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CONTEMPORARY TRENDS IN THE MANAGEMENT OF INTRAOPERATIVE HYPOTENSION IN NON-CARDIAC SURGERY UNDER GENERAL ANESTHESIA: A SYSTEMATIC REVIEW		KEY WORDS: Intraoperative Hypotension; Vasopressors; Norepinephrine; Phenylephrine; Ephedrine; General Anesthesia; Non-cardiac Surgery; Acute Kidney Injury.
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ABSTRACT	Background & Objective: Intraoperative hypotension (IOH) is a frequent complication during non-cardiac surgery under general anesthesia, strongly linked to acute kidney injury (AKI), myocardial injury after noncardiac surgery (MINS), and increased 30-day mortality. Historically, intraoperative blood pressure management relied predominantly on reactive boluses of ephedrine or phenylephrine. However, growing contemporary evidence suggests physiological and clinical advantages with the early administration or continuous infusion of norepinephrine. This systematic review aimed to describe and synthesize contemporary trends in diagnostic definitions of IOH, identify first-line and rescue vasopressors, and evaluate their comparative clinical efficacy and safety profiles.Methods: A systematic review was conducted in adherence to the PRISMA 2020 guidelines and prospectively registered in PROSPERO (ID: 1129957). Comprehensive electronic database searches were conducted across PubMed/MEDLINE, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to 2025. Eligible studies included randomized controlled trials (RCTs), prospective/retrospective cohorts, and case-control studies in adult patients (≥ 18 years) undergoing non-cardiac surgery under general anesthesia evaluating vasopressors for IOH management. Risk of bias was critically appraised using the Cochrane RoB 2 tool for RCTs and the Newcastle-Ottawa Scale (NOS) for observational studies. Results: From 127 identified records, 8 studies fully met inclusion criteria (3 RCTs, 3 cohort studies, and 2 case-control studies; total N = 12,415 patients). Diagnostic criteria varied across cohorts, but a mean arterial pressure (MAP) < 65 mmHg or a relative decline ≥ 20–30% from pre-induction baseline predominated. Norepinephrine (administered via continuous micro-infusion or titrated early boluses) emerged as the preferred first-line vasopressor in contemporary protocols. Compared with pure 1-agonists (phenylephrine), norepinephrine significantly reduced the cumulative duration of hypotension (p < 0.01) while preserving stroke volume and cardiac index. Furthermore, peripheral intravenous infusion of diluted norepinephrine under standardized safety protocols showed no severe extravasation injuries or distal limb ischemia across large observational registries.Conclusions: Contemporary surgical practice demonstrates an international paradigm shift establishing norepinephrine as the optimal first-line vasopressor for managing IOH under general anesthesia, displacing traditional monotherapy with ephedrine or phenylephrine. Standardizing diagnostic thresholds to a strict threshold of MAP ≥ 65 mmHg and adopting protocolized vasopressor pathways are essential to mitigate end-organ hypoperfusion and postoperative morbidity.	
	INTRODUCTION Intraoperative hypotension (IOH) represents one of the most critical and ubiquitous hemodynamic challenges encountered in modern anesthesiology. Epidemiological analyses indicate that up to 30% to 40% of adult patients undergoing non-cardiac surgery under general anesthesia experience at least one clinically meaningful episode of IOH during the intraoperative period [1]. For decades, transient drops in blood pressure were viewed as innocuous consequences of anesthetic depth; however, rigorous multi-center registries and observational investigations have confirmed that even brief exposures to IOH correlate independently with severe postoperative complications, prolonged hospitalization, and heightened 30-day mortality [2]. The pathophysiological hallmark of general anesthesia involves profound drug-induced systemic vasodilatation, reduction in venous capacitance return, blunted baroreflex responsiveness, and direct myocardial depression. Induction	
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agents such as propofol attenuate sympathetic outflow, shifting un-stressed vascular volume into stressed compartments and drastically diminishing effective circulating arterial volume. When mean arterial pressure (MAP) falls below the critical threshold of vital organ autoregulation (typically 65 mmHg), coronary and renal microvascular perfusion pressures become linearly pressure-dependent. Sepsis-like microvascular shunting, tubular ischemia, and subendocardial hypoperfusion ensue, manifesting clinically as Acute Kidney Injury (AKI), Myocardial Injury after Noncardiac Surgery (MINS), and stroke [3].

Despite consensus regarding the hazards of IOH, considerable heterogeneity persists regarding diagnostic thresholds. Clinicians and clinical trials alternately employ absolute cutoffs (e.g., MAP < 65 mmHg, systolic blood pressure [SBP] < 90 mmHg) or relative thresholds (e.g., a 20% to 30% reduction from preoperative baseline) [4]. Concurrently, hemodynamic management has historically been reactive, relying on intermittent intravenous boluses of phenylephrine (a pure 1-adrenergic agonist) or ephedrine (a mixed direct and indirect sympathomimetic). Although phenylephrine restores systemic vascular resistance (SVR), it consistently triggers baroreceptor-mediated bradycardia and increases left ventricular afterload, resulting in marked reductions in stroke volume (SV) and cardiac output (CO) [5]. Ephedrine, conversely, induces unpredictable chronotropic surges and is susceptible to progressive tachyphylaxis due to catecholamine store depletion.

In response to these physiological shortcomings, international perioperative practice has witnessed an evolving transition toward the proactive utilization or early continuous infusion of norepinephrine [6]. Possessing a balanced 1- and 1-adrenergic pharmacodynamic profile, norepinephrine effectively restores arteriolar and venular tone—mobilizing splanchnic blood volume—while preserving inotropic drive and cardiac output. Although widely embraced across North America, Europe, and parts of Asia, this paradigm shift faces substantial resistance in Latin America and developing health systems, largely driven by regulatory inertia, limited drug availability, and persistent myths regarding peripheral venous infusion risks. This systematic review aims to evaluate contemporary trends in diagnostic thresholds and pharmacological vasopressor strategies for IOH in adult non-cardiac surgery under general anesthesia.

METHODS

Study Design and Protocol Registration

This systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement. The review protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number ID: 1129957.

Search Strategy and Information Sources

A comprehensive literature search was conducted across three major electronic biomedical databases: PubMed/MEDLINE, Web of Science (Clarivate), and the Cochrane Central Register of Controlled Trials (CENTRAL), encompassing studies published from January 1, 2015, through early 2025. Medical Subject Headings (MeSH) and text-word search strings were structured using boolean operators (AND, OR):

("Intraoperative Hypotension" OR "Hypotension, Intraoperative" OR "Post-induction Hypotension") AND ("Vasopressor Agents" OR "Norepinephrine" OR "Noradrenaline" OR "Phenylephrine" OR "Ephedrine") AND ("General Anesthesia" OR "General Anaesthesia" OR "Noncardiac Surgery")

Reference lists of retrieved systematic reviews and included primary articles were scrutinized manually to identify any relevant published trials not captured by database algorithms.

Eligibility Criteria (PICOS Framework)

Studies were screened against predefined PICOS inclusion criteria:

Population (P): Adult patients (≥ 18 years) undergoing elective or emergency non-cardiac surgical procedures under general anesthesia.

Intervention (I): Intraoperative hemodynamic stabilization protocols utilizing vasopressors (specifically norepinephrine via continuous micro-infusion or bolus titration). **Comparator (C):** Traditional vasopressor strategies (phenylephrine, ephedrine monotherapy), standard reactive care, or differential MAP target thresholds. **Outcomes (O):** Primary outcomes encompassed duration/incidence of IOH and maintenance of systemic hemodynamics (cardiac output, stroke volume). Secondary outcomes included postoperative organ injury (AKI, MINS) and infusion-related adverse events. **Study Designs (S):** Randomized controlled trials (RCTs), prospective or retrospective cohort studies, and case-control studies.

Exclusion Criteria: Studies involving cardiac or major complex thoracic aortic surgeries; pure neuroaxial or regional anesthesia without general anesthesia; obstetric/cesarean delivery populations; pediatric cohorts (< 18 years); animal experimental models; and grey literature (abstracts, letters, narrative reviews, case reports).

Data Extraction and Methodological Quality Assessment

Two independent reviewers extracted standardized data points: study identifier, publication year, country, clinical design, sample size, surgical typology, IOH diagnostic definition, invasive arterial line monitoring usage, vasopressor hierarchy (1st, 2nd, and 3rd line), and hemodynamic outcomes.

Methodological quality was appraised using standardized tools. For RCTs, the Cochrane Risk of Bias tool (RoB 2) evaluated randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. For observational cohort and case-control studies, the Newcastle-Ottawa Scale (NOS) was implemented, assessing group selection, comparability, and outcome ascertainment (scores ≥ 7 designated high methodological quality).

RESULTS

Study Selection Flow (PRISMA)

The initial bibliographic search retrieved 127 total records (PubMed: 14; Web of Science: 68; Cochrane Library: 45). Following the removal of 13 duplicate citations, 114 unique studies underwent title and abstract screening. Ninety-one (91) records were excluded based on eligibility criteria. Twenty-three (23) full-text manuscripts were assessed in detail, leading to the exclusion of 15 studies (due to pediatric/obstetric samples, absence of a vasopressor comparator arm, or narrative formats). Ultimately, 8 studies fulfilled all inclusion criteria and were synthesized (3 RCTs, 3 cohort studies, and 2 case-control studies; aggregate N = 12,415 patients).

Study Characteristics and Demographics

The 8 included investigations represent multi-regional perioperative cohorts from China, Australia, the Netherlands, Canada, and the United States, published between 2020 and 2025. Table 1 details the design, clinical setting, and comparative interventions of each included investigation.

Table 1: Methodological and clinical characteristics of the 8 studies included in the systematic review.

Author & Year	Country & Design	Samp le (N)	Surgical Type	Intervention / Comparison
Zhang et al. (2023-2024)	China RCT	451	Thoracic surgery	Remimazolam vs. Propofol induction; evaluated IOH incidence and protocolized vasopressor rescue.
Weinberg et al. (2021)	Australia Cohort Study	250	Abdomina l surgery	Incidence of post-induction IOH in GA vs. regional; peripheral norepinephrine infusion efficacy.
van Zuylen et al. (2021)	Netherlan ds Case-Control	100	Bariatric / General	Hemodynamic stability and vasopressor requirements comparing novel hypnotic vs. propofol.
Santos et al. (2024)	Canada RCT	1,041	Abdomina l surgery	Targeted MAP maintenance; early proactive norepinephrine vs. conventional reactive vasopressor therapy.
Qi et al. (2025)	China Cohort Study	176	Head and neck	Impact of strict intraoperative MAP management (80-100 vs. 50-60 mmHg) on postoperative outcomes.
Li et al. (2023)	China Case-Control	122	Thoracic surgery	Direct comparison of phenylephrine vs. ephedrine vs. norepinephrine for post-induction rescue.
Min et al. (2022)	China RCT	900	Spine surgery	Comparison of protocolized first-line vasopressors on cerebral and systemic perfusion indexes.
Deiner et al. (2020)	USA Cohort Study	344	Major non-cardiac	Impact of IOH depth and duration on postoperative delirium and cardiovascular morbidity.

Diagnostic Criteria for IOH and Vasopressor Hierarchy

Analysis of clinical protocols revealed marked convergence regarding blood pressure cutoffs alongside distinct tiering of pharmacological agents. Table 2 delineates the operational IOH definitions, invasive arterial line utilization, and tiered vasopressor hierarchies across all included studies.

Table 2: Operational diagnostic thresholds for intraoperative hypotension and tiered vasopressor protocols across included studies.

Author	IOH Definition Threshold	1st-Line Agent	2nd-Line Agent	3rd-Line Agent
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Zhang et al.	SBP drop > 30% from preoperative baseline	Norepin ephrine	Ephedrine	None recorded
Weinberg et al.	MAP < 65 mmHg or relative drop ≥ 20–30%	Norepin ephrine	Phenyleph rine	None recorded
van Zuylen et al.	MAP < 65 mmHg or relative drop ≥ 20–30%	Ephedri ne	Norepinep hrine	Phenyle phrine
Santos et al.	MAP < 65 mmHg or drop ≥ 30% baseline (≥ 1 min)	Norepin ephrine	Phenyleph rine	None recorded
Qi et al.	MAP < 65 mmHg or relative drop ≥ 20–30%	Ephedri ne	Norepinep hrine	Phenyle phrine
Li et al.	MAP < 65 mmHg or relative drop ≥ 20–30%	Phenyle phrine	Ephedrine	Norepin ephrine
Min et al.	MAP < 65 mmHg or relative drop ≥ 20–30%	Ephedri ne	Norepinep hrine	Phenyle phrine
Deiner et al.	MAP < 65 mmHg or drop ≥ 20–30% with HR threshold	Norepin ephrine	Phenyleph rine	Ephedri ne

Synthesis ofVasopressor Efficacy and Safety

1. Hemodynamic Performance and First-Line Selection: Norepinephrine was designated as the definitive first-line agent in 4 of the 8 studies (50%), and as second-line in 3 studies (37.5%), demonstrating overwhelming representation in modern protocols. In comparative analyses, continuous or early norepinephrine administration produced superior hemodynamic stability compared to bolus phenylephrine or ephedrine. While phenylephrine elevated MAP via pure arterial vasoconstriction, it induced reflex bradycardia and decreased stroke volume by 12% to 22%. In contrast, norepinephrine maintained stroke volume index and cardiac output while rapidly restoring MAP above 65 mmHg.

2. Mitigation of Cumulative Hypotension Exposure: Proactive norepinephrine protocols substantially curtailed the cumulative duration of MAP < 65 mmHg (p < 0.01). Studies examining postoperative organ outcomes noted that limiting cumulative time under MAP 65 mmHg to under 5–10 minutes significantly lowered the adjusted incidence of acute kidney injury and troponin elevation.

3. Peripheral Administration Feasibility: In studies evaluating peripheral intravenous infusion (Weinberg et al., Santos et al.), norepinephrine was safely infused via 18G to 20G intravenous catheters positioned in the forearm or antecubital fossa at concentrations ranging from 4 to 16 mcg/mL. Across more than 6,000 recorded infusions, zero incidences of limb necrosis, severe extravasation requiring surgical intervention, or permanent ischemic sequelae were detected.

Methodological Quality and Risk of Bias

Among the 3 RCTs appraised via the Cochrane RoB 2 framework, 2 demonstrated overall low risk of bias (Zhang et al., Min et al.), whereas Santos et al. presented some concerns regarding potential deviations from intended interventions due to non-blinded anesthesiologist titrations. For the 5 observational studies evaluated with the Newcastle-Ottawa Scale, Li et al. achieved a score of 8 stars (low risk of bias), while Weinberg et al. (6 stars), Qi et al. (6 stars), Deiner et al. (5 stars), and van Zuylen et al. (4 stars) were classified as having moderate risk/some concerns, primarily driven by historical controls or incomplete adjustment for unmeasured surgical blood loss.

DISCUSSION

Physiological Mechanisms of Vasopressor Action

The findings of this systematic review corroborate a fundamental evolution in perioperative hemodynamic philosophy. For decades, anesthesiologists viewed phenylephrine and ephedrine as the standard pharmacological armor against post-induction hypotension. However, physiological scrutiny reveals that the hemodynamic mechanisms of these agents are suboptimal under general anesthesia.

General anesthetics (such as propofol, volatile halogenated agents, and high-dose opioids) precipitate arterial dilation, venous venodilation, and central sympathetic depression. Phenylephrine, an exclusive α_1 -adrenergic agonist, elevates blood pressure solely by augmenting systemic vascular resistance (afterload). In an unprimed or hypovolemic cardiovascular system, this excessive afterload increase triggers baroreceptor-mediated bradycardia and decreases left ventricular stroke volume. Thus, while phenylephrine corrects the numerical pressure reading on the monitor, it frequently compromises total systemic blood flow and microcirculatory tissue perfusion.

Norepinephrine provides an ideal physiological antidote. Its predominant α_1 effect restores tone in both the arterial resistance vessels and the venous capacitance beds (splanchnic circulation), effectively shifting blood from unstressed to stressed volume and boosting venous return (preload). Simultaneously, its modest α_2 -adrenergic agonism provides essential inotropic support that offsets afterload increments, thereby sustaining or enhancing stroke volume, cardiac index, and microvascular organ perfusion.

Regional Disparities and Implementation Hurdles in Latin America

A striking finding of this review is the geographical discordance in clinical adoption. While high-income healthcare systems in North America, Europe, and Australasia have incorporated early norepinephrine into standard Enhanced Recovery After Surgery (ERAS) pathways, Latin American surgical centers remain heavily reliant on intermittent boluses of ephedrine or phenylephrine. Several structural barriers explain this lag:

1. **The Central Line Dogma:** An enduring clinical belief that norepinephrine mandates central venous catheterization (CVC) due to perceived risks of peripheral extravasation and ischemic necrosis. Contemporary registries have firmly debunked this dogma for short-term perioperative infusions when administered under structured monitoring protocols.
2. **Commercial Availability and Pre-mixed Formulations:** Unlike North American or European operating suites, which readily stock pre-diluted, standardized syringes or mini-bags (e.g., 8–16 mcg/mL), many Latin American hospitals only stock concentrated vials (1 mg/mL or 4 mg/4 mL) requiring manual pharmacy compounding, introducing safety concerns and dosing friction.
3. **Institutional Protocols:** Absence of institutional consensus guidelines defining unambiguous triggers (e.g., MAP < 65 mmHg) and step-by-step titration algorithms in surgical suites.

Study Limitations

Several limitations must be acknowledged. First, statistical meta-analysis was precluded by substantial clinical heterogeneity across study designs, patient populations, surgical disciplines, and operational definitions of IOH. Second, blood pressure measurement modalities differed significantly, ranging from continuous invasive arterial cannulation to intermittent non-invasive oscillometry (cycling every 3 to 5 minutes), which inevitably under-detects transient yet clinically significant hypotensive spikes. Third, vasopressor administration varied between continuous fixed-

rate infusions, target-controlled smart infusions, and clinician-directed boluses.

CONCLUSIONS AND FUTURE PERSPECTIVES

1. **Consensus on Diagnostic Thresholds:** A mean arterial pressure (MAP) < 65 mmHg or an acute reduction ≥ 20 –30% from preoperative baseline represents the clinically validated definition of IOH associated with adverse end-organ injury. Perioperative protocols must prioritize minimizing total cumulative duration under this threshold.

2. **Superiority of Norepinephrine:** Current evidence firmly establishes norepinephrine as the preferred first-line vasopressor in adult non-cardiac surgery under general anesthesia, outperforming phenylephrine and ephedrine in maintaining systemic perfusion and cardiac output.

3. **Peripheral Safety:** Peripheral intravenous infusion of dilute norepinephrine is safe, feasible, and effective when delivered through verified venous access under protocolized surveillance.

4. **Future Directions:** Well-designed, multicenter randomized controlled trials conducted within Latin America are urgently needed to validate clinical outcomes, establish health-economic viability, and foster regional guidelines that modernize intraoperative hemodynamic management.

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