Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Of Size and Men: A Call for Larger Trials and Meta-Analyses on Vasopressors During General Anesthesia

What counts is not necessarily the size of the dog in the fight—it's the size of the fight in the dog.

—Dwight D. Eisenhower

Hypotension represents a common clinical challenge, typically managed by fluid administration, including blood transfusion (eg, in case of dehydration or hemorrhage), inotropes (eg, dobutamine), vasopressors (eg, epinephrine), cardiac chronotropic stimulation (eg, with atropine or pacing for bradycardia), and mechanical cardiopulmonary support (eg, extracorporeal membrane oxygenation).[1-5] Although many different agents are available for vasopressor purposes (eg, angiotensin II, argipressin, dopamine, dopexamine, ephedrine, epinephrine, norepinephrine, phenylephrine, pituitrin, selepressin, terlipressin, and vasopressin), such a plethora of alternatives constitutes a veritable challenge and area of persistent uncertainty.[6-7] Indeed, most of these agents have complex and multifaceted effects on patients, some direct and some indirect (eg, due to afterload increase or flow redistribution). Furthermore, the conundrum is also complicated by the limited predictability of in-hospital and long-term clinical events in light of immediate effects on surrogate endpoints, such as the scenario in which a vasopressor-induced adequate increase in systolic blood pressure is not associated with adequate tissue perfusion in crucial organs, with eventual excesses of morbidity and mortality.[8] Despite ongoing calls for reinforcing the role of qualitative, pathophysiologic, and observational research, most experts and organizations recognize the crucial and pivotal role of randomized clinical trials in shaping decision-making, and this holds even truer in specific clinical settings that go beyond the broader and quite heterogeneous indications, such as shock or hypotension.[9]

Hypotension during invasive procedures requiring general anesthesia represents a particularly challenging scenario, as several different mechanisms may cause hypotension (eg, myocardial dysfunction, hemorrhage, or neurogenic vasodilation).[10-11] Accordingly, uncertainty of the comparative efficacy and safety of vasopressors clearly applies in this clinical context as well. In particular, a focus of intense research has been the quest to identify the most effective vasopressor, capable of optimizing blood pressure as well as cardiac output, without undue effects on heart rate or, more in general, cardiac physiology (eg, myocardial perfusion pressure and myocardial oxygen demand), with the utmost interest being reserved for vasopressin (which leads to vasoconstriction by acting on peripheral V1 receptors, and fluid retention by acting on renal V2 receptors) and the vasopressin analog terlipressin.[12]

In this issue of the Journal, Hoshijima et al. reported the results of an updated meta-analysis of randomized controlled trials comparing vasopressin or terlipressin versus norepinephrine for the management of hypotension in patients undergoing general anesthesia.[13] They retrieved a total of 6 trials including 197 patients, with mean within-arm age ranging between 57 and 73 years, in whom indications for general anesthesia included abdominal surgery, carotid endarterectomy, and coronary artery bypass grafting. Outcomes of interest were mean blood pressure (reported by 5 trials), heart rate (reported by 5), central venous pressure (reported by 4), cardiac output (reported by 2), and cardiac index (reported by 3). No significant differences were found between these agents for any of such endpoints, despite evident statistical heterogeneity and inconsistency due to disparate between-study effect estimates (eg, p value at chi-squared test <0.001, tau-squared 27, and I-squared 84% for mean blood pressure), leading to quite large confidence intervals (for instance -5.9 to +4.2 mmHg for mean blood pressure). Additional analyses, including trial-sequential meta-analysis, confirmed the limited informativeness of the accrued evidence base, with minimum sample sizes for adequately powered future meta-analyses ranging between 93 (for central venous pressure) and 1,850 patients (for cardiac index).

Strengths of this work included the use of several established meta-analytic methods, including trial-sequential analysis, whereas key limitations included lack of details on additional endpoints, eg, death, stroke, infarction, renal failure, urine output, and so forth. In addition, small study effects and publication bias remain potential validity threats.[14]

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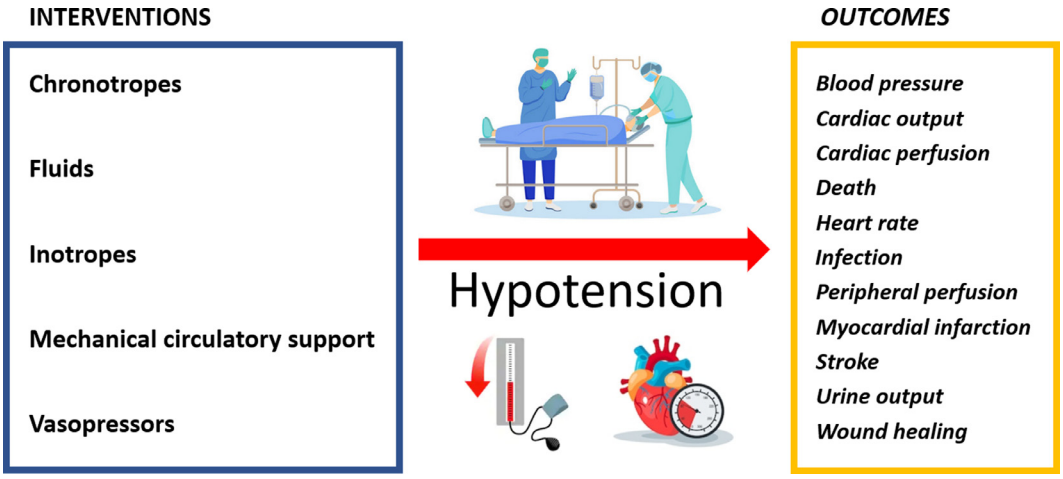

Fig 1. Graphical summary of interventions and outcomes of hypotension complicating general anesthesia.

Accordingly, the authors can infer from this work that, according to the evidence accrued to date, there is no significant difference in terms of immediate surrogate hemodynamic endpoints among vasopressin, terlipressin, and norepinephrine. Taking into account the lower cost of norepinephrine, this agent is thus probably the first choice drug for the management of general anesthesia complicated by hypotension and vasoplegic shock. Conversely, no conclusions can be drawn on all other and often more relevant outcomes in patients with hypotension during general anesthesia (Fig 1). More generally, the main conclusion of the meta-analysis by Hoshijima et al. was that researchers need to work more intensively and collaboratively to design and conduct larger trials on the comparative effectiveness and safety of vasopressors for hypotension. Randomized trials of adequate size, alone or combined within a meta-analysis (possibly based on an individual patient-level dataset), will be key to overcome the drawbacks of past studies on this topic and better inform clinical practitioners and researchers.[15]

In addition to simple head-to-head trials, researchers could envision adaptive and platform trials suitable for more flexible testing and comparison, similar to the ones recently adopted for coronavirus disease 2019 (COVID-19), given the need for refined research tools suitable for the complexities of management strategies for hypotension occurring during general anesthesia.[16] In particular, another theoretically appealing approach is combining different vasopressors or their sequential use in a stepwise fashion,[17] even if the evidence for such combination regimens is very limited.[18] Along the same lines, another intriguing area of research is timing and order of discontinuation in case 2 or more vasopressors are simultaneously used.[19]

In conclusion, larger and more numerous trials direly are needed to better inform clinical decision-making for patients undergoing general anesthesia with hypotension or shock. Meanwhile, equipoise between norepinephrine and vasopressin still holds, at least for surrogate hemodynamic endpoints such as mean blood pressure, heart rate, central venous pressure, cardiac output, and cardiac index.

Conflicts of Interest

G.B.-Z. has consulted for InnovHeart, Milan, Italy; Meditrial, Rome, Italy; and Replycare, Rome, Italy.

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