Comparison of Antimicrobial Effects of Different Propofol Ketamine Combinations

ABSTRACT

Introduction: The combined use of ketamine and propofol has been frequently preferred in general anesthesia applications in recent years. The aim of this study was to determine the reliable combination to prevent infection development by comparing different combinations of ketamine and propofol and safe usage period of the combination.

Methods: In the present study S. aureus, K. pneumoniae, E. coli, P. aeruginosa and C. albicans microorganisms were used. The turbidity data obtained at different hours and the zero-hour turbidity data were compared to determine the effect of microorganisms when they were kept at room temperature following the contamination of ketamine, propofol, and different ketamine + propofol mixtures by these microorganisms.

Results: For each microorganism studied, the growth rate within the first 36 hours was observed to be higher in the propofol group compared to the ketamine group and other ketamine + propofol groups. For each microorganism studied, the growth rate was observed to be lower at all time periods in the ketamine group compared to the propofol group and other ketamine + propofol groups. The growth rate was observed to be less when the ketamine ratio increased in the ketamine + propofol mixture for all microorganisms.

Conclusion: The growth rate was observed to be less in ketamine + propofol combinations due to the antibacterial effect of ketamine, compared to the group in which only propofol was used.

Keywords: Propofol, ketamine, antimicrobial, ketofol, intravenous anesthesia, sedation, intensive care.

INTRODUCTION

Propofol and ketamine are commonly used in general anesthesia applications. Propofol is a sedative-hypnotic agent with short action time and a short elimination half-life. It provides rapid recovery without residual psychomotor effect, but it does not have an analgesic feature. Ketamine has a quality analgesic effect and is preferred due to causing minimal respiratory depression. Furthermore, hemodynamic stability is provided by the combined use of these two drugs since propofol has a sympathetic depressant effect and ketamine has a sympathetic stimulating effect.[1,2] This combination is called ketofol.[1]

Although propofol is the most commonly used anesthetic agent and is considered an adequate medium due to its rich nutrient content, which contains soybean oil, glycerol and egg lecithin, serious infections have been reported to develop following the use of contaminated Propofol.[3,4] Therefore, it is recommended to put great attention while using it since it causes infection when used during general anesthesia induction, total intravenous anesthesia, and infusion in the intensive care unit.

Ketamine has a long shelf life and is reported to be used with safety. Furthermore, there are studies reporting that it has an antimicrobial effect.[5,6]

The combined use of ketamine and propofol is frequently preferred in anesthesia applications and the combination obtained is called ketofol. Anesthetic effects are used and it is tried to avert side effects with the combined use of both agents in different combinations.[7,-9] However, there is no consensus on the optimum combination. For this purpose, different combinations are used in the literature and there are many studies on their clinical effects.[10-12] Nonetheless, as a result of our English literature reviews, there is no study on the safe duration of combined use of ketamine and propofol in different combinations.

The aim of the study is to determine the safe combination and the second aim is the safe use period by comparing the different ketamine and propofol combinations for different microorganisms.

METHODS

This in vitro pre-clinical research was conducted in Beykent University Medical Faculty Microbiology Department Laboratory between 6-17 January 2020. Since our study is an in vitro preclinical study, ethics committee approval is not required.

S. aureus American type culture collection (ATCC) 29213, K. pneumoniae ATCC13883, E. coli ATCC 25922, P. aeruginosa ATCC 27853, and C. albicans ATCC 10231 strains obtained from the national reference center were cultivated in liquid Mueller Hinton broth and incubated at 37°C for 24 hours.

A vial of ketamine (Ketalar 50 mg/mL, Pfizer, Zentiva, Lüleburgaz, Turkey), and a vial of propofol (10 mg/mL, 1% propofol; Fresenius Kabi GmbH, Austria) were opened. Ketamine (50 mg/mL) (Group 1), Propofol (10 mg/mL) (Group 2), a ketamine-to-propofol ratio of 1:1 (10 mg/0.2 mL ketamine + 10 mg/1 mL propofol) (Group 3), a ketamine-to-propofol ratio of 1:2 (10 mg/0.2 mL ketamine + 20 mg/2 mL propofol) (Group 4), and a ketamine-to-propofol ratio of 2:1 (10 mg/0.2 mL ketamine + 5 mg/0.5 mL propofol) (Group 5) were added to five different 1.5-ml sterile microcentrifuge tubes. Sterile distilled water (Group 6) was also added to a 1.5-ml sterile microcentrifuge tube.

These microcentrifuge tubes were prepared for each of S. aureus ATCC 29213, K. pneumoniae ATCC 13883, E. coli ATCC 25922, P. aeruginosa ATCC 27853, and C. albicans ATCC 10231 strains grown on liquid Mueller Hinton broth. A standard suspension of 0.5 McFarland turbidity (with a final measurement concentration of $1.5x10^8$ CFU/mL) was prepared for each strain and the prepared suspensions were spiked into a microcentrifuge tube

for each group and vortexed well. Afterwards, they were incubated at room temperature (20°C).

A 100 µL was transferred from the microcentrifuge tubes to the wells (96-well plates) at 0 h (after spiking the microorganisms), 6 h, 12 h, 18 h, 24 h, 48 h, 72 h, 96 h, 120 h, and 144 h. The 96-well plates were read at 600 nm wavelength (OD600) using an Epoch spectrophotometer (BioTek Inst. Inc., Vermont, USA) and turbidity in the wells was measured. The turbidity data obtained at different hours and the zero-hour turbidity data were compared to determine the effect of microorganisms when they were kept at room temperature following the contamination of ketamine and propofol by these microorganisms after they were opened.

Statistical Analysis: There is no study similar to our study, therefore, when calculating the sample size, different preclinical studies were used. The measurements obtained as a result of the experiment were expressed as mean ± standard deviation. The trend of microbial change over time (at 0 h, 6 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 120 h, and 144 h) in six different groups was evaluated by repeated analysis of variance in repeated measurements. In repeated measurements, the interaction test was made to determine whether the trends differed between the groups over time; the group main effect test was made to determine whether there was a difference between groups when the change over time was ignored; the main effect of time test was made to determine whether there was a difference between time periods when the changes between groups were ignored. Where group-time interaction was found significant, the differences between hours were compared in each group via multiple comparison tests and the differences between groups at each hour were compared. In multiple comparison tests, Bonferroni corrected p values were given to control the Type-I error level. A value of $p<0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics v.23 package program.

RESULTS

Descriptive statistics and variance analysis results for five different bacterial species are given in Table 1–Table 5. The trend of microbial change over time for all bacterial types varied between groups (group-time interaction, $p<0.001$).

Levels in Group 1 were statistically significantly lower than Group 2, Group 3, Group 4 and Group 5 for each microorganism studied ($p<0.001$) (Figures 1–5).

Levels at the first 36 hours were statistically significantly higher in Group 2 than Group 1, Group 3, Group 4 and Group 5 for each microorganism studied ($p<0.001$) (Figures 1–5).

There was a statistically significant difference between Group 2 and Group 6 for each microorganism studied ($p<0.001$) (Figures 1–5).

When Group 2 and Group 5 were compared, levels in Group 5 at all time periods and in all microorganisms were found statistically significantly lower than Group 2 ($p<0.001$) (Figures 1–5).

Compared to Group 2 and Group 3, the levels at the first 48 hours for P. Aurigunosa and at all time periods for all other microorganisms were found to be statistically significantly lower in Group 3 than in Group 2 ($p<0.001$) (Figures 1–5).

When Group 2 and Group 4 were compared, levels at the first 36 hours for K. Pneumonia, levels at the first 48 hours for C. albicans and P. Aurigunosa, and levels at the first 120 hours for Staf Aureus and E. Coli were found statistically significantly lower in Group 4 than in Group 2 ($p<0.001$) (Figures 1–5).

The comparison of the propofol group and 2:1 ratio ketamine:propofol group showed that the bacterial growth in the group, in which the ketamine:propofol mixture was used at a 2:1

concentration, was significantly lower than the group, in which propofol was used alone, within the first 144 hours for each microorganism studied.

The comparison of the propofol group and 1:1 ratio ketamine:propofol group showed that the bacterial growth in the group, in which the ketamine:propofol mixture was used at a 1:1 concentration, was significantly lower than the group, in which propofol was used alone, within the first 48 hours for each microorganism studied.

The comparison of the propofol group and 1:2 ratio ketamine:propofol group showed that the bacterial growth in the group, in which the ketamine:propofol mixture was used at a 2:1 concentration, was significantly lower than the group, in which propofol was used alone, within the first 36 hours for each microorganism studied.

DISCUSSION

Several studies in the literature have reported that infection is developed following the use of contaminated Propofol.[3,4] Furthermore, there are also studies showing that ketamine has antimicrobial effects.[5,6] Nevertheless, the literature review has shown that there is no study on infection rates following the combined use of ketamine with antimicrobial effects and propofol with microbial effects.

In a study from the United States of America, Bennett et al.[13] presented 62 cases of propofol-induced infections, including blood circulation, surgical wound infection, and acute febrile episodes in seven hospitals. The authors reported that microorganism as S. aureus, C. albicans, Moraxella, Enterobacter, and Serratia species were responsible for these infections.

Muller et al.[14] reported that seven patients who underwent minor surgery developed sepsis due to Klebsiella pneumoniae and Serratia marcescens induced by contaminated propofol.

Henry et al.[15] reported that postoperative bacteremia and wound infection developed due to S. marcescens after propofol use.

In an in vitro study, an increase has been reported in the growth of microorganisms such as Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans, and Acinetobacter baumanni after the propofol use.[16]

In the present study, S. aureus, K. pneumoniae, E. Coli, P. aeruginosa and C. albicans microorganisms were used. Levels at the first 36 hours were found to be statistically significantly higher in Group 2 than Group 1, Group 3, Group 4 and Group 5 for each microorganism studied. In other words, the growth rate within the first 36 hours was observed to be higher in the propofol group compared to the ketamine group and other ketamine + propofol groups. The evaluation of the first 36 hours demonstrated that microbial growth was more in propofol. For each microorganism studied, a statistically significant difference was found between Group 2 and Group 6 in terms of growth rates at all time periods. The growth rate was found to be higher in the propofol group than in the control group. Center for Disease Control and Prevention suggested safe medication practices, including avoiding the use of syringes on multiple patients as well as avoiding single-use medication vials for multiple patients, and strictly adhering to aseptic techniques and infection control practices during propofol application.[17] Jansen et al.[18] reported that the rate of infection developed due to propofol decreased from 39 to nine in 1996 after the addition of EDTA. However, despite the precautions taken, there are still infection cases developing after the use of propofol. Therefore, there are ongoing studies and researches to prevent the development of propofol-induced infections.

In an in vitro study by Gocmen et al.[6], ketamine showed antimicrobial activity against streptococcus, staphylococcus, E. coli, and P. aeruginosa microorganisms at a concentration of 500-2,000 microg/mL. In our study, similarly, less growth was observed with ketamine.

Begec et al.[19] observed that ketamine had a potential antibacterial and antifungal activity on the tested strains. Regarding the organisms' types, they found P. aeruginosa and E. coli to be more resistant, and S. aureus were the most susceptible to ketamine.

In our study, the comparison of propofol and other ketofol groups showed that the growth rate was lower in the ketamine group. Ketamine was thought to have antimicrobial effects against microorganisms used in the present study. The growth rate was observed to be less when the ketamine ratio in the ketamine + propofol mixture increased for all microorganisms. In our study, it was observed that the safest combination with the longest usage time was 2: 1 propofol ketamine group.

In conclusion: The growth rate was shown to be less in ketamine + propofol combinations, compared to the groups in which only propofol was used. We believe that the drug may be less contaminated if the ketofol combinations are preferred, particularly in total intravenous anesthesia or sedation applications in the intensive care unit and the development of infection might be prevented. There is a need for new studies on this subject involving different microorganisms.

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FIGURES LEGENDS

Figure 1. The trend of microbial change over time for C. albicans fungus.

Figure 2. The trend of microbial change over time for E. Coli bacteria.

Figure 3. The trend of microbial change over time for K. pneumoniae bacteria.

Figure 4. The trend of microbial change over time for P. Aeruginosa bacteria.

Figure 5. The trend of microbial change over time for S. Aureus bacteria.

ABBREVIATIONS

ATCC: American type culture collection

S. aureus: Staphylococcus aureus

P. aeruginosa: Pseudomonas aeruginosa

E. coli: Escherichia coli

K. pneumoniae: Klebsiella pneumoniae

C. albicans: Candida albicans