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Propofol compared to etomidate inductions and attenuating propofol induced hypotension

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Introduction

Inducing anesthesia in the hemodynamically unstable patient has troubled anesthesia providers for years. Optimal drug performance would include a rapid onset, maintain adequate mean arterial pressure (MAP), and preserve the balance of myocardial oxygen supply and demand.[1] Propofol is the drug of choice for most types of anesthesia inductions but has limitations for use in the hemodynamically unstable patient. Propofol induced hypotension (PIH) occurs due to a theoretical decreased systemic vascular resistance (SVR), myocardial depression, and baroreceptor blunting.[1] Etomidate has long been the drug of choice for intubating the hemodynamically unstable patient due to rapid onset, cardioprotective nature, and hemodynamic stability. Recently, literature has been written highlighting the increased mortality rates associated with the use of etomidate in many types of patient populations.[2,3] Chan et al[2] found that a single dose of etomidate for induction of anesthesia was associated with increased 28-day mortality. With these findings in mind, possible alternatives to etomidate should be explored to induce anesthesia in hemodynamically compromised patients. The purpose of this review is to explore any adverse outcomes associated with the use of etomidate and to review the literature to find safe alternative drugs to induce anesthesia with a focus on propofol with ephedrine. The physiology of PIH will also be reviewed.

Pharmacology and physiology

Propofol

In order for researchers to develop ways to correct propofol's negative hemodynamic profile, we must first understand the physiology behind propofol's side effects. The exact mechanism for PIH is not precisely understood but researchers have attempted to solve this issue. The hemodynamic effects of propofol were initially considered to be caused by direct myocardial depression and decreased SVR caused by arterial, venous dilation and smooth muscle relaxation.[1] The venous and arterial dilation appear to be influenced by decreased sympathetic responses. In a controlled experiment by Robinson et al.[4] the effects of propofol on arterial and venous smooth muscle were compared to a known vasodilator, sodium nitroprusside (SNP). Robinson and his colleagues found that a propofol infusion into the brachial artery of conscious persons caused no significant arterial responses while a direct infusion of SNP caused profound vasodilation. The researchers concluded that propofol's hypotensive effects were not caused by direct arterial or venous vasodilation. They also performed a stellate ganglion blockade with propofol resulting in a profound vasodilation of the forearm. This indicates that the peripheral vascular actions of propofol appear to be due primarily to an inhibition of sympathetic vasoconstrictor nerve activity. Knowing propofol is not a direct-acting vasodilator on peripheral vasculature, appropriate interventions by using a combination of inotropic and vasoactive medications could be explored.

The myocardial depression and smooth muscle relaxation are theorized to be the result of decreased intracellular calcium mobilization causing a negative inotropic state.[1] Sprung et al.[5] found that propofol caused a decrease in the uptake of calcium into the sarcoplasmic reticulum making calcium concentrations diminished for myocytes to use for contraction. The researchers also found an important compensatory mechanism by the heart. With the presence of propofol, the myocyte filaments were much more sensitive to the low levels of calcium present. The hypotension is further magnified when propofol is used by the blunting of baroreceptors mechanisms that respond to decreases in blood pressure by increasing a patient's heart rate.

Ephedrine

Ephedrine is a synthetic noncatecholamine sympathomimetic used in anesthesia to increase blood pressure and heart rate.[1] Ephedrine is a combined alpha one and beta one receptor agonist. Alpha one receptor stimulation in peripheral vasculature causes vasoconstriction. Beta one receptor stimulation in the heart causes positive inotropic effects. Ephedrine has also been shown to indirectly release endogenous norepinepherine from sympathetic nerves.[6] Ephedrine produces a dose dependent effect on blood pressure and heart rate.[1] Often, ephedrine is the first drug used to alleviate hypotension caused by cardiac depression.

Methods

The literature search was performed through the databases PubMed, Ovid MEDLINE, CINHAL Plus with Full Text, and Cochrane Database of Systematic Reviews using the keywords "propofol," "induction," "hypotension," "vasopressor," "inotrope," "etomidate," "mortality," and "ephedrine" in various arrangements. The time frame of the search was from 1995 through 2015, resulting in a total of 67 potential articles. Further evaluation resulted in 12 randomized clinical trials with various levels of blinding and controls.

Two systematic reviews of etomidate's mortality influence (Level I evidence) were also found.[2,3] Articles were included in this review if they were a systematic review or met the following inclusion criteria: induction of anesthesia studied, being performed in a hospital setting, a control group was clearly identifiable, statistical analysis was sufficiently performed including p values, and all results were clearly stated and discussed. All of the clinical trials utilized a drop in blood pressure by 20% of baseline as criteria for hypotension. Mateo and Kirchhoff's[7] hierarchy of evidence was utilized to establish each article's level of evidence. Of the 13 clinical trials, all articles were randomized controlled trials (Level II evidence). All trials were blinded at least once to the anesthetist performing the inductions. Each trial had a different set of variables to be tested with different combinations of drugs but was deemed appropriate for this review. Each study paid close attention to group characteristics including age, sex, weight, height, co-morbidities, and medications to maintain consistency. All trials were blinded at least once to the anesthetist performing the inductions. Each trial had a different set of variables to be tested with different combinations of drugs but was deemed appropriate for this review.

Results

Etomidate

Two systematic reviews of etomidate's mortality influence (Level I evidence) were found.[2,3] Mortality served as one primary end point with the presence of adrenal insufficiency as a secondary end point in both reviews. Adrenal insufficiency was determined using a cosyntropin stimulation test in all of the included studies. Komatsu et al.[3] reviewed 31,148 patient records with 2616 class III or IV patients received etomidate inductions where 28,532 received propofol inductions. The researchers found that patients given etomidate had 2.5 times greater odds of dying than those given propofol. The etomidate patients also had significantly greater odds of having cardiovascular morbidity. Both systematic reviews concluded that a single dose of etomidate for induction of anesthesia was associated with increased 28-day mortality.[2,3] With a total of 865 patients, five studies were used that assessed mortality of patients receiving etomidate in the meta-analysis by Chan et al.[2] Chan et al.2 saw an increased 28-day mortality rate, with 43% compared to 31%, was found in patients who received etomidate compared with patients who received propofol. Etomidate induced adrenal insufficiency has long been the suspected culprit for the negative impact on survival. Etomidate has consistently been found to induce adrenal insufficiency up to 48 hours after a single dose by inhibiting the 11-β-hydroxylase and the conversion of 11-deoxycortisol into cortisol.[1]

Propofol and ephedrine bolus

Twelve studies were found and reviewed using ephedrine to prevent PIH. Each trial was randomized and at least single blinded with careful attention to having uniform group characteristics. They all had a minimum p value for significance of <.05. Dosing of ephedrine varied from single bolus dosing to weight based dosing ranging from 10-15 mg to 0.07-0.2 mg/kg.[6,8–16] Most trials had a timeframe for recording vitals ranging from 4-6 minutes with all trials showing similar results in this time frame. The variable of intubating the patient seemed to have a significant influence on how effective each drug was at preventing PIH. The only outlier was a study that did not have an intubation as part of their study and will be further discussed.[11] The clinical trial by El Tahan[6] was an extensive and thorough study on the dose dependent hemodynamic effects of ephedrine compared to a control and phenylephrine. The study also had cerebral oximetry to study ischemia with each vasoactive medication. In the placebo group, 81% of patients, who only received saline after induction with fentanyl and propofol, developed hypotension compared to 30% receiving 0.07 mg/kg ephedrine, 20% receiving 0.1 mg/kg ephedrine, and about 2% receiving 0.2 mg/kg ephedrine. The 0.2 mg/kg ephedrine dosing caused much more tachycardia and ischemic episodes than the other ephedrine groups. Dhungana et al. (2008) had similar results. The control group had a hypotension incidence of 67.5%, while the ephedrine group that received 0.2 mg/kg showed 22.5% hypotension. Similar attenuation or complete prevention of hypotension were reported in eight other studies using ephedrine 0.1 mg/kg or 10-20 mg boluses.[8–10,12,15,16] El Tahan[6] also found that ephedrine improves ventricular contractility without causing relevant changes of left ventricular afterload. El Tahan[6] concluded that 0.07-0.1mg/kg was the ideal dose for pretreatment with ephedrine because this does had the best balance of attenuating hypotension and decreasing tachycardic episodes. One outlier study performed by El Beheiry[11] indicated ephedrine did not effectively decrease the incidence of hypotension at a dose of 0.07 mg/kg. This study's procedure did not intubate the patient and tracked the patient the longest amount of time (10 minutes) showing an initial attenuation of blood pressure followed by a progression to hypotension. This initial attenuation of hypotension lasted until the five minute mark where there was then a progression towards hypotension. This author concludes the initial ephedrine dose was too small without intubating the patient to attenuate PIH, and also the ephedrine dose might not have lasted beyond the five minute mark.

Discussion

Implications for anesthesia practice

The purpose of this review was to have a better understanding of etomidate's role in anesthesia and to find alternatives for induction of anesthesia. The two systematic reviews, Chan et al.[2] and Komatsu et al.[3] highlight the possible need for alternatives to the use of etomidate for inductions in the hemodynamically compromised patient. It is important for advanced practice nurses to frequently review the literature, analyze the information, and determine best practices for their current situation. Another purpose of this review was to present alternatives to the use of etomidate for inductions in the hemodynamically unstable patient. Propofol as an induction agent with the addition of ephedrine, phenylephrine, ketamine, or calcium chloride could be used. The quality of supporting evidence in this review is fairly strong when analyzing ephedrine given that 12 well designed randomized controlled trials were found. After the review, 11 of the 12 studies supported the use of ephedrine in a dose dependent manner. Given this analysis, pretreatment with ephedrine using 0.075-0.2 mg/kg before the induction of anesthesia with propofol is the best way to prevent or attenuate hypotension. This conclusion is drawn from 11 trials studying ephedrine supported ephedrine dosing to decrease hypotension. Interestingly, ephedrine was also found to have positive effects on patient satisfaction by decreasing pain on injection when compared to plain Propofol.[9] Based on the current evidence, the effective ephedrine dose to prevent PIH appears to be between 0.075 -0.15 mg/kg. Nurse anesthetists respect the moral and legal rights of their patients, preserve human dignity, and support the safety and well being of the patients under their care.[17] An ethical dilemma now faces anesthesia providers when considering etomidate. The ethics of the use of etomidate is now in question given the recent literature published by Chan et al.[2] and Komatsu et al.[3] In practice,

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this author has found that many practitioners have stayed away from etomidate completely except in the most vulnerable populations. The current evidence supports inductions of anesthesia with judicious dosing of propofol can help maintain adequate hemodynamics with additives such as ephedrine, phenylepherine, and ketamine. Ethically, it is this author's opinion that the underlying fear of doing harm with etomidate and the unknown long term effects keeps practitioners from using etomidate more extensively.

Conclusion

In light of the recent literature indicating an increased mortality associated with etomidate, alternative methods of inducing anesthesia must be explored. An alternative induction drug such as propofol could be a solution to this anesthesia problem if propofol's side effects are addressed. PIH is the real limiting factor to the use of propofol to induce anesthesia in the hemodynamically unstable patient. Research has demonstrated many ways to prevent or attenuate the hypotensive effects of propofol after induction of anesthesia with the use of ephedrine, phenylephrine, or calcium chloride. The use of ephedrine is the most studied and has the most compelling evidence for its use. The effective ephedrine dose appears to be between 0.075 -0.15 mg/kg with endotracheal intubation. For now, etomidate has too many questions about its safety for this author to ethically use as an induction agent.

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Conflicts of interest

The author declare that there is no conflict of interest.

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