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## SCIENTIFIC ARTICLE

# The antimicrobial activity of ephedrine and admixture of ephedrine and propofol: an in vitro study



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### KEYWORDS

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### Abstract

**Introduction:** Propofol and Ephedrine are commonly used during anesthesia maintenance, the former as a hypnotic agent and the later as a vasopressor. The addition of propofol to ephedrine or administration of ephedrine before propofol injection is useful for decreasing or preventing propofol related hemodynamic changes and vascular pain. This in vitro study evaluated the antibacterial effect on common hospital-acquired infection pathogens of ephedrine alone or combined with propofol.

**Material and method:** The study was performed in two stages. In the first, the Minimum Inhibitory Concentration of propofol and ephedrine alone and combined was calculated for *Escherichia coli*, *Enterococcus faecium*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and a clinical isolate of *Acinetobacter* spp. at 0, 6, 12 and 24 h, using the microdilution method. In the second stage, the same drugs and combination were used to determine their effect on bacterial growth. Bacterial solutions were prepared at 0.5 MacFarland in sterile 0.9% physiological saline and diluted at 1/100 concentration. Colony numbers were measured as colony forming units.mL<sup>-1</sup> at 0, 2, 4, 6, 8, 10 and 12th hours.

**Results:** Ephedrine either alone or combined with propofol did not have an antimicrobial effect on *Escherichia coli*, *Enterococcus faecium*, or *Pseudomonas aeruginosa* and this was similar to propofol. However, ephedrine alone and combined with propofol was found to have an antimicrobial effect on *Staphylococcus aureus* and *Acinetobacter* species at 512 mcg.mL<sup>-1</sup> concentration and significantly decreased bacterial growth rate.

**Conclusion:** Ephedrine has an antimicrobial activity on *Staphylococcus aureus* and *Acinetobacter* species which were frequently encountered pathogens as a cause of nosocomial infections.

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**PALAVRAS-CHAVE**

Efedrina;  
Propofol;  
Antimicrobiano

**A atividade antimicrobiana de efedrina e da combinação de efedrina e propofol: um estudo *in vitro*****Resumo**

**Introdução:** Propofol e efedrina são fármacos comumente usados durante a manutenção da anestesia, o primeiro como agente hipnótico e o segundo como vasopressor. A adição de propofol à efedrina ou a administração de efedrina antes da injeção de propofol é útil para diminuir ou prevenir alterações hemodinâmicas e dor vascular relacionadas ao propofol. Este estudo *in vitro* avaliou o efeito antibacteriano de efedrina, isolada ou em combinação com propofol, em patógenos comuns implicados em infecção hospitalar.

**Material e método:** O estudo foi realizado em duas etapas. Na primeira, a concentração inibitória mínima (CIM) de propofol e de efedrina isolada e em combinação foi calculada para *Escherichia coli*, *Enterococcus faecium*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* e um isolado clínico de *Acinetobacter spp* às 0, 6, 12 e 24 horas, usando o método de microdiluição. Na segunda etapa, o mesmo fármaco e sua combinação foram utilizados para determinar seus efeitos no crescimento bacteriano. As soluções bacterianas foram preparadas em soro fisiológico a 0,9% em 0,5 McFarland e diluídas a uma concentração de 1/100. Os números das colônias foram medidos como cfu.mL<sup>-1</sup> às 0, 2, 4, 6, 8, 10 e 12 horas.

**Resultados:** Efedrina isolada ou em combinação com propofol não apresentou efeito antimicrobiano sobre *E. coli*, *E. faecium* ou *P. aeruginosa*, um resultado semelhante ao de propofol. Porém, efedrina isolada e em combinação com propofol apresentou efeito antimicrobiano sobre *Staphylococcus aureus* e *Acinetobacter spp*, em concentração de 512 mcg.mL<sup>-1</sup>, e redução significativa da taxa de crescimento bacteriano.

**Conclusão:** Efedrina tem atividade antimicrobiana em *S. aureus* e *Acinetobacter spp*, que são patógenos frequentemente identificados como causa de infecções nosocomiais.

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**Introduction**

Propofol a commonly used hypnotic agent for the induction and maintenance of anesthesia is known to be a microbial growth-promoting agent that is prone to contamination, due to its lipid emulsion structure.<sup>1,2</sup> Despite awareness of the potential of contaminated propofol, sepsis and endotoxemia are still observed, sometimes even causing mortality.<sup>3-5</sup> Several agents have been used in combination with propofol to decrease its risk of contamination, including lidocaine that is also helpful in reducing the pain observed during administration.<sup>2,6-8</sup> Propofol is, of course, not the only source of bacterial contamination in operating rooms and intensive care units, and several medications and devices can lead to the complications of bacterial contamination, including sepsis.

Ephedrine is a commonly used vasopressor agent that has been used for several purposes in anesthesia practices.<sup>9,10</sup> Studies have demonstrated that the addition of propofol as an admixture to ephedrine or administration of ephedrine before propofol injection is useful for decreasing or preventing propofol related hemodynamic changes and propofol related vascular pain.<sup>11-13</sup> A recently published study reported that ephedrine had an antimicrobial effect on *Escherichia coli* at certain concentrations.<sup>14</sup> We are unaware of any similar studies.

This *in vitro* study was performed to evaluate the antibacterial effect on common hospital-acquired infection pathogens of ephedrine alone or combined with propofol.

**Material and method****Drugs and microorganisms**

Ephedrine (Efedrin Hidroklorür ampul 0.05 g.mL<sup>-1</sup>, Biosel, Türkiye) and 1% propofol (Propofol 1% Fresenius, Türkiye) was used in this study. The study was designed with two stages. In the first stage, the Minimum Inhibitory Concentrations (MIC) of ephedrine and propofol separately and combined were determined using the broth microdilution method according to the procedures outlined by the Clinical and Laboratory Standards Institute (CLSI).<sup>15</sup> In the second stage, the effect on growth rate of organisms found to be affected by these drugs was measured. *Staphylococcus aureus* ATCC 25923, *E. coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Enterococcus faecium* RSKK 01.016 and a clinical isolate of a multidrug resistant *Acinetobacter spp*. were used as control microorganisms. These strains of bacteria were obtained from American Type Culture Collection, USA (ATCC) and Refik Saydam National Type Culture, Collection, Turkey (RSKK).

**Determination of MIC**

**Step 1: Preparation of drug mixtures:** Aseptic drug mixtures for Ephedrine (E), Propofol (P) and mixture of Ephedrine and Propofol (E+P) were prepared separately in 0.9% sterile physiologic saline with final concentrations of 512 µg.mL<sup>-1</sup>, 256 µg.mL<sup>-1</sup>, 128 µg.mL<sup>-1</sup>, 64 µg.mL<sup>-1</sup>,

**Table 1** Minimum Inhibitory Concentration (MIC) values of Ephedrine (E) and Propofol & Ephedrin (E + P) admixtures at 0, 6th, 12th and 24th hours for different microorganisms. NI, No Inhibition at any concentration.

	0 hour		6th hour		12th hour		24th hour	
	E ( $\mu\text{g.mL}^{-1}$ )	E + P ( $\mu\text{g.mL}^{-1}$ )	E ( $\mu\text{g.mL}^{-1}$ )	E + P ( $\mu\text{g.mL}^{-1}$ )	E ( $\mu\text{g.mL}^{-1}$ )	E + P ( $\mu\text{g.mL}^{-1}$ )	E ( $\mu\text{g.mL}^{-1}$ )	E + P ( $\mu\text{g.mL}^{-1}$ )
<i>E. coli</i>	NI	NI	NI	NI	NI	NI	NI	NI
<i>P. Aeruginosa</i>	NI	NI	NI	NI	NI	NI	NI	NI
<i>E. faecium</i>	NI	NI	NI	NI	NI	NI	NI	NI
<i>S. aureus</i>	NI	NI	512	512	512	512	512	512
<i>Acinetobacter</i>	NI	NI	512	512	512	512	512	512

32  $\mu\text{g.mL}^{-1}$ , 16  $\mu\text{g.mL}^{-1}$ , 8  $\mu\text{g.mL}^{-1}$ , 4  $\mu\text{g.mL}^{-1}$ , 2  $\mu\text{g.mL}^{-1}$ , 1  $\mu\text{g.mL}^{-1}$  and 0.5  $\mu\text{g.mL}^{-1}$ .

**Step 2: Preparation of bacterial solutions:** Solutions were prepared at 0.5 MacFarland in sterile 0.9% physiological saline for each bacterium.

**Step 3: Preparation of microwells:** 0.1 mL of drug mixture and 0.01 mL of bacterial solution ( $5 \times 10^5$  Colony-Forming Units per milliliter [CFU.mL<sup>-1</sup>]), 0.1 mL CAMHB (Cation-Adjusted Mueller Hinton Broth) were placed into microwells for all drug and bacteria combinations.

**Step 4: Subcultures and colony count:** Subcultures from all microwells were taken at 0, 6th, 12th and 24th hours of incubation. Each subculture was incubated at  $36 \pm 2^\circ\text{C}$  for 18 h. After incubation, colonies were counted for all preparations.

### Determination of bacterial growth rate

This section of the study was only performed for microorganisms found to be inhibited by E, P or E + P.

**Step 1: Preparation of drug solutions:** Eight sets of tubes were prepared for E, P and E + P respectively. Each tube was prepared to have a concentration of 512  $\mu\text{g.mL}^{-1}$  with a total of 1 mL in each tube. One tube in each set was assigned as the control tube.

**Step 2: Preparation of bacterial solutions:** Bacterial solutions were prepared at 0.5 MacFarland in 0.9% sterile solution that was diluted to 1/1000.

**Step 3: Combination of drug and bacterial solutions:** 50  $\mu\text{L}$  of bacterial solution was added to each set of drug solution except for the three control tubes.

**Step 4: Determination of colony numbers:** All tubes were incubated at  $36 \pm 2^\circ\text{C}$ . At 0, 2nd, 4th, 6th, 8th, 10th and 12th hours, samples were obtained and diluted to 1/100 with 0.9% sterile saline solution. 100  $\mu\text{L}$  of this dilution was inoculated into sheep blood agar. Plaques were incubated at  $36 \pm 2^\circ\text{C}$  for 24 h. Colony numbers (CFU.mL<sup>-1</sup>) were measured by a second researcher.<sup>16,17</sup>

### Results

The MIC values for microorganisms in different drug solutions are shown in Table 1. The MIC values of microorganisms in ephedrine were determined as follows at 6th hour: *E. coli*, *P. aeruginosa* and *E. faecium* were above 512  $\mu\text{g.mL}^{-1}$ ; *S. aureus* and *Acinetobacter* spp. were 512  $\mu\text{g.mL}^{-1}$  and after

24 h the MIC values were the same for all the isolates. In propofol studied strains grew within 3–6 h.

The MIC values of ephedrine in propofol were the same as ephedrine alone. Ephedrine has antibacterial effects on *S. aureus* and *Acinetobacter* spp. which are frequently encountered in hospital settings, but when these drugs are administered as an infusion alone or with propofol, it should be used at concentrations equal to or greater than 512  $\mu\text{g.mL}^{-1}$ .

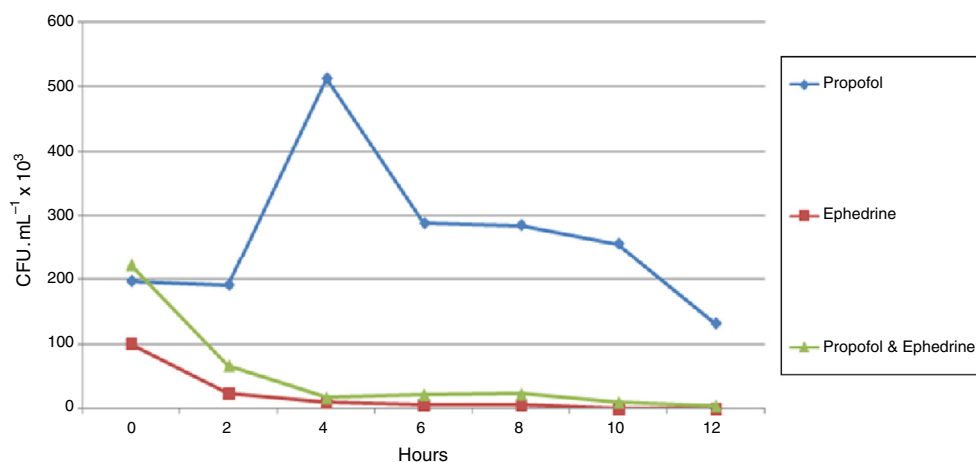
In the second stage, the growth rates of *S. aureus* and *Acinetobacter* spp. in ephedrine alone and ephedrine plus propofol were determined. These rates are shown in Figs. 1 and 2. Ephedrine alone or combined with propofol was found to significantly decrease the growth rate of these microorganisms.

### Discussion

Propofol, as shown in this study, is a strong bacterial growth promoting emulsion. Ephedrin either alone or combined with propofol did not have an antimicrobial effect on *E. coli*, *E. faecium* or *P. aeruginosa* and this was similar to propofol. However, ephedrine alone and combined with propofol was found to have an antimicrobial effect on *S. aureus* and *Acinetobacter* spp. at 512 mcg.mL<sup>-1</sup> concentration and significantly decreased bacterial growth rate.

Contaminated propofol can lead to many infectious complications. The administration of lidocaine before propofol injection or its addition to propofol is commonly used to prevent propofol injection related pain. Several studies have shown the antibacterial effect of lidocaine at high concentrations. However, Vidovich et al.<sup>18</sup> reported that lidocaine alone or combined with propofol did not have an effect on *S. aureus*, *Serratia marcescens*, *Pseudomonas aeruginosa* and *Candida albicans* at low concentrations (1%). Ozer et al.<sup>7</sup> reported antimicrobial effect of lidocaine on *E. coli*, *S. aureus*, *S. epidermidis* and *P. aeruginosa* at a high concentration of 2%, but no antimicrobial effect at low concentrations of 0.05–0.1%. Similar to the previously mentioned reports, many studies have demonstrated that propofol is a strong bacterial growth promoting agent.

In addition to the above mentioned studies, Masaki et al.<sup>19</sup> evaluated the physicochemical compatibility of propofol and lidocaine mixture. In this study, 5–10–20–40 mg lidocaine was added to 20 mL of 1% propofol. Firstly, chemical stability was evaluated



**Figure 1** *Staphylococcus aureus* growth rates in different drugs and admixture. CFU, Colony Forming Units.

using gas chromatography. Secondly, for formation of microprecipitation or oil droplets for evaluated with scanning electron microscopy in randomly selected fields. The authors reported a linear decrease in lidocaine concentration after 4 h in the mixture that included 40 mg lidocaine and electron microscopy showed droplets with diameters of  $\geq 5 \mu\text{m}$  appearing 30 min after preparation of mixture. Due to these findings, the authors drew attention to the possibility of emboli at high doses of lidocaine in propofol mixture. There are no similar studies for ephedrine and propofol.

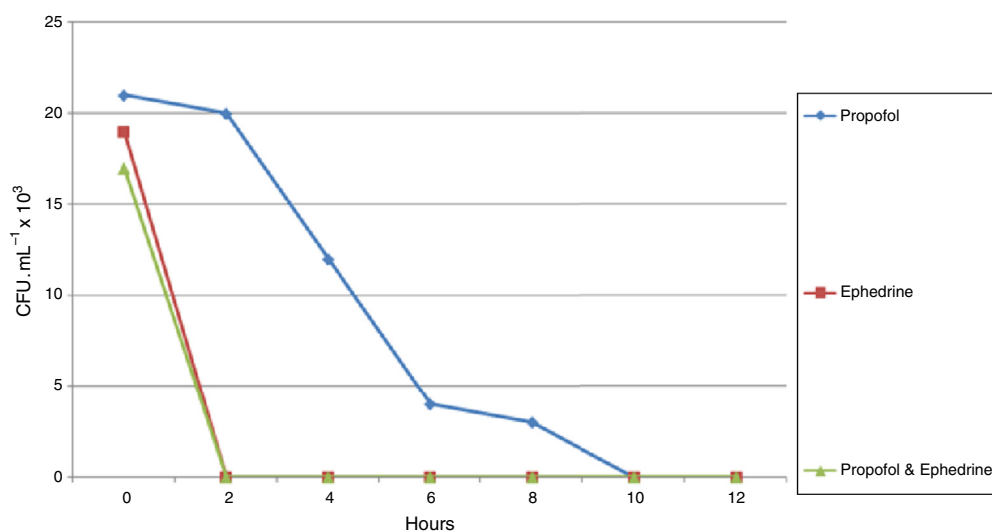
The antimicrobial effect of many anesthetic agents has previously been studied. Begec et al.<sup>2</sup> evaluated the antimicrobial effect of ketamine–propofol combination, commonly used for anesthesia induction and sedoanalgesia. Their study reported antimicrobial effect on *E. coli*, *P. aeruginosa* and *C. albicans* at high ketamine concentration of admixture, but no such effect on *S. aureus*.

In a study evaluating the antimicrobial effect of 1–10–100  $\mu\text{g.mL}^{-1}$  concentrations of remifentanyl in propofol, the authors found a dose-related significant

antimicrobial effect on *S. aureus* and *P. aeruginosa*, and a similar but less effect on *E. coli* and *C. albicans*.<sup>20</sup> Another in vitro study reported the antimicrobial effect of remifentanyl on *S. aureus*, *S. epidermidis*, *E. faecalis*, *E. coli*, *P. aeruginosa* and a clinical isolate of a multidrug resistant *Acinetobacter* spp.<sup>17</sup>

The antimicrobial effect of anesthetic agents is mostly compared with propofol or the agent is used as an admixture with propofol. In our study, we evaluated the antimicrobial effect of ephedrine alone and as an admixture with propofol. We found that ephedrine both alone and in combination was effective at inhibiting bacterial growth of *S. aureus* and *Acinetobacter* spp. The same effect was not observed with other microorganisms.

The only previous study on antimicrobial effect of ephedrine was published by Zhao et al.<sup>14</sup> Using ephedrine at a concentration of 328.76  $\text{mcg.mL}^{-1}$  at 37 °C, they found that *E. coli* growth was inhibited by 50%. The authors therefore concluded that ephedrine could be a potential antibacterial agent of clinical importance. This report was the inspiration for the current study. In the current



**Figure 2** *Acinetobacter* spp. growth rates in different drugs and admixture. CFU, Colony Forming Units.

study, however, we were unable to determine any effect of ephedrine on inhibiting growth of *E. coli*.

In order to determine the effect of ephedrine on *E. coli*, Zhao et al.<sup>14</sup> used microcalorimetric tests to calculate the half inhibitory concentration. Microcalorimetric tests are non-invasive and non-destructive techniques that demonstrate the interaction of a drug and the microbial cell. Microcalorimetric studies have been used to evaluate the effect of single or a combination of antibacterial drugs.<sup>14,21,22</sup> Although this technique has a high sensitivity, accuracy and is simple to perform, it is also expensive and is not available at our institute. Therefore, we used microdilution and microbial culturing in our study. In addition, propofol's lipid content causes it to act as a growth promoting agent<sup>6</sup> while we hypothesized that Ephedrine on the other hand is antimicrobial. We were unable to find a study that utilized microcalorimetric techniques for the evaluation of a combination of growth promoting and antimicrobial agents. Therefore, we do not believe that microcalorimetric techniques would be appropriate for this study.

Although the *E. coli* strains of our study and that of Zhao et al. were not the same, we cannot explain our different findings as both strains were of international standards. While Zhao et al. used 99.9% concentrated ephedrine and cultured *E. coli* in peptone culture and then transferred to LB tubes, we used commercial form of ephedrine and blood agar for culture material. Zhao et al. used methanol to dilute ephedrine while we used isotonic NaCl. The discrepancy in the findings of these two studies cannot therefore be attributed to one, but many differences in study methodologies. Further investigations would be necessary to clearly explain this discrepancy.

The use of ephedrine with propofol admixture is not common in anesthesia practice. Several studies have reported good results when ephedrine is used before propofol injection or as an admixture with propofol for decreasing propofol injection pain and propofol related hemodynamic changes.<sup>11,12,23,24</sup> We determined antimicrobial effect of ephedrine at a concentration of 512 mcg.mL<sup>-1</sup>. However, more precise studies may find this concentration to be between 256 mcg.mL<sup>-1</sup> and 512 mcg.mL<sup>-1</sup>. Even when propofol admixture is prepared with 512 mcg.mL<sup>-1</sup> concentration, the dosage of ephedrine given at induction is 125 mcg.kg<sup>-1</sup>. This is similar or less than other reports.<sup>11,12,23,24</sup> Studies on single doses of ephedrine have reported even higher doses.<sup>25</sup>

In addition to its antimicrobial effect, the use of ephedrine with propofol during induction has several additional benefits. There may be a decrease in propofol injection pain.<sup>11-13</sup> Propofol is the most commonly used anesthetic-hypnotic agent and is associated with hypotension at induction.<sup>26</sup> Ideally, an anesthetic agent should provide adequate hypnosis with minimal hemodynamic changes in order to maintain hemodynamic stability. Many studies have reported the use of ephedrine for prevention of propofol associated hemodynamic changes.<sup>10,23,24,26</sup> However, the use of propofol-ephedrine mixture should be used with caution in hypertensive patients.

Ephedrine is a commonly used agent especially used in neuraxial anesthesia for urgent vasopressor requirements.<sup>9,27,28</sup> When used as a vasopressor, we do not believe that the low concentration will lead to antimicrobial

effect. However, increased use of propofol-ephedrine admixture for prevention of hemodynamic changes after propofol injection may decrease the contamination rates of propofol and decrease postoperative infectious complications. Also, when we consider the long term use of propofol as an agent for total intravenous anesthesia and for sedation in intensive care units, the admixture with ephedrine may decrease infectious complications. Further clinical and pharmacological studies are required to determine the safe dose range. This is especially important when we consider its antimicrobial effect on *Acinetobacter* spp. Our study is the first to clearly demonstrate the antimicrobial effect of ephedrine on several microbial agents.

Although there are several studies on the clinical use of different concentrations of ephedrine-propofol mixtures, there are no physicochemical compatibility or dosage safety studies. Therefore we are unable to draw a clear conclusion with regard to the clinical use of this antimicrobial effect. The use of ephedrine-propofol admixture in anesthesia and intensive care practice may lead to a decrease in infectious complication. Randomized controlled trials are required to determine the efficacy in clinical settings.

## Conclusion

Our study has demonstrated that ephedrine alone or combined with propofol has an inhibitory effect at 512 mcg mL<sup>-1</sup> concentration on bacterial growth rate of *S. aureus* and *Acinetobacter* spp.

## Conflicts of interest

The authors declare no conflicts of interest.

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