.005
JNC class		
I	1	<0.0001
II	0.9 (0.8–1.0)	
III+IV	1.2 (1.0–1.4)	
Preoperative antihypertensive medication		
ACEI–based or ARB	1.1 (0.9–1.2)	0.5
Other	1	
DM	1.4 (1.2–1.7)	<0.0001
PD duration >10 years	1.2 (1.1–1.3)	0.001
mUPDRS >35	1.1 (1.0–1.2)	0.1

Preoperative hypertension was removed from analysis as it is collinear with JNC class.
ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CI = confidence interval, DM = diabetes mellitus, JNC = Joint National Commission classification of hypertension, mUDPRS = motor component of the Unified Parkinson's Disease Rating Scale, PD = Parkinson's disease, RR = relative risk, SD = standard deviation.
[a] One year increments.

Table 4
Association between predictors and antihypertensive medication boluses after adjusting for procedure duration

Factors	Multivariable RR (95% CI) for increase of one bolus	*p* value
Age[a]	1.01 (1.00–1.02)	0.0004
JNC class		
I	1	0.02
II	0.9 (0.7–1.1)	
III+IV	1.2 (0.9–1.6)	
Preoperative antihypertensive medication		
ACEI or ARB	1.0 (0.8–1.3)	
Other	1	0.8
DM	1.5 (1.2–2.0)	<0.0001
PD duration >10 years	1.2 (1.0–1.4)	0.003
mUPDRS >35	1.1 (0.9–1.3)	0.1
Duration of total procedure, per 1 hour increase	1.1 (1.0–1.2)	0.0004

Data are presented as number (%) unless otherwise stated.
ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, CI = confidence interval, DM = diabetes mellitus, JNC = Joint National Commission classification of hypertension, mUDPRS = motor component of the Unified Parkinson's Disease Rating Scale, PD = Parkinson's disease, RR = relative risk, SD = standard deviation.
[a] One year increments.

The unique nature of pathological and pharmacological changes in advanced PD resulting in autonomic failure can result in the incremental use of antihypertensives during the DBS surgery [15–17]. Any surgical intervention in patients with advanced PD is complicated due to the disease itself or the medication related biochemical aberrations leading to a number of clinically significant manifestations including intraoperative cardiovascular lability, orthostatic hypotension and increased risk of mortality [18].

One of our initial hypotheses was that patients needing higher dose of levodopa or LED medications may need higher number of intraoperative boluses of antihypertensive medications. The rationale for this was based on the effects of sudden withdrawal of dopaminergic medication in PD patients. Since the dopaminergic medications are stopped the night before surgery, this sudden withdrawal can lead to hypertension in a small number of patients, in rare instances resulting in Parkinson's hyperpyrexia syndrome [19]. This may be secondary to levodopa induced modulation in central dopaminergic activities, alterations in central serotonin metabolism or changes in peripheral and central sympathetic outflow. It is also suggested that levodopa/carbidopa is an inhibitor of peripheral catecholamine synthesis [20] so any abrupt cessation can cause hypertension. No difference was noted in the mean dose of levodopa ($p = 0.1$) and LED ($p = 0.4$) between the low (I/II) and high severity (III/IV) JNC classes. Since the requirement of levodopa and LED equivalent was not high among JNC III and IV classes, the higher requirement of intraoperative antihypertensive boluses cannot be attributed to levodopa and LED equivalent withdrawal in these categories.

In a study on 267 hypertensive patients receiving chronic ACEI/ARB therapy, discontinuation of ACEI/ARB therapy at least 10 hours before anesthesia was associated with a reduced risk of hypotension immediately after induction [21]. However in this study by Comfere et al. there were no differences between those who held their ACEI/ARB for more than 10 hours and those who did take their medication closer to anesthesia in the incidence of severe hypotension or use of vasopressors during the 31–60 minutes after induction, and the incidence of moderate or severe hypotension was similar in the two groups. In our study the preoperative use of ACEI or ARB predicted the incremental increase in requirement of each antihypertensive bolus although this effect was lost in the multivariate analysis (RR 1.1; 95%CI 0.9–12; $p = 0.5$). It is a standard practice at our institution to withhold ACEI or ARB on the day of surgery with some exceptions. Although the number of patients included in our study is small, by seeing these results there may be a need to revisit this policy for this group of patients. Future studies are required to examine this practice among patients undergoing DBS due to their higher risk of intraoperative hypertension and consequent risk of intracerebral hemorrhage. The unique anesthetic method of asleep-awake-asleep in DBS placement may be another reason for seeing hypertension in the awake portion of patients who have stopped their antihypertensive medications.

We used labetalol as the primary antihypertensive medication, although beta blockers have been used to treat essential tremors and small studies have shown some effect in reducing the severity but not complete cessation of tremors [22,23]. A Cochrane review did not find good evidence concerning their efficacy in cessation of tremors [24] and this was evident in the current study in that the use of labetalol did not prevent us from eliciting the tremors when needed to in order to monitor the electrode stimulation.

Our study did not show any difference between the type of anesthetic agents used and incremental use of intraoperative antihypertensive medications. Dexmedetomidine is a relatively selective alpha 2-adrenoceptor agonist and is commonly used in DBS surgeries [25,26]. In our study, addition of dexmedetomidine to the propofol infusion did not make any difference to the mean number of antihypertensive boluses required ($p = 0.38$).

The incidence of intraoperative hemorrhage in our study was 1.47% (two out of 136 patients). Pathological changes in the walls of small and medium-sized vessels lead to an increased risk of hemorrhage during surgery. Chronic arterial hypertension, advanced age and number of passes of the microelectrode play an important role [9]. It has been suggested that anatomic peculiarity of the vasculature in the GPi region may be responsible for the increased incidence of hemorrhage. The GPi is supplied by the lenticulostriate arteries that come from the anterior circulation. These arteries are more prone to the effects of hypertension and may also be developmentally different [27].

Full discovery of predictive factors has not yet been achieved. Being retrospective, our study may reveal some of the possible predictors and future directions to evaluate and identify patients who could pose a higher risk for intraoperative hypertension and intracranial hemorrhage during DBS insertion for advanced PD. Our paper has limitations since it was a retrospective study; also the choice of antihypertensives was decided by the anesthesiologist on the case. Whether acute intraoperative hypertension contributes to perioperative hemorrhage is still to be determined by future studies.

5. Conclusions

Our study demonstrates that elderly patients who are hypertensive with JNC class III/IV, treated with ACEI/ARB, have DM, with a history of PD >10 years and mUPDRS score >35 will need sustained and intensive management of intraoperative hypertension during the awake part of the DBS procedure. Anticipating this, a preoperative strategy for intraoperative blood pressure control in this group may lead to a more stable blood pressure control which ultimately may result in better postoperative outcomes.

Conflicts of Interest/Disclosures

Dr. Deogaonkar – Consultancy (honoraria): Medtronic.

Dr. Rajan – Grant: Hospira.

Dr. Avitsian – Grants: Hospira; Payment for Visiting Professorship lectures; Patents: Cleveland Clinic Innovations and Parker Hannifin.

The other authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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