


Perioperative Hypertension Etiologies in Patients Undergoing Noncardiac Surgery in University Health Network Hospitals—Canada from 2015–2020

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Introduction: Perioperative hypertension, defined as increased blood pressure around the surgery, is a known risk factor for perioperative complications, including cardiovascular events. Identifying reasons associated with hypertension in each period is of great help in preventing and better managing perioperative hypertension.

Objective: The aim of the study was to explore common etiologies of hypertension during the perioperative period (pre, intra, and post-operation) in patients who underwent noncardiac surgeries in University Health Network (UHN) hospitals, Canada, from 2015 to 2020.

Patients and Methods: We retrospectively analyzed the medical records of 174 patients undergoing noncardiac surgeries who experienced perioperative hypertension. We assessed the prevalence of 10 reasons for perioperative hypertension as a whole and also each period separately according to the physicians' notes in patients' medical records. Two-way measurements ANOVA was used to determine the change of mean hypertension among patients for specific etiology.

Results: The common etiologies of perioperative hypertension were poorly controlled hypertension (21.8%), excessive fluid therapy (19.5%), excessive vasopressor (18.4%), and medication withdrawal (13.7%). Regarding each period separately, the most common reasons were poorly controlled hypertension for pre (42.9%) and intraoperative period (22.7%) and fluid overload for the postoperative period (20.1%). Poor control of hypertension showed both within-subject statistical significance for systolic and between-subject statistical significance for diastolic blood pressure.

Conclusion: Poorly controlled hypertension is the most significant etiology of perioperative hypertension in patients undergoing noncardiac surgeries. Apart from poorly controlled hypertension, as a patient-related factor, iatrogenic factors such as excessive vasopressor therapy, aggressive fluid replacement and poor management of antihypertensive medications can also cause perioperative hypertension.

Keywords: hypertension, intraoperative, perioperative, postoperative, surgery

Introduction

Hypertension is modifiable comorbidity and a known risk factor for premature death, affecting 1.13 billion people worldwide.^{1,2} In Canada, according to a report published in 2010, around 20% of the adult population had high blood pressure, and hypertension-related economic burden exceeded CAD\$13 billion per year, which was estimated to double by 2020.³

Surgery is among the clinical settings in which the importance of hypertension is even more pronounced.⁴ Perioperative hypertension is an unfavorable complication occurring before, during and after operation in patients with and without preexisting hypertension. Perioperative hypertension remains a major risk factor for poor surgery outcomes, including brain stroke, renal failure and cardiovascular events. Proposed etiologies for perioperative hypertension vary

according to the period it emerges. Preoperatively, it is associated with anxiety, poorly controlled preexisting hypertension, and the induction of anesthesia, especially when no preemptive opioid analgesic is administered. Intraoperatively, it can occur due to vasoconstriction following pain-induced sympathetic activation. Postoperatively, it is linked to hypothermia, hypoxia, cessation of long-term antihypertensive drugs, and excessive fluid intake. The latter may persist for three days after surgery.^{5–7}

Although complications and management of perioperative hypertension have been studied for years, common causes linked to perioperative hypertension have been left unaddressed for decades. It has been suggested that intraoperative hypertension negatively affects surgery outcomes by prolonging hospital stay and increasing mortality.⁸ The goal of perioperative hypertension management is to maintain adequate myocardial perfusion, which can be best achieved by considering patients' general conditions, the type of surgery, presumed hypertension causes, and baseline blood pressure.^{9–11}

Given the research gap and the crucial role of identifying common causes for perioperative hypertension in the prevention and proper management, the present study aimed to explore the common reasons for pre, intra and post-operative hypertension in patients who underwent non-cardiac surgeries in University Health Network (UHN) hospitals, Canada, from 2015 to 2020.

Patients and Methods

Study Design

In this multi-center retrospective study, we evaluated common reasons for perioperative hypertension using data from Electronic Patient Record (EPR) of patients who underwent noncardiac surgery in University Health Network (UHN) hospitals; including Princess Margaret Cancer Center, Toronto General Hospital, Toronto Rehabilitation Institute, Toronto Western Hospital, from January 1, 2015, to January 1, 2020. The study was approved by the Research Ethics Board (REB) at the University Health Network (REB number 18–5720). This includes the Constant Waiver Request approval; as personal health information was collected, used or disclosed without consent from the individuals. The consent can be waived because the data was deidentified for confidentiality purposes and therefore did not require explicit patient consent. This was in line with UHN policy that patients provide consent to use their data for research purposes when admitted to UHN hospitals. This research project is also in line with the Helsinki Declaration. After selecting the patients and comprehensively reviewing their medical records, we evaluated the causes of perioperative hypertension by classifying them into ten reasons.

Patient Selection

The perioperative period is defined as the time around surgery, which is divided into three phases:

- Preoperative: The time from admission to the beginning of a surgical procedure;
- Intraoperative: The time between the transfer of a patient to OR and the end of surgery;
- Postoperative: This period starts immediately after surgery and lasts up to 48 hours after surgery.

We extracted blood pressure values that were noninvasively measured and recorded in patients' charts and enrolled patients who experienced hypertension in any of the perioperative phases (pre-, intra-, post-operative) according to the below criteria:

- Preoperative hypertension: Systolic Blood Pressure (SBP) \geq 130 OR Diastolic Blood Pressure (DBP) \geq 80
- Intraoperative hypertension:
- Low baseline BP (SBP, $<$ 90 mm Hg, or DBP, $<$ 50 mm Hg): $>$ 20% increase from the baseline
- Normal baseline BP (SBP, 90–129 mm Hg, and DBP, 50–79 mm Hg): $>$ 10% increase from the baseline OR BP $>$ 130/80
- High baseline BP (SBP, \geq 130 mm Hg, or DBP, \geq 80 mm Hg): $>$ 10% increase from the baseline OR SBP $>$ 160
- Postoperative hypertension:

- the first 4 hours: >10% increase from the baseline BP
- 4–48 hours after surgery: SBP \geq 130, DBP \geq 80¹⁰

Data Collection

Preoperative data consisted of demographic and medical characteristics (age, gender, body mass index [BMI], previous comorbidity), length of stay in the hospital (LOS), American society of anesthesiology (ASA) classification, preoperative hemoglobin, past medical history, medication, alcohol and drug use, as well as blood pressure and heart rate before surgery. Intraoperative data included in the analysis were the type of surgery, type of anesthesia, blood transfusion, positive fluid balance, use of antihypertensive drugs, use of vasopressors, and the type of antihypertensive medication in the intraoperative phase. The data relating to the postoperative phase were intensive care unit (ICU) admission, LOS in ICU, LOS after surgery, and in-hospital mortality.

Inclusion Criteria

All patients undergoing noncardiac surgery from 2015 to 2020 at UHN hospitals who experienced perioperative hypertension (pre, intra, post-operative hypertension) were included.

Exclusion Criteria

Pregnant women, pediatrics, patients who underwent radiological imaging with contrast before surgery, patients with incomplete data, and patients with a documented diagnosis of secondary hypertension before surgery were excluded from the study.

Definition of Reason Codes

According to clinical notes of responsible internists/anesthesiologists and using the following definitions, we considered ten reasons for perioperative hypertension:

- Poorly-controlled hypertension: patients with a documented pre-existing essential hypertension whose baseline BP was equal or above 130/80 in non-diabetics and 140/90 in diabetics.¹²
- Excessive vasopressor administration: Vasopressors are used in severe hypotension to maintain Mean Arterial Pressure (MAP) between 60–65 mmHg.^{13,14} We considered excessive vasopressor administration for patients with an episode of severe hypotension whose blood pressure surged suddenly to a level of equal or above 180/110 right after vasopressor administration.
- Excessive fluid therapy:
 - Intraoperative:
 - For major invasive surgeries, optimal fluid replacement is attained by zero-balanced strategy, which is up to 3cc/kg/h of crystalloid for sensible and insensible losses plus crystalloid-to-blood volume ratio of 1.5:1 for blood loss. Patients who were given intraoperative fluid more than the amounts mentioned above, followed by hypertension and tachycardia, were considered to have received excessive fluid intraoperatively.¹⁵
 - For minimally/moderately invasive surgery, the optimal fluid replacement is up to 2 L above, which were considered excessive fluid therapy in patients developing hypertension and tachycardia.^{16,17}
 - Postoperative: more than 10% increase in patient's weight from the preoperative value in combination with respiratory signs was considered postoperative volume overload, showing excessive intraoperative fluid therapy.¹⁸
- Renovascular: The diagnosis of renovascular hypertension was recorded after the surgery date in the patients' charts by an internist or a nephrologist using a recorded angiography report.
- Adrenal: hypertension due to primary hyperaldosteronism was noted in endocrinologists' consulting reports. The patients were referred to a specialist after surgery due to resistance or difficulty in controlling hypertension.

- Alcohol withdrawal: In Canada, over three and two drinks/day or ten and 15 drinks/week is considered at-risk alcohol use in men and women, respectively.¹⁹ The specialists clinically diagnosed alcohol withdrawal in patients with a history of at-risk drinking and no other reason for blood pressure increase.
- Cocaine Use: History is taken from the patient to confirm the use of cocaine prior to the admission. The related data were extracted from the patient's record based on history.
- Angiotensin-Converting Enzyme Inhibitors (ACEIs)/Angiotensin Receptor Blockers (ARBs) withdrawal: hypertensive patients receiving ACEIs/ARBs who had their medications quitted by physicians 24 hours prior to surgery.¹²
- Pain & anxiety
- Uncertain: Some causes for hypertension are recorded in the patient's chart; however, certain reason codes cannot accurately explain perioperative hypertension.

Statistical Analysis

Shapiro–Wilk test was used to test for normality, which helped identify distribution-related tests. Continuous variables following normal distribution were expressed as mean (SD), while variables not following normal distribution were reported as the median and interquartile range (IQR). Percentage of the total was used for nominal variables. Outliers were identified and removed when the value was above (75th percentile + 1.5 * IQR) or below (25th percentile - 1.5 * IQR).

The Bonferroni-adjusted two-way repeated-measures ANOVA was used to test the within- and between-subjects SBP and DBP. The within-subjects incorporated the repeated measurements of pre, intra, and postoperative SBP and DBP over time. The Mauchly's W sphericity test or Greenhouse–Geisser correction when necessary. Significance was defined as $P \leq 0.05$. The data were analyzed using SPSS version 23.0 (IBM Corporation, Armonk, NY, USA).

Results

Table 1 shows the characteristics of 174 patients who experienced perioperative hypertension. The mean age of the study population was 62.83 (\pm 15.17), with 77 (43%) being female. History of diabetes and dyslipidemia were recorded in 39 (24%) and 35 (20.1%), respectively. Patients' length of stay (LOS) was highly skewed to the right, with the mean LOS of 9.1 (SD= 14.22) and a minimum of one and a maximum of 132 days. The reasons for perioperative hypertension are presented in Table 2, categorized based on pre, intra and post-operative systolic and diastolic hypertension. The etiologies of perioperative hypertension in order of prevalence were poorly controlled hypertension (21.8%), excessive fluid therapy (19.5%), excessive vasopressor (18.4%), and medication withdrawal (13.7%). Regarding each period, the most common reasons were poorly controlled hypertension for pre (42.9%) and intraoperative period (22.7%) and fluid overload for the postoperative period (20.1%).

Table 1 Patients Characteristics

Patient Characteristic (N=174)	Mean	SD
Age (years)	62.83	15.17
Female N (%)	77	43
BMI (kg/m ²)	28.48	6.58
Past medical history of hypertension- N (%)	116	66.7
Past medical history of diabetes - N (%)	39	24
Past medical history of dyslipidemia - N (%)	35	20.1
LOS (days) - median (IQR)	5	7

Abbreviation: LOS, length of stay.

Table 2 Factors Related to Perioperative, Intraoperative and Postoperative Hypertension

Factors	Perioperative HTN (N=174)		Intraoperative HTN (N=163)		Postoperative HTN (N=164)	
	Number	Percent	Number	Percent	Number	Percent
Pain or anxiety	5	2.9	–	–	4	2.4
Poor hypertension control	38	21.8	37	22.7	38	23.2
Excessive fluid therapy	34	19.5	31	19.0	33	20.1
Alcohol withdrawal	11	6.3	11	6.7	11	6.7
Excessive vasopressor	33	18.4	33	20.2	27	16.5
Medication withdrawal	24	13.7	20	12.3	24	14.6
Renovascular	5	2.7	5	3.1	4	2.4
Adrenal	12	7.5	12	7.3	8	4.9
Cocaine use	1	0.7	1	0.6	1	0.6
Uncertain	14	8.2	13	8.0	14	8.5

Abbreviation: HTN, hypertension.

A repeated-measures ANOVA with a Greenhouse-Geisser correction determined that systolic blood pressure was statistically significant between time points ($F(1.9, 322.86) = 51.71, p < 0.001$). Post hoc tests using the Bonferroni correction revealed that systolic blood pressure increased from pre-operation (Mean = 151.11, $sd = \pm 22.81$) to Intra-operation (Mean = 178.05, $sd = \pm 29.55$) and then decreased in post-operation (Mean = 167.41, $sd = \pm 21.27$). The change in systolic blood pressure was not statistically between patients diagnosed with volume overload compared to those without volume overload.

The most important factor for elevated blood pressure and hypertension was poor control of hypertension. Figure 1 compares the systolic blood pressure of patients with poorly controlled and patients with well-controlled hypertension. The mean systolic hypertension changes from time 1 to 3 were statistically significant among patients with poorly controlled hypertension compared to well-controlled hypertension ($F(1, 168) = 27.16, P < 0.001$). In both groups of poorly controlled and well-controlled hypertension, the blood pressure was raised during surgery (intraoperative period). The differences in the mean SBP in three-time points (within-group differences) were statistically significant ($F(1.89, 308.05) = 26.6, p < 0.001$). Due to the violated Sphericity assumption, the Greenhouse-Geisser p-value was reported. When comparing poorly controlled hypertensives with normotensives and well-controlled hypertensives, it was evident that the first group displayed remarkably higher SBP and DBP throughout surgery, including pre, intra, and postoperative periods (Figures 1 and 2).

Figures 3 and 4 show the repeated measurement results for systolic and diastolic blood pressure for patients having their medication withdrawn compared to patients with other hypertension reasons. The results show a statistically significant difference for systolic blood pressure in patients with ACEIs/ARBs withdrawal and patients with other reasons for hypertension ($F(1, 198) = 10.50, P = 0.001$). The results were not statistically significant for differences in diastolic blood pressure ($F(1, 198) = 2.38, P = 0.13$).

Discussion

Surgical stress is a natural systemic response to surgery, which comprises sympathetic, metabolic and hematologic changes, including blood pressure variation. While this variation mainly occurs within the normal range, some factors may predispose patients to high blood pressure before, during, and after surgery, together known as perioperative hypertension.²⁰ The findings of our study revealed that the main etiology of perioperative hypertension was poorly controlled hypertension (21.8%) and other reasons were excessive fluid therapy (19.5%), excessive vasopressor (18.4%),

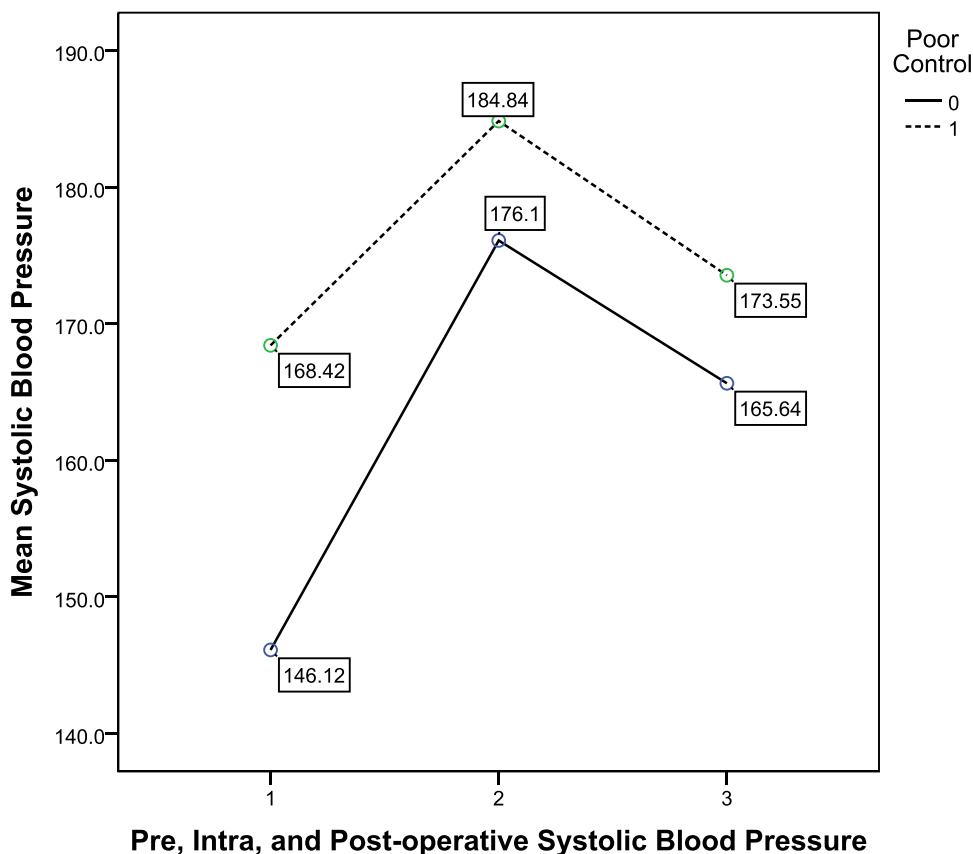


Figure 1 The mean SBP of poorly controlled hypertensive patients compared to normotensive and well controlled hypertensive patients in population in pre, intra and postoperative period.

and medication withdrawal (13.7%). Regarding each period separately, the most common reasons were poorly controlled hypertension for preoperative (42.9%) and intraoperative period (22.7%) and fluid overload for the post-operative period (20.1%).

Poor hypertension control can lead to perioperative hypertension in various ways. Generally, hypertensive patients are more susceptible to blood pressure fluctuations due to arterial remodeling and increased vascular resistance in adaptation to chronic high-pressure load.^{21,22} In addition, the anesthesia itself provokes hypertensive response through catecholamine release. Following laryngoscopy and endotracheal intubation, blood pressure may increase by 20–30 mmHg in normotensives and up to 90mmHg in uncontrolled hypertensives. Similarly, during the recovery, when anesthetic agents wean off and patients regain consciousness, another blood pressure elevation happens.^{23,24} In our population, the most common reason for perioperative hypertension was poorly controlled hypertension. In early 1970, Prys-Robert et al compared the effect of anesthesia on cardiovascular response between three groups of patients including normotensives, treated hypertensives and untreated hypertensives.²⁵ Dynamic evaluation of cardiovascular response during four surgical stages demonstrated that the impact of anesthesia on perioperative hemodynamic was closely bound up with preoperative blood pressure values. While normotensive and well-controlled hypertensive patients reacted the same way to anesthesia, untreated or inadequately treated patients experienced more notable variation in Mean Arterial Pressure (MAP) values during operation, including sharper MAP drop after induction of anesthesia and a marked MAP elevation by the end of the surgery, mainly due to a significant alteration in vascular resistance between stages.

We found excessive fluid therapy as the second most common etiology of post-operative hypertension (20.1%). The optimal perioperative outcome is dependent on judicious fluid therapy, meaning that both inadequate, and more commonly, excessive fluid therapy increases surgical complications, including hypertension, pulmonary edema, and

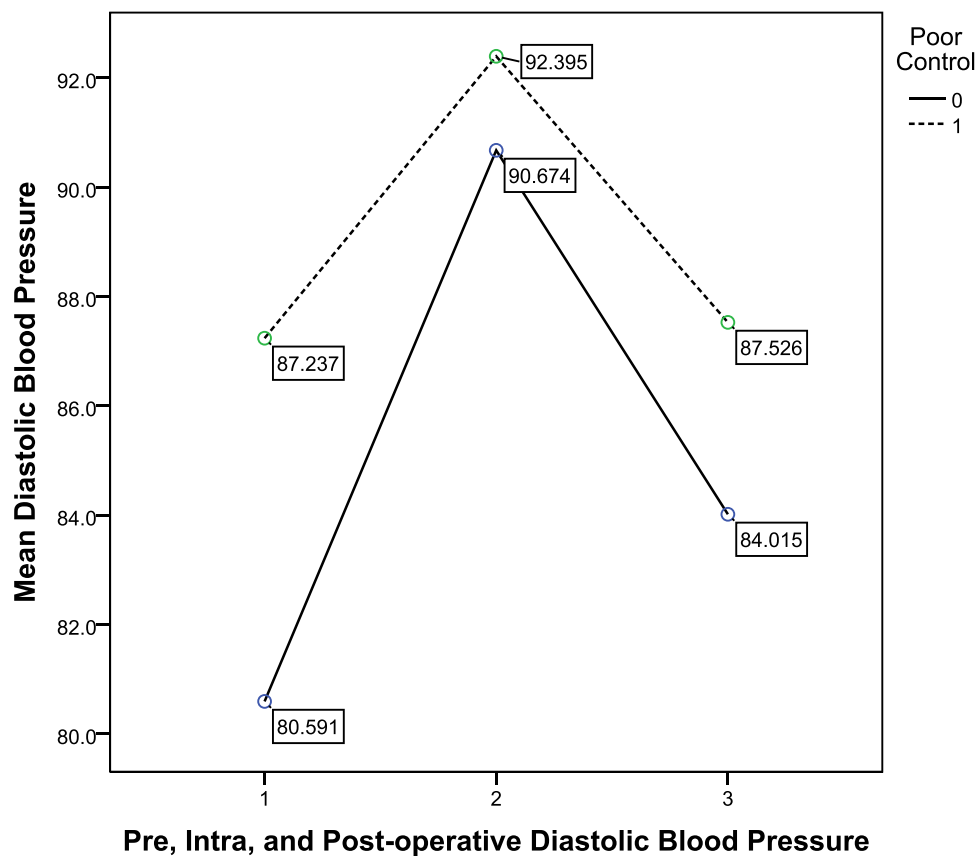


Figure 2 The mean DBP of poorly controlled hypertensive patients compared to normotensive and well controlled hypertensive patients in population in pre, intra and postoperative period.

decreased gastrointestinal motility.^{18,26} Hypervolemia is especially difficult to diagnose in patients with longstanding hypertension and requires a high index of suspicion. The idea of liberal fluid administration was first proposed by Shires et al who found a decrease in functional extracellular volume (ECV) due to fluid sequestration in traumatized tissues during surgery, especially major surgeries.²⁷ Over time, studies contradicted this approach due to resultant volume overload and endorsed restrictive fluid therapy as surgical stress response induces water and sodium retention mediated by increased renin-angiotensin, Anti-Diuretic Hormone (ADH), Atrial Natriuretic Peptide (ANP), and aldosterone. In line with our findings, Lowell et al reported a 40% incidence of volume overload (>10% weight gain) among 48 patients in surgical ICU. In their study, among fluid-overloaded patients, those who gained more weight (>20%) had received more intraoperative IV fluids than those with weight gain of 10–20%.²⁸

The use of vasopressors during surgery is a double-edged sword.¹⁴ Inducing general vasoconstriction, vasopressors are widely used in hypovolemic patients who are unresponsive to fluid resuscitation in order to maintain adequate perfusion to vital organs.²⁹ Intraoperative vasopressor administration, though preventing fatal complications of hypotension, can inadvertently cause hypertension if not controlled tightly.³⁰ According to our results, vasopressors were the third most common reason for perioperative hypertension. Excessive vasopressor administration as an etiology of perioperative hypertension is reported by previous studies, including a retrospective study of 3623 ICU and surgery patients who were given vasopressors. In this study, Rinehart et al reported that 40% of cases passed the MAP target range of 60–80 mmHg during vasopressor therapy, with 19% of them even experiencing MAP > 90mmHg.³¹ It appears that due to the lack of close monitoring or excessive concerns about hypotension outcomes, patients are overly treated with vasopressors and MAP commonly exceeds the introduced target of 60–65mmHg during vasopressor therapy.^{14,32} This underlines the room for improvement in intraoperative care and closer surveillance of drug titration during surgery.

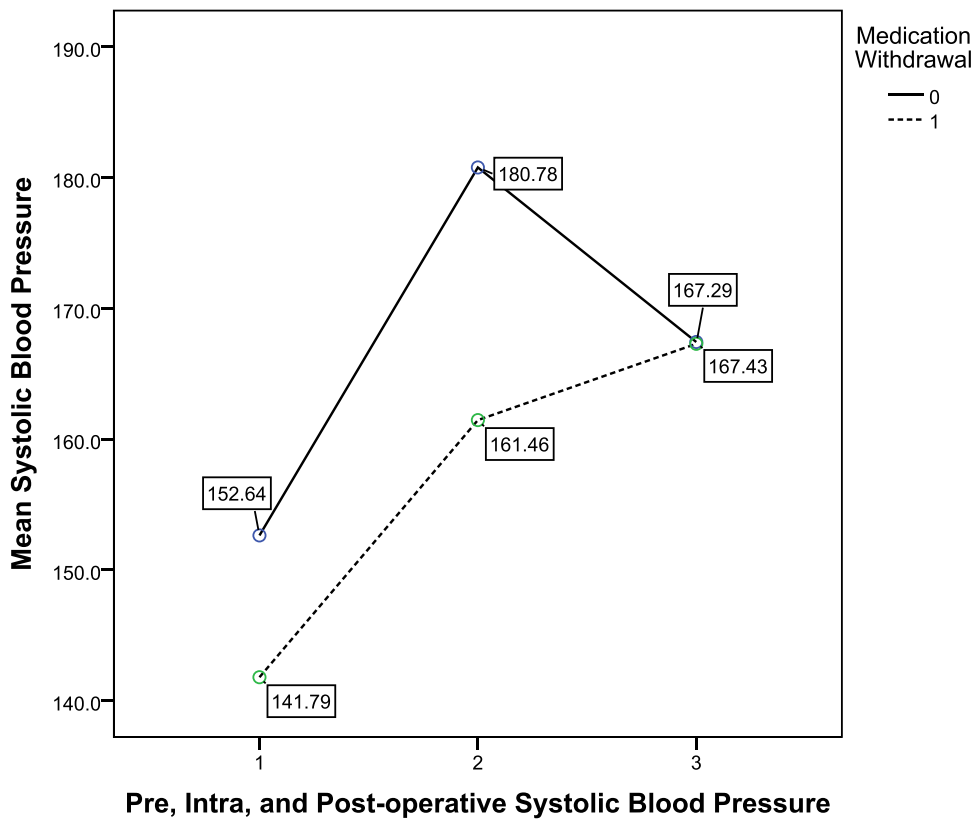


Figure 3 The mean SBP of patients with medication withdrawal compared to the rest of patients in population in pre, intra and postoperative period.

Around 50% of the patients undergoing noncardiac surgeries use various medications regularly. Accordingly, past medication history affects perioperative conditions and surgery outcomes.³³ The optimization of chronic medications in such patients, still remains a challenge; specifically, their use during the perioperative period. This is even more controversial in chronically used antihypertensive agents especially ACEIs and ARBs.³⁴ The American heart association in its latest guideline recommends considering ACEIs/ARBs discontinuation before surgery due to the induced refractory hypotension after induction of general anesthesia.¹² Our study found medication withdrawal the fourth most prevalent reason for perioperative hypertension. According to between-subject analysis in our study, although patients who had their ACEIs/ARBs discontinued did not develop intraoperative hypertension, they did experience a significant blood pressure surge post-operatively. In a prospective study on 40 patients who underwent elective Coronary Artery Bypass Graft surgery, Pigott et al concluded that even though preoperative ACEIs holding reduced the incidence of hypotension and the need for intraoperative vasopressors, it increased the need for post-operative vasodilators.³⁵ Various studies in recent decades have only focused on hypotension or on the treatment and complications of perioperative hypertension. In our study, we provided novel data on different reasons for perioperative hypertension that have been overlooked for years. We also discussed each period separately. However, some limitations should be taken into account. First, our study had a retrospective design with a relatively small sample size. Second, we included both elective and emergent surgeries. We suggest more large-scale prospective studies with emphasis on perioperative hypertension for future work to better identify and prevent factors leading to increased perioperative blood pressure.

Conclusion

Poorly controlled hypertension is the most significant reason for perioperative hypertension in patients undergoing noncardiac surgeries. Apart from poorly controlled hypertension, as the main patient-related factor, in nearly half of patients, iatrogenic perioperative hypertension emerges because of excessive vasopressor or fluid replacement and poor

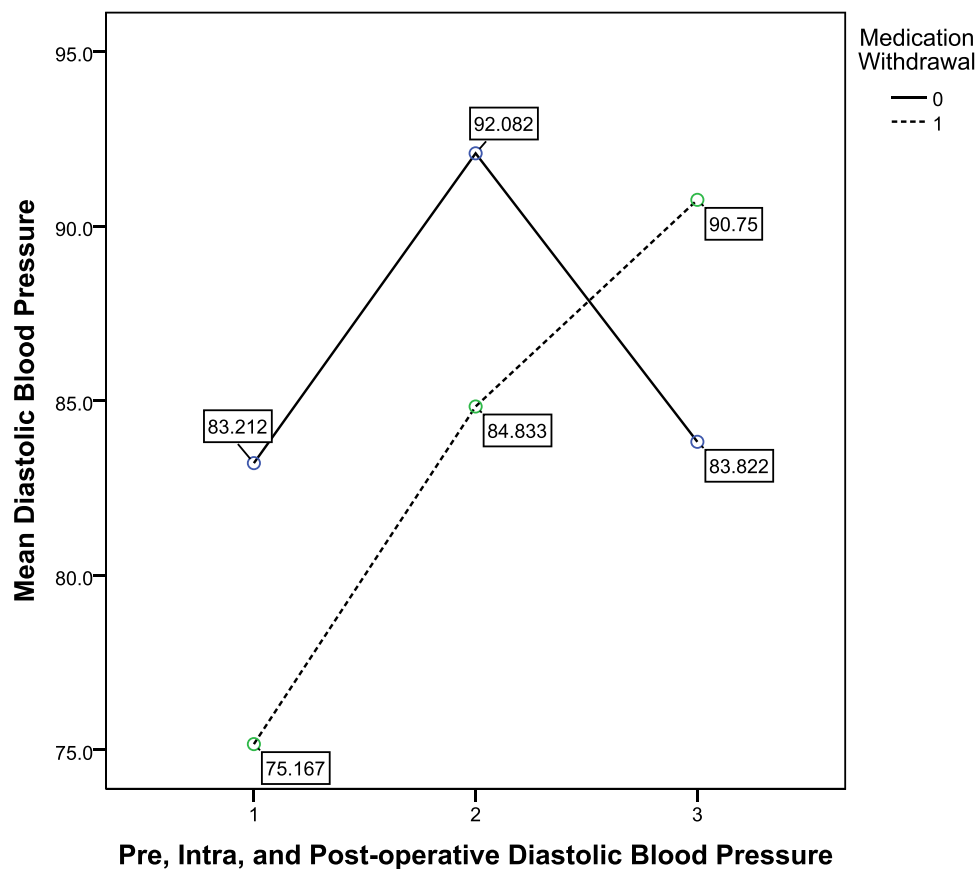


Figure 4 The mean DBP of patients with medication withdrawal compared to the rest of patients in population in pre, intra and postoperative period.

management of chronic medication. This study highlights that to optimize surgery outcomes, along with preoperative hypertension and medication management, intraoperative care and keeping a close monitoring of vasopressors and fluid administration are essential in perioperative hypertension prevention.

Disclosure

The authors report no conflicts of interest for this work.

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