Given the underlying assumption that reasonable maternal hemodynamics can be achieved with either ephedrine or phenylephrine, this focused meta-analysis addresses the impact of vasopressor choice on resultant neonatal Apgar scores during regional anesthesia. The literature was systematically searched for randomized trials of obstetric vasopressor use employing standard search tools. Only the highest quality trials were included. Of 142 studies retrieved, 9 met the defined inclusion criteria. Apgar scores at 1 and 5 minutes in the ephedrine group (served as control) vs the phenylephrine group did not differ at either time epoch; no abnormal values prevailed in either group (relative risk, 0.88; CI, 0.79-1.16). This meta-analysis focused on the most clinically relevant, immediately available information pertinent in the obstetric suite, the Apgar score, and found that ephedrine and phenylephrine did not differ in their effect on this metric. The current meta-analysis provides an updated, evidence-based validation of vasopressor use from the American Society of Anesthesiologists’ 2007 “Practice Guidelines for Obstetric Anesthesia.”

Keywords: Apgar score, meta-analysis, neuraxial hypotension, obstetric hypotension, obstetric vasopressor, vasopressor.

Two clinical goals are of greatest relevance to the anesthesia provider caring for the obstetric patient during vaginal or cesarean delivery: (1) avoidance of maternal physiological instability as assessed by hemodynamic measures and (2) avoidance of low Apgar scores in the neonate. Given the underlying assumption that reasonable maternal hemodynamics can be achieved with either ephedrine or phenylephrine, this focused meta-analysis addresses the impact of vasopressor choice on resultant neonatal Apgar scores during regional anesthesia.

Methods
Institutional review board approval was waived. The literature was systematically searched for randomized trials of obstetric vasopressor use employing PubMed, MEDLINE, Embase, OmniMedicalSearch, Google Scholar, and Cochrane search engines using terms noted in Table 1. Discovered trials were assessed using Jadad scaling for methodologic quality. Trials were considered only if they used neuraxial management of anesthesia. Only high-quality trials with Jadad scores of 4 or greater reporting neonatal Apgar scores at 1 and 5 minutes that were published since 1991 were included in the analysis. Additional entry criteria are listed in Figure 1.

Publication bias was assessed by using the Egger test and by visual inspection of funnel plots. Given absence of bias, the plot assumes a symmetrical, inverted funnel shape. A random effects model using Epi Meta statistical software (US Centers for Disease Control and Prevention, Atlanta, GA) for applications to epidemiologic data was used on the ranked Apgar scores at 1 and 5 minutes after conversion to median and range data. The process focuses on procedures that estimate the weighted average for parameters of interest, in this case the relative risk (RR).
A total of 142 studies were retrieved. Attrition resulted if studies did not meet the a priori entry criteria and because 17 studies appeared to be duplicate or near-duplicate publications (Figure 1). Funnel plots were symmetrical, indicating no evidence of publication bias. Nine trials met the defined inclusion criteria for the current study (Table 2 and Figure 2).

Apgar scores at 1 and 5 minutes in the ephedrine group (served as control) vs the phenylephrine group did not differ at either time epoch; no abnormal values prevailed in either group (RR, 0.88; CI, 0.79-1.16). Figure 2 is the resultant forest plot. There was no significant difference between the vasopressor groups at either time epoch.

Apgar, an anesthesiologist, devised a clinically meaningful scoring system providing a rapid method of assessing the status of the newborn at 1 minute of age, assessing the need for prompt intervention. A subsequent report evaluating a larger number of neonates was published in 1958, securing the Apgar score as a valid metric. Apgar's system consists of 5 components: heart rate, respiratory effort, muscle tone, reflex irritability, and color, each of which is given a score of 0, 1, or 2. The score is now reported at 1 and 5 minutes after birth. The Apgar score continues to provide a convenient and clinically meaningful mechanism to report the status of the neonate. A review of the Apgar system is provided in Table 3.

This quantitative systematic review of high-quality randomized trials performing head-to-head comparison of ephedrine and phenylephrine revealed no difference in Apgar scores at either 1 or 5 minutes after delivery. Because these agents are in widespread use and are highly effective in achieving rapid hemodynamic endpoints, the current study focused entirely on the most meaningful and clinically relevant neonatal outcome metric used in contemporary obstetric suites, the Apgar score. Although some might challenge the Apgar score as a crude assessment of fetal well-being, it is the most commonly applied and readily interpretable metric available in real time to the clinician in the delivery suite.

Many hierarchies of evidence consider the meta-analysis as the highest level of evidence. While not questioning it as a powerful research tool, there are many potential pitfalls regarding its interpretation. Unless great analytical care is taken, meta-analyses of multiple small trials are susceptible to publication bias and conclusions

Figure 1. Disposition of Discovered Trials
Table 2. Alphabetized List of Included Trials With Relevant Information

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of patients</th>
<th>Anesthesia</th>
<th>Vasopressor use</th>
<th>Phenylephrine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ayorinde</td>
<td>81</td>
<td>Subarachnoid or subarachnoid + epidural</td>
<td>45 mg IM</td>
<td>2 or 4 mg IM</td>
</tr>
<tr>
<td>Cooper</td>
<td>143</td>
<td>Subarachnoid</td>
<td>1 mg/min lnF; 50% of each vasopressor per minute of lnF</td>
<td>33 μg/min lnF; 50% of each vasopressor per minute of lnF</td>
</tr>
<tr>
<td>Hall</td>
<td>29</td>
<td>Subarachnoid</td>
<td>6 mg IV + 1 or 2 mg/min lnF</td>
<td>20 μg IV + 10 μg/min lnF</td>
</tr>
<tr>
<td>Hennebry</td>
<td>70</td>
<td>Subarachnoid + epidural</td>
<td>1.5 mg/min lnF</td>
<td>16 μg/min lnF</td>
</tr>
<tr>
<td>LaPorta</td>
<td>40</td>
<td>Subarachnoid</td>
<td>5- to 10-mg IV increments</td>
<td>40- to 80-μg IV increments</td>
</tr>
<tr>
<td>Moran</td>
<td>61</td>
<td>Subarachnoid</td>
<td>5- to 10-mg IV increments</td>
<td>40- to 80-μg IV increments</td>
</tr>
<tr>
<td>Prakash</td>
<td>60</td>
<td>Subarachnoid</td>
<td>6-mg IV increments</td>
<td>100-μg IV increments</td>
</tr>
<tr>
<td>Pierce</td>
<td>26</td>
<td>Subarachnoid</td>
<td>5- to 10-mg IV increments</td>
<td>40- to 80-μg IV increments</td>
</tr>
<tr>
<td>Thomas</td>
<td>38</td>
<td>Subarachnoid</td>
<td>5-mg IV increments</td>
<td>100-μg IV increments</td>
</tr>
</tbody>
</table>

Abbreviations: lnF; intravenous infusion of vasopressor; IV; intravenous bolus administration; IM = intramuscular administration; +, plus.

Vasopressor use may be dominated by the inclusion of a particularly large trial in the presence of smaller ones. Likewise, unique patient factors (individual variability) must always be taken into consideration when one applies research findings, making contextual consideration a cornerstone of evidence-based decision making.16

Maternal hypotension is an adverse consequence of neuraxial blockade with important maternal and fetal effects. Despite titration of neuraxial drugs, intravenous hydration, use of left uterine displacement, and compressive leg devices, hypotension commonly occurs. Persistent hypotension may decrease uterine blood flow, jeopardizing fetal outcome; thus, it is common to administer a vasopressor. Whereas numerous studies have demonstrated differences in umbilical artery pH, generally favoring phenylephrine, no study has shown a
difference in long-term neonatal outcome.\textsuperscript{17,18}

This meta-analysis focused on the most clinically relevant, immediately available information pertinent to anesthesia decision makers in the obstetric suite, the Apgar score, and found that ephedrine and phenylephrine did not differ in their effect on this metric. Furthermore, the current meta-analysis provides an updated, evidence-based validation of the American Society of Anesthesiologists' 2007 “Practice Guidelines for Obstetric Anesthesia,” which stated that “intravenous ephedrine and phenylephrine are both acceptable drugs in treating hypotension during neuraxial anesthesia.”\textsuperscript{19} These guidelines are further supported by Habib,\textsuperscript{20} who noted that the optimal phenylephrine regimen is unclear, and its use in preeclampsia and placental insufficiency states requires investigation. Those seeking more information regarding a phenylephrine bolus vs infusion strategy for spinal induced hypotension during cesarean delivery will find a recently published clinical trial, revealing little clinical benefit of one approach over the other, illuminating.\textsuperscript{21}

**REFERENCES**


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