Original Research

Comparison of Hemodynamic Responses to Administration of Vasopressin and Norepinephrine Under General Anesthesia: A Systematic Review and Meta-analysis of Randomized Controlled Trials with Trial Sequential Analysis

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Objective: The authors performed a meta-analysis to determine if vasopressin improves hypotension more than norepinephrine under general anesthesia.

Design: Meta-analysis.

Setting: Operating room.

Patients: Patients who underwent surgery, with general anesthesia.

Interventions: Administration of vasopressin or norepinephrine in order to increase blood pressure.

Measurements and Main Results: The primary outcome of this study was to determine if vasopressin increased mean blood pressure more effectively compared with norepinephrine for patients under general anesthesia. The secondary outcome was to see if vasopressin increased heart rate (HR), central venous pressure (CVP), cardiac output (CO), and cardiac index (CI) more significantly compared with norepinephrine under general anesthesia. The authors calculated the weighted mean difference, with 95% confidence interval (CI) using the random-effects model, and calculated the required information size (RIS) by performing trial sequential analysis (TSA).

The authors selected 6 studies for analysis. Vasopressin did not improve hypotension compared with norepinephrine under general anesthesia. (weighted mean difference = −0.84 mmHg, 95% CI: −5.90 to 4.23, p = 0.75, Cochran Q = 24.6, I² = 84%) In TSA, only 35.5% of RIS was achieved. Similarly, vasopressin and norepinephrine were not significantly different in terms of HR, CVP, CO, and CI. In TSA, only 23.7% of the RIS was reached for HR but RIS was almost achieved for CVP and CO.

Conclusions: Vasopressin did not improve hypotension compared with norepinephrine under general anesthesia. The RIS was not reached in TSA, and Grading of Recommendations Assessment, Development and Evaluation is very low. Therefore, further research is needed to reach more robust conclusions.

Key Words: Vasopressin; norepinephrine; hypotension; heart rate

INTRAOPERATIVE HYPOTENSION causes inadequate tissue perfusion, which may lead to multiple organ dysfunction and death during surgery.1,2 When intraoperative
hypotension cannot be avoided, prompt treatment must be instituted.\textsuperscript{3,4}

Norepinephrine has been used to treat intraoperative hypotension, and its use has been studied extensively.\textsuperscript{5-7} Norepinephrine regulates blood pressure and heart rate via activation of α- and β-adrenergic receptors. However, norepinephrine has well-known side effects, such as increased myocardial oxygen consumption and arrhythmias, which may ultimately worsen prognosis despite positive hemodynamic effects.\textsuperscript{8,9}

Vasopressin has been used as a substitute for norepinephrine. Vasopressin acts on vasopressin V1 receptors expressed on vascular smooth muscle cells to cause peripheral vasoconstriction, which leads to increased blood pressure. Vasopressin also increases blood pressure by acting on vasopressin V2 receptors expressed in the renal tubules, leading to tubular reabsorption of water.\textsuperscript{10,11} Vasopressin has a potential vasoconstrictive effect and can increase cardiac afterload. It also can improve left ventricular function, and increase cardiac output and coronary blood flow by increasing coronary perfusion pressure.\textsuperscript{12} Some studies have indicated that vasopressin can be used to effectively treat hypotension intraoperatively, especially in patients unresponsive to norepinephrine, phenylephrine, and other catecholamine-based vasoactive drugs.\textsuperscript{13,14}

Several anecdotal reports have suggested that vasopressin was preferable to norepinephrine for treating intraoperative hypotension during general anesthesia.\textsuperscript{15,16} In a 2003 study by Boccara et al., ephedrine-unresponsive hypotensive patients, who were having elective carotid endarterectomy, were randomly administered intravenous vasopressin or norepinephrine. They concluded that vasopressin was more effective for rapidly maintaining normal systolic arterial blood pressure than norepinephrine.\textsuperscript{16} On the other hand, it has been reported that vasopressin exhibits the same pressor action as norepinephrine.\textsuperscript{17,18} Yimin et al. reported that there were no significant differences in changes in mean blood pressure (MBP) or heart rate between vasopressin and norepinephrine after administration of either vasopressin or norepinephrine to patients undergoing coronary artery bypass grafting surgery.\textsuperscript{18} Thus, it is still unclear as to whether vasopressin or norepinephrine is superior in maintaining circulatory dynamics under general anesthesia.

In this study, the authors performed a systematic review and meta-analysis of randomized controlled trials (RCTs) that compared MBP between vasopressin and norepinephrine during general anesthesia. The authors also compared heart rate (HR), central venous pressure (CVP), cardiac output (CO), and cardiac index (CI) after administration of either vasopressin or norepinephrine under general anesthesia. In addition, the authors performed a subgroup analysis that separated studies using vasopressin and terlipressin. In order to analyze the effects of vasopressin and norepinephrine depending on the type of surgery, a separate subgroup analysis was performed for studies that included surgery with coronary artery bypass grafting (CABG) and studies with other surgeries.

**Methods**

This article was prepared in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.\textsuperscript{19} Before commencing this study, the authors established a systematic search strategy and determined the inclusion and exclusion criteria to be used. The study protocol was registered with the University Hospital Medical Information Network (registration number: UMIN000036089; Principal Investigator: H. Hoshijima; registration date: 5 August 2019).

**Search Strategy**

The authors conducted a comprehensive search of the literature using PubMed, the Cochrane Central Register of Controlled Trials, and EMBASE. The authors’ strategy combined free text and Medical Subject Headings (MeSH) terms, and was devised for the PubMed search as follows: (“vasopressins”[MeSH Terms] OR “vasopressins”[All Fields] OR “vasopressin”[All Fields]) AND (“norepinephrine”[MeSH Terms] OR “norepinephrine”[All Fields])) AND (“hemodynamic”[MeSH Terms] OR “hemodynamics”[MeSH Terms] OR “hemodynamic”[All Fields] OR “hemodynamics”[All Fields] OR “hemodynamic”[All Fields] OR “hemodynamics”[All Fields]) AND responses[All Fields]). In addition, the authors manually searched references listed in reports and reviews returned by the search. The authors also included terlipressin, an analog of vasopressin. No restrictions on the language of the article or publication type were imposed, and the most recent search was performed in January 2020.

**Inclusion and Exclusion Criteria**

The authors used the following PICO (Patient/Problem/Population; Intervention/Exposure; Comparison and Outcomes) criteria for this meta-analysis:

- **Population:** an adult patient undergoing surgery under general anesthesia;
- **Interventions:** vasopressin or terlipressin used as a vasopressor;
- **Comparisons:** norepinephrine used as a vasopressor;
- **Outcomes:** analyze the change in MBP before and after using vasopressors.

The primary outcome was whether vasopressin improved MBP more effectively compared with norepinephrine under general anesthesia. The secondary outcome were the changes in HR, CVP, CO, and CI induced by vasopressin and norepinephrine under general anesthesia. In addition, the authors performed a subgroup analysis that separated studies using vasopressin and terlipressin. In order to analyze the effects of vasopressin and norepinephrine depending on the type of surgery, a subgroup analysis was performed for studies that included surgery for CABG and studies with other surgeries.
Selection of Included Studies

Two authors (H.H. and T.S.) independently screened the titles and abstracts of studies from the search results for potentially effective studies. The authors independently assessed the selections of each of the authors to determine if the extracted articles were suitable for use in the study. In addition, disagreements over the assignment of article values or analysis used in the study were resolved through discussion. Where it was possible that the results of a report had been duplicated and published, only those reports that had analyzed the latest data were added to this study. If missing data or inconsistencies were found in the extracted articles, the authors contacted the author directly to obtain the missing data and to resolve the inconsistencies.

Critical Appraisal of Study Quality

Risk of Bias Assessment and Quality of Evidence Assessment

The authors evaluated the risk of bias to assess the limitations of the study with reference to the Cochrane Handbook (Supplemental Material 1). The authors assessed the quality of evidence of the main outcomes using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Supplemental Material 2).

Statistical Analysis

Statistical analysis was performed using Review Manager software (ver. 5.2, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). The authors used DerSimonian and Laird random effects models for statistical processing. Pooled differences in MBP, HR, and CVP between vasopressin and norepinephrine administration were expressed as the weighted mean difference (WMD) with 95% confidence interval (CI). The authors tested the homogeneity of the effect size across trials by using the Cochrane Q statistic and the I² statistic, which are indicative of the percentage of variability due to heterogeneity rather than sampling error. The authors performed sensitivity analysis using the Hartung-Knapp-Sidik-Jonkman method, when the number of studies was small (<10). Moreover, the authors performed a sensitivity analysis excluding studies using milrinone.

The authors also performed a trial sequential analysis (TSA) to assess sensitivity so as to prevent type I errors resulting from multiple testing of the effect in the meta-analysis. The authors began by calculating the required sample size (required information size [RIS]) and set the risk of type I and type II errors at 5% and 10%, respectively.

For the TSA, the authors used a minimum clinically meaningful mean difference of 10 beats/min for HR, 5 mmHg for MBP, 2 mmHg for CVP, 1 L/min for CO, and 0.5 L/min/m² for CI. The authors calculated the alpha-spending boundaries of the meta-analysis and adjusted CIs. The authors plotted the cumulative Z-curve of the meta-analysis to determine whether trial sequential monitoring boundaries were crossed for assessing type I and type II errors and if further trials were needed. TSA was performed using TSA viewer (version 0.9.5.9 beta, Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark).

To assess publication bias, the authors tested the symmetry using a funnel plot and evaluated the symmetry of the funnel plot using Begg’s test. Publication bias is considered present when the p value of Begg’s test is <0.1. The authors did not evaluate publication bias when fewer than 9 studies were included in the analysis.

Results

Characteristics of the Studies Included in the Meta-analysis

The authors identified 557 articles for review through their initial search of the electronic databases, and excluded 446 studies because they were unrelated. The remaining 111 articles were thoroughly examined to determine whether they met the inclusion criteria. Studies were excluded because they were animal studies (n = 51), were not RCTs (n = 33), did not involve hemodynamic trials (n = 17), or did not use norepinephrine and vasopressin (n = 4). In total, 6 studies satisfied the inclusion criteria and contained data, which were amenable to meta-analysis as shown in Fig 1.

Table 1 depicts the studies’ characteristics the authors selected. In this study, the patients included were older, with most patients having an average age of 60 years or older. Regarding the types of surgery, the coronary artery bypass graft surgery was the most frequent surgery type being listed in 3 of the 6 studies. Carotid endarterectomy surgery was included in 2 studies, and 1 study contained abdominal emergency surgery. The doses and methods of vasopressin and norepinephrine administration differed in each study. In most studies, both vasopressin and norepinephrine were administered in a continuous infusion, but some studies administered a bolus dose.
Table 1
Characteristics of the Assessed Studies

<table>
<thead>
<tr>
<th>Author Name</th>
<th>Publish Year</th>
<th>Age (V/N)</th>
<th>Number of Patients (V/N)</th>
<th>Administration of Vasopressin or Norepinephrine</th>
<th>Type of Surgery</th>
<th>Anesthesia Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yimin H</td>
<td>2013</td>
<td>N/A</td>
<td>10/10</td>
<td>Drug dosage: V; 0.4 ± 0.11 mg, N; 3.6 ± 1.2 U</td>
<td>CABG surgery</td>
<td>Anesthesia induction program: midazolam 0.05 mg/kg, etomidate 0.1-0.2 mg/kg, vecuronium bromide 0.15 mg/kg, fentanyl 5-10 μg/kg. Anesthesia maintenance program: propofol 6-10 mg/kg/h, atracurium 5-10 μg/kg/min, fentanyl intermittently. The total fentanyl dosage was controlled to 30-50 μg/kg.</td>
</tr>
<tr>
<td>Abdullah MH</td>
<td>2012</td>
<td>V; 57.3 ± 4.1, N; 61.5 ± 4.6</td>
<td>17/17</td>
<td>Bolus dose of vasopressin (1 mg over 30 min) followed immediately by a continuous infusion of 2 μg/kg/h or norepinephrine infusion at a starting dose of 0.1 μg/kg/min.</td>
<td>Emergency abdominal surgery</td>
<td>General anesthesia was induced with propofol 2 mg/kg IV, fentanyl 1 μg/kg IV, and IV followed by endotracheal intubation, which was facilitated by rocuronium 1.2 mg/kg. Anesthesia was maintained cisatracurium–isoflurane keeping entropy reading between 40 and 60. Consisting of sufentanil and midazolam supplemented by sevoflurane in an oxygen and air mixture. Vecuronium bromide was used for muscle relaxation.</td>
</tr>
<tr>
<td>Park SY</td>
<td>2011</td>
<td>V; 60.2 ± 9.3, N; 60.7 ± 8.6</td>
<td>20/21</td>
<td>Continuous infusion: V; 0.2 U/mL, N; 8 μg/mL.</td>
<td>CABG surgery</td>
<td>Anesthesia was induced with midazolam (0.1 mg/kg), etomidate (0.15 mg/kg), sufentanil (3 μg/kg), and vecuronium (1-1.5 mg/kg). Anesthesia was maintained until the end of operation with continuous infusion of midazolam (0.05 mg/kg.h).</td>
</tr>
<tr>
<td>Jeon Y</td>
<td>2006</td>
<td>V; 62 ± 6.6, N; 61 ± 7.9</td>
<td>25/25</td>
<td>The concentrations of vasopressin (0.171 U/mL) and norepinephrine (0.286 μg/mL) were chosen so that the starting infusion volume was 7 mL/h.</td>
<td>CABG surgery</td>
<td>A standardized induction technique was performed: 0.4 μg/kg of sufentanil were administered slowly (40 s) and then propofol was administrated using a target-controlled total intravenous anesthesia device (Diprifusor) to reach a target drug concentration of 4 μg/mL at the effect site in 1.5 min. After loss of consciousness, atracurium 0.5 mg/kg was given to facilitate intubation. Anesthesia was maintained with propofol in target concentration at the site effect (2.5-4 μg/mL) to maintain BIS between 40 and 60. Sufentanil boluses (5 μg) were administered as required in the presence of intraoperative hypertension or tachycardia related to surgical stimulation.</td>
</tr>
<tr>
<td>Morelli A</td>
<td>2005</td>
<td>V; 67.8 ± 6.0, N; 70 ± 7.0</td>
<td>16/16</td>
<td>Drug dosage: V; 1 mg, N; 1 mg</td>
<td>Carotid endarterectomy</td>
<td>Patients received a loading dose of 0.5 μg/kg of sufentanil within 30 s, with additional boluses if required. Target-controlled infusion of propofol (Diprifusor) was administered, with a plasma concentration target of 2 μg/mL within 3 min. It was progressively increased until loss of consciousness and a BIS below 60 had been obtained. After 0.5 mg/kg infusion of atracurium and tracheal intubation.</td>
</tr>
</tbody>
</table>

Abbreviations: BIS, bispectral index; CABG, coronary artery bypass grafting; IV, intravenous; N, norepinephrine; U, unit; V, vasopressin.
Meta-analysis Results

Primary Outcome

Mean Blood Pressure (MBP) was evaluated in 5 studies, and meta-analysis showed that vasopressin did not improve MBP compared with norepinephrine (WMD = −0.84 mmHg, 95% CI: −5.90 to 4.23, p = 0.75, Cochran Q = 24.6, I² = 84%) (Fig 2). TSA adjusted the CI to −10.2 to −8.5 and showed that 35.5% (n = 177) of the RIS was achieved (n = 499).

Secondary Outcome

Heart Rate

Meta-analysis of the 6 trials revealed that vasopressin and norepinephrine had a similar effect on HR during general anesthesia (WMD = −4.92 beats/min, 95% CI: −7.10 to 7.17, p = 0.42, Cochran Q = 17.2, I² = 97%) (Fig 3). TSA adjusted the CI to −32.5 to −22.7 and showed that 23.7% (n = 147) of the RIS was achieved (n = 621).

Central Venous Pressure

CVP did not differ significantly between vasopressin and norepinephrine (WMD = 0.03 mmHg, 95% CI: −0.92 to 0.99, p = 0.95, Cochran Q = 7.61, I² = 97%) (Fig 4). TSA corrected the 95% CI to 0.94 to 1.01. The accrued sample size (n = 91) almost reached the estimated RIS (n = 93).

Cardiac Output

Cardiac output was not significantly different between vasopressin and norepinephrine (WMD = 0.16 L/min, 95% CI: −0.20 to 0.50, p = 0.37, Cochran Q = 0.26, I² = 0%) (Fig 5). TSA adjusted the CI to −0.28 to 0.61 and showed that 70% (n = 84) of the RIS was achieved (n = 120).

Subgroup Analysis

The authors performed a subgroup analysis that separated studies using vasopressin and terlipressin. In addition, the authors performed separate subgroup analysis for studies that included CABG and studies that contained other surgeries. However, the result of subgroup analyses showed no significant differences in these outcomes.
cant differences in the use of vasopressin and norepinephrine (Table 2).

Sensitivity Analysis

The authors performed sensitivity analysis using the Hartung-Knapp-Sidik-Jonkman method, when the number of studies was small (<10). All analyses revealed a level of significance similar to the results of the DerSimonian and Laird random-effects model (Table 3). In this study, sensitivity analysis was performed excluding studies using milrinone. Vasopressin and norepinephrine had similar increase in blood pressure in the analysis excluding a milrinone study (MBP; WMD = 1.69 mmHg, 95% CI: −0.43 to 3.80, p = 0.12, Cochran Q = 2.05, I² = 0%).

Quality of Evidence

The quality of evidence was graded as very low for the effect of vasopressin, as compared with that of norepinephrine, for all 3 parameters (MBP, HR, CVP, CO, and CI) investigated. The range of TSA-adjusted 95% CI was wide, indicating a high level of statistical imprecision. All articles included in the meta-analysis had a high risk of bias and high heterogeneity, so the authors downgraded the quality of evidence to very low (Supplemental Material 3). Small study effects could not be assessed using funnel plots, as the number of studies was less than 9. The assessments of risk of bias are summarized in Supplemental Material 4.

Discussion

Explanation of Results

The findings of this systematic review and meta-analysis suggested that vasopressin and norepinephrine have similar effects on MBP during general anesthesia. In addition, administration of vasopressin and norepinephrine under general anesthesia showed similar effects on HR, CVP, CO, and CI.

Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of Trials</th>
<th>WMD (95% CI)</th>
<th>p Value</th>
<th>Cochran Q</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP</td>
<td>Vasopressin</td>
<td>3</td>
<td>−3.29 (−11.9 to 5.28)</td>
<td>0.45</td>
<td>14.9</td>
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<tr>
<td></td>
<td>Terlipressin</td>
<td>2</td>
<td>2.49 (−0.48 to 5.40)</td>
<td>0.10</td>
<td>1.17</td>
</tr>
<tr>
<td></td>
<td>CABG surgery</td>
<td>3</td>
<td>−3.29 (−11.9 to 5.28)</td>
<td>0.45</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td>Other surgery</td>
<td>2</td>
<td>2.49 (−0.48 to 5.40)</td>
<td>0.10</td>
<td>1.17</td>
</tr>
<tr>
<td>HR</td>
<td>Vasopressin</td>
<td>3</td>
<td>−2.89 (−8.33 to 2.54)</td>
<td>0.30</td>
<td>0</td>
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<td></td>
<td>Terlipressin</td>
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<td>−6.16 (−23.4 to 11.1)</td>
<td>0.48</td>
<td>123.9</td>
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<tr>
<td></td>
<td>CABG surgery</td>
<td>3</td>
<td>−2.89 (−8.33 to 2.54)</td>
<td>0.30</td>
<td>0</td>
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<tr>
<td></td>
<td>Other surgery</td>
<td>2</td>
<td>−6.16 (−23.4 to 11.1)</td>
<td>0.48</td>
<td>123.9</td>
</tr>
<tr>
<td>CVP</td>
<td>Vasopressin</td>
<td>3</td>
<td>−0.45 (−1.24 to 0.35)</td>
<td>0.27</td>
<td>0.77</td>
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<tr>
<td></td>
<td>Terlipressin</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>CABG surgery</td>
<td>3</td>
<td>−0.45 (−1.24 to 0.35)</td>
<td>0.27</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>Other surgery</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CO</td>
<td>Vasopressin</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td></td>
<td>Terlipressin</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td></td>
<td>CABG surgery</td>
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<td>N/A</td>
<td>N/A</td>
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</tr>
<tr>
<td></td>
<td>Other surgery</td>
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<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CI</td>
<td>Vasopressin</td>
<td>2</td>
<td>−0.02 (−0.31 to 0.27)</td>
<td>0.89</td>
<td>0.16</td>
</tr>
<tr>
<td></td>
<td>Terlipressin</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>CABG surgery</td>
<td>2</td>
<td>−0.02 (−0.31 to 0.27)</td>
<td>0.89</td>
<td>0.16</td>
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<tr>
<td></td>
<td>Other surgery</td>
<td>1</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations: 95% CI, 95% confidence intervals; CABG, coronary artery bypass grafting; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; HR, heart rate; MBP, mean blood pressure; N/A, not applicable; WMD, weight mean difference.
However, the TSA results suggested that additional studies are needed to confirm these findings.

Because norepinephrine is a catecholamine, it increases blood pressure by stimulating $\alpha$- and $\beta$-adrenergic receptors. In contrast, vasopressin acts on $V_1$ receptors to cause vasoconstriction, and thus increases blood pressure. It also acts on $V_2$ receptors and promotes renal tubular reabsorption of water to maintain blood pressure.\textsuperscript{10,11} In their meta-analysis, the authors found that the pressor action of vasopressin was equivalent to that of norepinephrine under general anesthesia.

Additionally, vasodilatory shock is mainly treated by administration of a vasoconstrictor such as norepinephrine, which is currently the most commonly used drug. Now that physicians have begun to recognize the side effects of catecholamines and the pathophysiology of shock, alternative vasoconstrictors are needed to treat critically ill patients with severe hypotension.\textsuperscript{8}

The most important change associated with vasodilatory shock at the cellular level in vascular smooth muscle cells is the continuous opening of ATP-sensitive $K^+$ channels in the cell membrane. This results in cellular hyperpolarization that contributes to sustained vasodilation, and is a cause of the poor responsiveness to catecholamines in late shock.\textsuperscript{14} Also, changes in the activation of inducible nitric oxide synthase produces excessive nitric oxide, causing refractory vasodilation that is resistant to catecholamines.\textsuperscript{14} Furthermore, adrenergic receptors are downregulated and desensitized after prolonged treatment with high doses of catecholamines.\textsuperscript{30} These mechanisms collectively contribute to the persistence of refractory shock.

The action of vasopressin as a noncatecholaminergic vasoconstricor and endogenous hormone involved in osmotic and cardiovascular homeostasis has been the subject of extensive study. Plasma vasopressin levels were reported to be abnormally low in patients with vasodilatory shock.\textsuperscript{31} Experimental and clinical studies have shown that vasopressin may neutralize the cellular mechanisms in vasodilatory shock described above.\textsuperscript{31} The mechanism by which vasopressin acts to maintain hemodynamics is thought to be as follows. During vasodilatory shock, the vasoconstrictive effects of vasopressin that negatively affect both the heart and kidneys are offset by an increase in systemic mean arterial pressure, which overrides these effects to ultimately improve organ perfusion.\textsuperscript{32,33}

The promising results of a recent pilot study,\textsuperscript{34} a large, multicenter, randomized clinical trial was conducted to assess the use of vasopressin for septic shock.\textsuperscript{35}

In this study, vasopressin did not cause any change in heart rate compared with norepinephrine under general anesthesia. Norepinephrine is known to increase heart rate by acting on $\beta_1$-adrenergic receptors, and it also has the effect of reflexively reducing heart rate by vasoconstriction action by $\alpha_1$-adrenergic receptor activity. Presumably, these effects vary with the patient’s condition. Vasopressin has no effect on $\beta_1$ receptors, and therefore does not affect heart rate. Thus, vasopressin may be effective for treatment of hypotension with severe tachycardia, but further research is needed.

Several meta-analyses comparing vasopressin and norepinephrine in critical care units have been reported.\textsuperscript{36-38} Wang et al. administered vasopressin and norepinephrine to patients with hepatorenal syndrome and compared recovery rates from this syndrome. They concluded that the rate of recovery was equivalent for vasopressin and norepinephrine (odds ratio = 1.01, 95% CI: 0.65-1.57, $p = 0.96$).\textsuperscript{36} Furthermore, Belletti et al. reported that the mortality rate was the same with the administration of either vasopressin or norepinephrine in patients with septic shock.\textsuperscript{36} Thus, administration of vasopressin in critical care units has proven effective when compared with norepinephrine. However, vasopressin is reported to be associated with more complications than norepinephrine, such as abdominal cramps, arrhythmia, and cyanosis of the toe,\textsuperscript{39} and the occurrence of excessive hypotension after administration of vasopressin has been reported in septic shock.\textsuperscript{36,37} More studies are needed to further elucidate these complications and side effects. Although undetectable in this study, vasopressin has some other beneficial effects reported in the literature. Vasopressin may reduce mortality when used in combination with steroids.\textsuperscript{40} It also may reduce the deterioration of renal function in patients with preoperative renal dysfunction.\textsuperscript{33} Furthermore, it has been reported that vasopressin, when used in combination with other catecholamines, reduces the use of catecholamines and improves mortality.\textsuperscript{41} However, vasopressin and norepinephrine are known to show different responses to coronary collateral circulation after coronary artery occlusion. In a 1989 animal study, vasopressin was reported to significantly enhance the contraction of coronary collateral arteries.\textsuperscript{42} On the other hand, it has been reported that norepinephrine does not reduce blood flow in coronary collateral arteries.\textsuperscript{43} From these results, it may be better to use norepinephrine than vasopressin in patients after coronary artery occlusion.

**Limitations**

One limitation of this study was the small number of patients. Thus, the study might have had insufficient power to detect small, but clinically important, stabilization of hemodynamic changes caused by vasopressin. Other limitations included those inherent to all meta-analyses, including heterogeneity due to the various designs of the original studies. Controversy remains as to whether the results of studies with

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**Table 3**

Comparison of Vasopressin With Norepinephrine for Hemodynamic Responses in Sensitivity Analysis

<table>
<thead>
<tr>
<th>Number of Trials</th>
<th>WMD (95% CI)</th>
<th>p Value</th>
<th>t Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP 5</td>
<td>$-0.84$ ($-8.25$ to $6.57$)</td>
<td>0.77</td>
<td>$-0.31$</td>
</tr>
<tr>
<td>HR 5</td>
<td>$-4.92$ ($-17.6$ to $7.72$)</td>
<td>0.34</td>
<td>$-1.08$</td>
</tr>
<tr>
<td>CVP 4</td>
<td>0.03 ($-1.37$ to $1.43$)</td>
<td>0.95</td>
<td>0.07</td>
</tr>
<tr>
<td>CO 2</td>
<td>0.16 ($-11.39$ to $11.45$)</td>
<td>0.99</td>
<td>0.03</td>
</tr>
<tr>
<td>CI 3</td>
<td>$-0.37$ ($-2.10$ to $2.16$)</td>
<td>0.96</td>
<td>0.06</td>
</tr>
</tbody>
</table>

**Abbreviations:** 95% CI, 95% confidence intervals; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; HR, heart rate; MBP, mean blood pressure; N/A, not applicable; WMD, weight mean difference.
different protocols can be combined justifiably to calculate pooled RR and to draw general conclusions. In addition, differences in patient populations, doses of vasopressin and norepinephrine, doses of fentanyl or propofol, types of surgery, and modes of anesthesia can contribute to heterogeneity. Milrinone increases contraction of myocardium. It also has a vasodilator effect and reduces the afterload of the heart leading to improved heart function. Thus, inclusion of studies using milrinone may have increased the bias of the authors’ meta-analysis, unlike other studies not using milrinone. This study also included terlipressin, an analog of vasopressin.45 Terlipressin is a long-acting synthetic analog of vasopressin, which acts via the vasopressin system. Because terlipressin and vasopressin are not exactly the same drug, this may increase bias. RCTs included in the authors’ meta-analysis were not the most recent trials. Since these studies were published between 2003 and 2013, the surgical methods and surgical equipment could have been different from the latest methods. These differences may have different consequences when conducting new clinical studies. Taken together, these factors potentially may have resulted in significant bias, and thus conclusions drawn from the authors’ meta-analysis examining hemodynamic effects should be interpreted with caution.

Conclusions

The findings suggested that vasopressin and norepinephrine have similar effects on MBP during general anesthesia. In addition, administration of vasopressin and norepinephrine under general anesthesia showed similar effects on HR, CVP, CO, and CI. However, the TSA results suggested that additional studies are needed to confirm these findings and that GRADE was very low. Therefore, further research is needed to reach more robust conclusions.

Conflict of Interest

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2020.08.011.

References