ORIGINAL CLINICAL RESEARCH REPORT

Risk of Major Complications After Perioperative Norepinephrine Infusion Through Peripheral Intravenous Lines in a Multicenter Study

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BACKGROUND: Continuous infusions of norepinephrine to treat perioperative hypotension are typically administered through a central venous line rather than a peripheral venous catheter to avoid the risk of localized tissue necrosis in case of drug extravasation. There is limited literature to estimate the risk of skin necrosis when peripheral norepinephrine is used to counteract anesthesia-associated hypotension in elective surgical cases. This study aimed to estimate the rate of occurrence of drug-related adverse effects, including skin necrosis requiring surgical management when norepinephrine peripheral extravasation occurs.

METHODS: This retrospective cohort study used the perioperative databases of the University Hospitals in Amsterdam and Utrecht, the Netherlands, to identify surgical patients who received norepinephrine peripheral intravenous infusions (20 μg/mL) between 2012 and 2016. The risk of drug-related adverse effects, including skin necrosis, was estimated. Particular care was taken to identify patients who needed plastic surgical or medical attention secondary to extravasation of dilute, peripheral norepinephrine.

RESULTS: A total of 14,385 patients who received norepinephrine peripheral continuous infusions were identified. Drug extravasation was observed in 5 patients (5/14,385 = 0.035%). The 95% confidence interval (CI) for infusion extravasation was 0.011%–0.081%, indicating an estimated risk of 1–8 events per every 10,000 patients. There were zero related complications requiring surgical or medical intervention, resulting in a 95% CI of 0%–0.021% and indicating a risk of approximately 0–2 events per 10,000 patients.

CONCLUSIONS: In the current database analysis, no significant association was found between the use of peripheral intravenous norepinephrine infusions and adverse events. (Anesth Analg 2020;131:1060–5)

KEY POINTS

- **Question:** Is the use of peripheral diluted intravenous norepinephrine during elective surgery under general anesthesia associated with skin necrosis or drug extravasation requiring an intervention?
- **Findings:** The incidence of skin necrosis and drug extravasation was 0% and 0.035%, respectively, with the upper bounds of the 95% confidence intervals (CIs) for skin necrosis and drug extravasation of 0.0271% and 0.021%, respectively.
- **Meanings:** In the current database analysis, no association was found between the use of peripheral intravenous norepinephrine infusions used to counteract anesthesia-induced hypotension during elective surgical cases and adverse events.

GLOSSARY

ADE = adverse drug event; **AMC** = Academisch Medisch Centrum; **ASA** = American Society of Anesthesiology; **CI** = confidence interval; **PACU** = postanesthesia care unit; **QA** = quality assessment; **SD** = standard deviation; **SQUIRE** = Standards for Quality Improvement Reporting Excellence; **TIVA** = total intravenous anesthesia; **UMC** = Universitair Medisch Centrum

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Intraoperative hypotension occurs during general anesthesia with an incidence varying from 5% to 99%[1] and is commonly treated with phenylephrine, a short-acting α_1-adrenoceptor agonist that causes vasoconstriction[2] and an accompanied decrease in cardiac output.[2,3] On the other hand, norepinephrine, by virtue of its α_1- and β_1-adrenoreceptor agonist activity, increases systolic, diastolic, and pulse pressure and has a positive net impact on cardiac output.[4,5]

RATIONALE

While commonly used in perioperative anesthesia care in Northern Europe,[6] peripherally administered norepinephrine is not commonly used in the US anesthetic practice due to concerns that drug extravasation could result in significant arterial and venous constriction with associated permanent skin damage.[7,8] Safety data related to its peripheral venous use are lacking. The concerns regarding norepinephrine's potential tissue ischemic complications are justified by its profound arterial and venous constriction properties. Experimental studies looking at norepinephrine's vasoconstrictive properties conducted in ex vivo human radial arteries have found that norepinephrine is 7 times more potent than phenylephrine.[9] Moreover, the in vivo relative vasoconstrictive potency of norepinephrine is 76% higher than phenylephrine in human saphenous veins.[10]

STUDY OBJECTIVE

The aim of this retrospective observational study was to estimate the risk of skin damage requiring medical or surgical intervention after accidental dilute norepinephrine extravasation (20 µg/mL) through peripheral intravenous lines.

METHODS

Analysis and interpretation of the present study followed the Standards for Quality Improvement Reporting Excellence (SQUIRE) guidelines.[11] The research protocol and prespecified analysis plan were presented, approved, and registered with the departmental Anesthesia Clinical Research Committee before data extraction and analysis.

Context

This retrospective study analyzed 14,385 patients who received peripheral intravenous norepinephrine infusion while undergoing surgery between January 2012 and January 2016 at the Academisch Medisch Centrum (AMC) in Amsterdam and the Universitair Medisch Centrum (UMC) in Utrecht, the Netherlands, together performing approximately 45,000 surgeries per year. Norepinephrine peripheral infusions are commonly handled by the departments of anesthesiology at these 2 medical centers.

Written informed consent requirement was waived by the local Institutional Review Boards (for AMC: waiver W16_357, issued December 1, 2016; for UMC: waiver 16/704-C, issued December 6, 2016) due to the retrospective nature of the study.

Measures

Both hospitals participating in this study had introduced electronic health records for the perioperative phase several years before the study was initiated, with mature and stable documentation processes. These electronic health record data have previously been used for multicenter clinical research.[12,13] We first queried the electronic health record databases of both hospitals to identify patients who had received norepinephrine via a peripheral infusion line perioperatively. The specific fields we searched for included "general," "anesthesia," and "norepinephrine," to identify possible general anesthetic procedures where norepinephrine was used. Query parameters included all adult patients undergoing general anesthesia from January 2012 to January 2016. In addition, at these 2 institutions, each complication/event is entered in a secure hospital database by anesthesiologists, nurse anesthetists, and postanesthesia care nurses and linked, but the complication/event is not part of the electronic health record for quality assessment (QA) and further evaluation.

Outcome

The primary outcome chosen here was an adverse drug event (ADE) linked to peripheral norepinephrine administration, specifically focusing on extravasation associated with tissue injury requiring medical or surgical intervention. We queried this QA database to obtain ADEs. As before, free-text queries for relevant phrases included "norepinephrine," "drug," and "extravasation" to identify possible drug extravasation related to norepinephrine.

For detecting medical and surgical treatments related to a possible norepinephrine peripheral infusion extravasation, the terms "phentolamine, plastic surgery, skin, and graft" were queried; because these medical and surgical interventions could be indirect measures of norepinephrine extravasation in the event, there was a missed or unreported extravasation injury through our ADE database. The flowchart for patient selection is presented in the Figure.

Standard norepinephrine peripheral infusions used at these 2 institutions are constituted at a concentration of 0.002% in normal saline so that the final dilution is 20 µg/mL. When a norepinephrine infusion is deemed clinically useful, an initial infusion dose of 0.01–0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ is commonly started and then titrated as per desired targeted blood pressure. The infusion dose range in patients included here typically varied between 0.01 and 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with the resulting total volume per hour approximating 2–15 mL/h.

When peripheral extravasation of norepinephrine occurred, it was the hospitals' current practice to stop the infusion, observe the site of extravasation for several hours postoperatively, and consult plastic surgery for additional recommendations, if necessary. The diagnosis of extravasation is made by the faculty anesthesiologist who documents the episode in the anesthetic record and is required to file an adverse event report. In the event that the nurse anesthetists

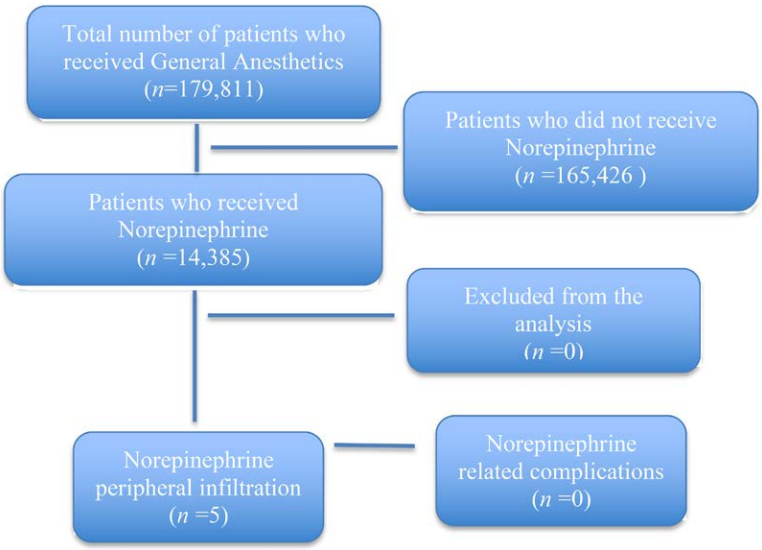

Figure. Patient selection flowchart of patients receiving norepinephrine peripheral infusion during general anesthesia.

Table 1. Grades of Infusion Site Extravasation According to Common Terminology Criteria for Adverse Events[18]

Adverse Event	Infusion-Related Reaction
Grade 1	Intact skin
Grade 2	Blanched skin, erythema
Grade 3	Necrosis or ulceration causing severe tissue damage; indicates surgical intervention
Grade 4	Life-threatening consequences; indicates immediate intervention
Grade 5	Death

or the postanesthesia care unit (PACU) nurse notes any drug extravasation, the faculty anesthesiologist is notified, diagnosis is made, and the adverse event report is filed by any of the anesthesia providers involved in the patient care intra- or postoperatively.

Score

Once the reviewers identified a norepinephrine extravasation event, if no signs of irritation or only some skin erythema were reported, a grade of 1 and 2 was assigned, respectively. If skin necrosis or life-threatening injuries were reported, the reviewers assigned a grade of 3 and 4, respectively, to the extravasation injury as previously validated[14–17] (Table 1).

Moreover, for these patients who had norepinephrine extravasation, we reviewed patient characteristics such as age, sex, weight, height, American Society of Anesthesiology (ASA) physical status score, emergent nature of surgery, comorbidities, size of the intravenous catheter placed, site of catheter placement, duration, and total dose of norepinephrine administration. Our data collection began at the time of norepinephrine infusion and ended at discharge from the hospital.

Statistical Analysis

The frequency of norepinephrine-related complications and the patients experiencing infusion extravasation was calculated and expressed as rates per 10,000 patients. Exact 2-sided 95% confidence intervals (CIs) were calculated using the Clopper-Pearson method. If the outcome event did not occur in a sample with n subjects, we additionally used the "rule of three" to estimate a 95% CI as 0–3/n, for the rate of occurrences in the population, as a sensitivity analysis.[19]

Patient characteristics for infusion extravasation cases were summarized by peripheral intravenous infusion site. All continuous patient characteristics were assessed for normality via histograms and qq-plots. Approximately normally distributed data are presented as mean ± standard deviation (SD), and nonparametric data are presented as median (25–75th percentile). Categorical patient characteristics are reported as frequency counts and percentages.

All the analyses were performed using SAS software (version 9.4; SAS Institute Inc, Cary, NC).

RESULTS

During the study period, 179,811 patients underwent surgery, of whom 14,385 (8%) received intravenous peripheral norepinephrine infusions during the study period. Of those 14,385 patients who received norepinephrine infusions, 5 (0.035%) experienced extravasation. The 95% Clopper-Pearson CI for infusion extravasation was 1–8 events per every 10,000 patients (95% CI, 0.011%–0.081%). There were zero related complications, with a corresponding 95% CI indicating an estimated risk of 0–3 events per 10,000 patients (95% CI, 0%–0.0271%). For the sensitivity analysis performed by using the "rule of 3," we found that the estimated risk rate for related complications was 0–2 events per 10,000 patients (95% CI, 0%–0.021%).

One peripheral norepinephrine infusion was on the lower extremities during an ophthalmology surgical case, while all the other infusions were started in

Table 2. Characteristics of Patients With Norepinephrine Extravasations During Surgery

Extravasated Peripheral Norepinephrine Infusions	Overall (n = 5)
Demographics	
Age, mean ± SD	66.2 ± 18.4
Female, n (%)	3 (60)
Body mass index, mean ± SD	24.2 ± 3.8
Comorbidities, n (%)	
Cancer	2 (40)
Coronary heart disease	1 (20)
Peripheral vascular disease	1 (20)
None	1 (20)
ASA physical status, n (%)	
I	1 (20)
II	2 (40)
III	2 (40)
Size of IV line, median (Q1, Q3)	18 (18, 18)
Duration of administration (min), median (Q1, Q3)	20 (20, 25)
Total dose administered (μg), median (Q1, Q3)	40 (35, 50)
Total dose administered (mL/h), median (Q1, Q3)	6 (6, 7)
Peripheral IV infusion site, n (%)	
Antecubital	3 (60)
Hand	1 (20)
Lower extremities	1 (20)

Abbreviations: ASA, American Society of Anesthesiology; IV, intravenous; Q1, lower quartile; Q3, upper quartile; SD, standard deviation.

the upper extremities (Table 2). The norepinephrine infusions that extravasated were in an administered dose range of 0.02–0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and the total median norepinephrine infusion duration across these 5 patients was 20 minutes with interquartile range of 20–25 minutes (Table 2). The median (interquartile range) norepinephrine dose administered was 40 μg (35–50), the total estimated norepinephrine dose that extravasated ranged between 33 and 80 μg, and consisted of a volume ranging between 1.67 and 4 mL.

None of the patients were given a complication severity score >1, indicating that all complications were minor and resolved without any medical and surgical intervention or permanent skin damage. Two patients had cancer as comorbidity, 1 patient suffered from peripheral vascular disease, 1 patient had diagnosed coronary artery disease, and 1 had no comorbidities (Table 2).

DISCUSSION

In the current study, we estimated the risk of skin damage requiring medical or surgical intervention after accidental dilute norepinephrine extravasation through peripheral intravenous lines during surgery. The estimated risk was 1–8 events per every 10,000 patients. No case of peripheral extravasation required surgical or pharmacological intervention, and no harm was caused to upper or lower extremities.

Our data suggest that norepinephrine peripheral intravenous infusion, in a diluted solution of 20 μg/mL, is rarely associated with adverse events related to extravasation when used to counteract hypotension associated with general anesthesia. Safety and risk data related to using higher norepinephrine concentrations through a peripheral infusion line are lacking.

Even though no patients in the current study experienced short- or long-term complications related to norepinephrine extravasation, when peripheral norepinephrine extravasation occurs, damage can range from skin damage to limb amputation.[7,8,20,21] Severe damage seems to occur most often in patients with several comorbidities and on critical care units, while treating circulatory shock of various etiologies using high concentration infusions. However, in a prospective study investigating adverse events after peripheral vasopressor infusions in 50 patients diagnosed with septic, cardiogenic, hypovolemic, or hemorrhagic shock who received norepinephrine, 3 patients (6%) had extravasation of norepinephrine (2 in their hand, 1 in the antecubital fossa) with only minor complications not requiring any intervention.[22] Along the same line, Lewis et al[15] in an intensive care unit setting reported a 4% incidence of peripheral vasopressor extravasation that was similar whether phenylephrine (20–400 μg/mL) or norepinephrine (16–64 μg/mL) infusions were used. Four patients received norepinephrine and 4 patients received phenylephrine at the time of extravasation, and none of them experienced complications that required medical or surgical treatment.[15]

The incidence of peripheral vasopressor extravasation in intensive care unit seems to be higher compared to our series even though the incidence of tissue damage is low, particularly with proper adherence to safety protocols. Cardenas-Garcia et al[23] implemented an extensive protocol for peripheral administration of vasopressors that included ultrasound-guided insertion of peripheral vascular catheters in a vein >4 mm, assessment of the peripheral vascular access site every 2 hours, maximum of 72 hours duration of infusion per site, and a protocol for the rapid administration of antidotes in the event of an extravasation.[23] In fact, these investigators reported a norepinephrine extravasation rate of 3% (16/506), all of which were managed with local phentolamine injection and observed no major complications in a medical intensive care unit setting. In our series, local phentolamine was never given since the clinicians deemed it not necessary; nevertheless, we observed no damage requiring medical or surgical intervention in our patients. Delgado et al[24] adhered to a protocol which mandated 18-gauge peripheral vascular catheters proximal to the wrist, a limit for the maximum vasopressor concentration and infusion rate, and nursing education of the institution's extravasation protocol. Similar to previous investigators, they reported only a minor complication in 1 patient who did not require further intervention.[24] This suggests that the risk for extravasation injury is low, and the damage related to it can be further reduced by implementation of a strict protocol for the use of peripheral vasopressors.

Despite the large discrepancy in risk between our population and the ones from intensive care unit setting, we hypothesize that the difference in the incidence of extravasation events is that in elective surgical cases, anesthesiologists can provide direct hypervigilant surveillance of the patient position and the infusions site more regularly, while it may be more difficult to adhere to these practices in emergent surgical cases and in intensive care unit settings.

We hypothesize 3 reasons extravasated norepinephrine did not cause limb damage in our patient population: first, the volume extravasated was relatively small since the complication was detected within minutes and therefore mechanical tension was limited and failed to compromise the microcirculation and cause tissue hypoxia; second, this study was performed on perioperative patients, who rarely experience massive circulatory shock or limb underperfusion frequently seen on intensive care units where the extravasated substance could be reabsorbed relatively fast; and third, all patients' extravasations happened during elective surgical cases where routine clinical practice was followed according to internal hospital policies. We are not able to draw any conclusions regarding extravasations that would happen under emergent surgical conditions since all observed events happened in elective cases.

The current analysis has several limitations. First of all, we relied on a voluntary self-report system where the clinicians, nurse anesthetists, and PACU nurses enter the information in the database when peripheral norepinephrine extravasation occurs. Even though self-reported complications are known to be subject to selection bias due to their voluntary nature[25] and only a fraction of events tend to be captured, we expect that only a minority of events went unreported due to the robust adverse event report system in place at the 2 institutions. Second, physicians tend to underreport near misses and report more harm incidents.[26] It is possible that, while our analysis might have caught drug extravasations causing skin damage, any near-miss or extravasation that, at that time, was not considered relevant based on the physician's discretion, could have gone unnoted and therefore underestimated. However, because nurses at our institutions are actively involved in documenting untoward incidents and they are known to report a broader spectrum of adverse events relative to physicians,[27] we hypothesize that, if underreported events happened, they were limited in number. Third, because the incidence of the extravasation is low, it is hard to define risk factors related to general surgical practices that might differ among different hospitals. Risk factors may include the infusion sites being covered under the drapes or the accessibility of the extravasation site when the operating room table is turned 180° away from the anesthesiologist, as is done in a variety of surgical cases. Fourth, the use of total intravenous anesthesia (TIVA) in Europe has been widespread and it is possible that patients' infusion sites receiving TIVA are checked more often than other patients receiving balanced or inhalational anesthesia.[28,29] More data are needed before drawing any conclusions as to what type of anesthetic may trigger more checks for drugs extravasation. Fifth, the analysis comes from 2 academic European centers with a different care model compared to the United States. The academic centers in Amsterdam and Utrecht have been using norepinephrine peripheral infusions for a decade, and therefore, the low incidence of adverse events might be related to the clinical daily experience and practices that have been part of the hospital routine and been implemented over the course of several years. It is, therefore, challenging to generalize our results to US hospitals and other nonacademic European centers without caution. Sixth, the time from extravasation to detection in our settings was remarkably brief and with low volume of extravasate; it is unclear how consistently other anesthesia practices could duplicate this level of vigilance in the operating theater. In addition, these results may not be applicable to patients who receive peripheral norepinephrine infusion for longer periods of time during elective or nonelective cases. Seventh, we are aware that, in other countries, it is far more common to use peripheral phenylephrine or dopamine instead of norepinephrine. We do not have any data comparing the incidence of extravasation of these 2 drugs with that of norepinephrine and that might represent an additional limitation to the current research. However, peripheral vasopressor extravasations are also rare when looking at years 1970–2014 from the Anesthesia Closed Claims database: while no claims were identified with the use of norepinephrine, probably because the rarity of its peripheral use, 17/7924 claims were associated to soft tissue damage from 1 or multiple combined peripheral vasopressors during procedures or surgery involving dopamine (n = 6/17), calcium (n = 5/17), phenylephrine (n = 2/17), calcium plus phenylephrine (n = 1/17), epinephrine (n = 1/17), dobutamine (n = 1/17), and "multiple" vasopressors (n = 1/17); many of these extravasations were difficult to detect since they occurred with tucked arms. Current infusion pumps may facilitate to detecting obstructions in flow through more sensitive alarms (Karen Domino, University of Washington, personal communication, September 10, 2019). Finally, our analysis is constrained by the usual limitations of large retrospective observational studies: the inability to validate the reported observations, the unknown accuracy of clinical assessments, the lack of understanding of treatments that were administered at the time extravasation occurred, and the role of other factors in preventing undesirable outcomes.

In conclusion, when counteracting anesthesia-induced hypotension during surgical cases at 2 European academic centers, no significant association was found

between the use of peripheral dilute norepinephrine infusions and adverse events related to extravasation.

DISCLOSURES

Name: Carlo Pancaro, MD.
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