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ARTICLE

Effects of ketamine in methicillin-resistant *Staphylococcus aureus* and in silico interaction with sortase A

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Abstract: Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the main human pathogens and is responsible for many diseases, ranging from skin infections to more invasive infections. These infections are dangerous and expensive to treat because these strains are resistant to a large number of conventional antibiotics. Thus, the antibacterial effect of ketamine against MRSA strains, its mechanism of action, and in silico interaction with sortase A were evaluated. The antibacterial effect of ketamine was assessed using the broth microdilution method. Subsequently, the mechanism of action was assessed using flow cytometry and molecular docking assays with sortase A. Our results showed that ketamine has a significant antibacterial activity against MRSA strains in the range of 2.49–3.73 mM. Their mechanism of action involves alterations in membrane integrity and DNA damage, reducing cell viability, and inducing apoptosis. In addition, ketamine had an affinity for *S. aureus* sortase A. These results indicate that this compound can be used as an alternative to develop new strategies to combat infections caused by MRSA.

Key words: methicillin-resistant *Staphylococcus aureus*, ketamine, repositioning of drugs, flow cytometry, molecular docking, sortase A.

Résumé : *Staphylococcus aureus* résistant à la méthicilline (SARM) est l'un des principaux agents pathogènes chez l'humain et il est responsable de nombreuses maladies allant des infections cutanées aux infections plus invasives. Ces infections sont dangereuses et coûteuses à traiter, car ces souches sont résistantes à un grand nombre d'antibiotiques conventionnels. Cela dit, l'effet antibactérien de la kétamine contre les souches de SARM, son mécanisme d'action et son interaction in silico avec la sortase A ont été évalués. L'effet antibactérien de la kétamine a été évalué par la méthode de microdilution en milieu liquide. Par la suite, son mécanisme d'action a été évalué à l'aide de la cytométrie en flux et d'essais d'arrimage moléculaire avec la sortase A. Les résultats obtenus par les auteurs ont montré que la kétamine exerce une activité antibactérienne significative contre les souches de SARM dans une gamme de 2,49 à 3,73 mM. Son mécanisme d'action implique des modifications de l'intégrité de la membrane et des dommages à l'ADN, réduisant la viabilité des cellules en provoquant la mort par apoptose. De plus, la kétamine avait une affinité pour la sortase A de *S. aureus*. Ces résultats

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indiquent que ce composé peut être une solution de rechange dans le développement de nouvelles stratégies pour combattre les infections causées par le SARM. [Traduit par la Rédaction]

Mots-clés : *Staphylococcus aureus* résistant à la méthicilline, kétamine, repositionnement des médicaments, cytométrie en flux, arrimage moléculaire, sortase A.

1. Introduction

Staphylococcus aureus is a versatile microorganism that is part of the normal human microbiota. It is found colonizing the nostrils of approximately 20%–30% of the adult population (Mulcahy and McLoughlin 2016; Krismer et al. 2017), and current studies have also shown the occurrence of *S. aureus* and methicillin-resistant *S. aureus* (MRSA) in healthy children and youth (Hussein et al. 2015; Kateete et al. 2019). MRSA is associated with a variety of infections that cause high morbidity, mortality, and healthcare costs, such as hospitalization in the intensive care unit (ICU), generating considerable socioeconomic impacts (Chatterjee et al. 2018; van Rijt et al. 2018) Fouda et al. (2016) corroborate this finding, in which 70% of healthcare professionals were stable MRSA carriers. To address this issue, systematic surveillance and research efforts are required (Rasigade et al. 2014).

Currently, the greatest concern for healthcare professionals and researchers is related to the resistance of this pathogen to conventional drugs used in the clinical treatment of *S. aureus*, such as methicillin, vancomycin, daptomycin, and mupirocin (Monecke et al. 2011; Miller et al. 2016; Lakhundi and Zhang 2018; Dadashi et al. 2020). This apprehension mainly involves individuals with certain risk factors, such as immunocompromised patients, ICU patients, hemodialysis patients, diabetes mellitus patients, and patients with a history of hospitalization or who have undergone a surgical procedure (Cadena et al. 2016).

In this context, the resistance of bacterial pathogens to antimicrobials is a challenge, resulting in high morbidity and mortality. Due to the scarcity of effective therapies, lack of new antibiotics, and successful prevention measures, the development of new therapeutic strategies is necessary (Frieri et al. 2017). Among these is the repositioning of non-antibiotic drugs with a known toxicity profile for the treatment of bacterial infections (Serafin and Hörner 2018). Repositioning of drugs with well-established pharmacological and toxicological properties has the advantage of reducing costs for the development of new drugs (Siles et al. 2013).

Molecular docking is an important technique for the prediction and evaluation of the interactions of substances with a target protein, by selecting the compounds through virtual libraries, allowing not only the discovery of new drugs, but also understanding the behavior of the target drug in question (Kontoyianni 2017). Sortase A is an enzyme present in the cell membrane of gram-positive bacteria, such as *S. aureus*, which is responsible for the adhesion and virulence processes (Schneewind and Missiakas 2019). This has attracted the search for molecules capable of inhibiting this enzyme through the screening of potential therapeutic agents (Clancy et al. 2010).

Recently, studies on the repositioning of drugs have shown that ketamine is a promising drug with antimicrobial activity against various pathogenic microorganisms. This substance, known for its use as a general anesthetic, has shown antifungal and antibacterial effects in in vitro studies (Gocmen et al. 2008; Begec et al. 2013*b*; Torres et al. 2018; de Andrade Neto et al. 2020). In addition, studies on the genotoxicity and mutagenicity of ketamine in eukaryotic and prokaryotic models have shown low cytotoxic effects and no mutagenesis (Cavalcanti et al. 2020).

Thus, this study evaluated the in vitro activity of ketamine against MRSA strains and analyzed its mechanism of action using flow cytometry. In addition, molecular docking was used to assess the in-silico interaction of ketamine with sortase A, which is involved in the pathogenesis of *S. aureus* infection.

2. Materials and methods

2.1. Microorganisms and drugs

Six clinical strains of MRSA and one strain of *S. aureus* (ATCC 6538p) from the collection of the Laboratory for Bioprospection of Antimicrobial Molecules of Federal University of Ceará (LABIMAN/FF/UFC) were used. All strains were obtained from specimens submitted between 2014 and 2015 to the St. Joseph Hospital for Infectious Diseases (HSJCE) and were isolated from a variety of sources, including blood, respiratory secretions, wounds, and tissues. Ketamine hydrochloride and sodium oxacillin monohydrate were purchased from Sigma–Aldrich (USA).

2.2. Determination of minimum inhibitory concentration (MIC)

The MIC values of the drugs were determined by broth microdilution using 96-well plates according to document M07-A9 (CLSI 2012). Ketamine was evaluated at concentrations ranging from 0.772 to 4.94 mM, and oxacillin at concentrations ranging from 0.125 to 64 μg/mL. The plates were incubated at 35 °C for 20 h, after which the bacterial growth inhibition was visually analyzed, with negative control and positive control used for each experiment. The MIC value corresponded to the lowest concentration that inhibited bacterial growth by 99%.

2.3. Bacterial cell exposure to ketamine

A strain of MRSA (MRSA 1) was selected to determine membrane integrity and DNA fragmentation using the comet assay. The strain was incubated in BHI broth at 37 °C for 20 h to obtain a suspension in the exponential phase of bacterial growth. The cells were collected,

centrifuged (1600*g* for 10 min), washed twice with 0.85% saline solution (1200*g* for 5 min), and resuspended in HEPES buffer solution (Sigma Chemical Co., USA) supplemented with 2% glucose at pH 7.2 to obtain a final concentration of approximately 10^6 cells/mL (Williams et al. 1998; Shi et al. 2007; Silva et al. 2011; de Andrade Neto et al. 2020). The bacterial suspension of MRSA at a concentration of 5×10^6 CFU/mL was incubated at 35 °C for 20 h with ketamine at MIC and 2× MIC and with oxacillin at MIC.

2.4. Determination of membrane integrity and cell viability

The integrity of the bacterial cell membrane was evaluated using 2 mg/L of propidium iodide (PI) by the exclusion test. After 20 h of incubation with the drugs at the determined concentrations, aliquots were evaluated using flow cytometry (FACSCalibur flow cytometer; Becton Dickinson, San Jose, CA, USA) (de Andrade Neto et al. 2020; Av Sá et al. 2020). A total of 10 000 events were evaluated in the experiment, with cell debris omitted from the analysis.

2.5. DNA fragmentation analysis

With respect to DNA fragmentation analysis, the terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) method was used (de Andrade Neto et al. 2020). The treated cells were fixed with 7% paraformaldehyde, lysed with 1% Triton X-100 for 10 min on ice, and subsequently incubated with the TUNEL reaction mixture for 1 h at 37 °C. Finally, the cells were evaluated using a fluorescence microscope (Olympus, Tokyo, Japan), with 200 cells counted per sample to determine the percentage of positive cells (de Andrade Neto et al. 2020; Av Sá et al. 2020).

2.6. Comet assay

The standard alkaline test was performed as described by Collins (2004). After treatment, the cells were washed with cold PBS, trypsinized, and resuspended. Then, the bacterial suspension (0.7×10^5 cells/mL) was added to 0.75% agarose with a low melting point, and spread on a glass slide that was previously coated with 1% agarose with a normal melting point, so that the agarose was left at 4 °C for 5 min. Subsequently, the slides were incubated with cold lysis solution (NaCl 2.5 M, Tris 10 mM, EDTA 100 mM, 1 % Triton X-100, and 10% DMSO, pH 10.0) at a temperature of 4 °C for at least 1 h, followed by electrophoresis. The gel was then neutralized, stained with ethidium bromide (1 mg/mL), and visualized by fluorescence microscopy (Pinkerton et al. 2010; de Andrade Neto et al. 2020). Images were obtained from 100 randomly chosen cells for each experimental group. The rate of DNA damage was ranked according to the following categories: ranging from 0, characterized as completely undamaged (100 cells × 0) to 400, with indication of maximum damage (100 cells × 4).

2.7. Statistical analysis

Antimicrobial sensitivity tests were performed on three different days, and the geometric means of the results were calculated. Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by the Newman–Keuls test ($p < 0.05$). Mean values acquired from the *C. albicans* biofilm formation supernatant reading were evaluated using the ANOVA parametric test, followed by Tukey's test ($p < 0.05$).

2.8. Molecular docking

2.8.1. Binder preparation

The two-dimensional ketamine structure (CID3821) was selected in the PubChem repository (https://pubchem.ncbi.nlm.nih.gov/) and optimized at physiological pH from the energy minimization protocol using the steepest descending algorithm with cycles of 50 interactions and MMFF94 force field (Halgren and Nachbar 1996), established in the MarvinSketch (Csizmadia 1999) and Avogadro (Hanwell et al. 2012) codes.

2.8.2. Obtaining the three-dimensional structure and preparing sortase A

The enzyme was obtained from the Protein Data Bank (https://www.rcsb.org/), PDB ID: 2KID, validated by the NMR method solution; conformers calculated: 400; conformers submitted: 20; selection criteria: structures with acceptable covalent geometry, classified as hydrolase/hydrolase inhibitor, *S. aureus* organism, and *Escherichia coli* expression system (Suree et al. 2009). In an attempt to favor adequate protonation states for molecular docking simulations (Milite et al. 2019), the complexed residue (PHQ)LPA(B27) peptide was removed from the enzyme using the UCSF code Chimera (Pettersen et al. 2004), and polar hydrogen was added through the AutoDockTools (Morris et al. 2009) code.

2.8.3. Molecular docking

The simulation routines were performed using the Lamarckian genetic algorithm. All simulations were performed using 3-way multithreading, grid box space delimited at center_x = −0.324, center_y = 4.617, center_z = −0.469, size_x = 126, size_y = 114, size_z = 114, spacing = 0.425, and exhaustiveness = 8. One hundred independent simulations were performed, configured to obtain 10 poses per simulation. After screening, 27 independent simulations were performed to validate the results. The fitting simulations were performed with the AutoDockVina code (version 1.1.2) (Trott and Olson 2009), the two- and three-dimensional renderings were generated using the Discovery Studio Visualizer (Dassault Systèmes Biovia 2019) and UCSF Chimera (Pettersen et al. 2004) viewer.

2.8.4. Selection and validation criteria

As a selection criterion, simulations were selected that present bond-free energy equal to or less than −6.0 kcal/mol and root mean square deviation (RMSD) up to 2.0 Å (Yusuf et al. 2008; Shityakov and Förster 2014).

3. Results

3.1. Ketamine exhibits antibacterial activity against MRSA strains

The minimum inhibitory concentration (MIC) of oxacillin in MRSA-tested strains ranged from 0.125 to 64 μg/mL, as shown in Table 1. For the control strain of *S. aureus* (ATCC 6538p), the MIC of oxacillin was 1.66 μg/mL. Regarding the antibacterial effect of ketamine, the MIC of most strains was 2.49 mM, with the exception of MRSA 3, for which the MIC corresponded to 3.73 mM.

3.2. Ketamine alters membrane integrity and reduces cell viability following exposure to MRSA strains

The cells treated with oxacillin and ketamine showed significant membrane damage ($p < 0.05$) compared to the control (Fig. 1) at the concentrations tested, with greater damage to non-viable cells in the 2× MIC concentration of ketamine for the strain used in the test. The percentage of non-viable cells treated with the oxacillin MIC was 38.81% ± 4.98%, while at the ketamine MIC it resulted in 27.09% ± 2.20%, and in ketamine 2× MIC it was 44.79% ± 7.88%, while the control (untreated) obtained 7.02% ± 1.85% non-viable cells.

3.3. Ketamine causes DNA fragmentation in MRSA strains as assessed by the TUNEL assay

Figure 2 demonstrates that treatment of MRSA cells with oxacillin and ketamine promoted a significant increase in TUNEL-positive cells ($p < 0.05$) compared to the control, indicating DNA fragmentation. It is important to note that at the 2× MIC concentration of ketamine, DNA fragmentation increased. For oxacillin at MIC, the result was 46.96% ± 1.59% of TUNEL positive cells, while for ketamine at MIC the result was 35.50% ± 7.36%, and for ketamine at 2× MIC concentration it was 53.65% ± 1.96%. The control (untreated) result was 5.56% ± 2.27% TUNNEL-positive cells.

3.4. Ketamine generates damage to DNA strands as assessed by the comet test

Figure 3 shows that in MRSA cells treated with oxacillin and ketamine, there was a significant increase in DNA damage ($p < 0.05$). For oxacillin at MIC, the result was 44.48% ± 4.77%, for ketamine at MCP it was 18.37% ± 2.96%, and for ketamine at 2× MIC it was 39.49% ± 2.90%, while the control (untreated) result was 9.64% ± 2.56% DNA damage.

3.5. Ketamine interacts with sortase A

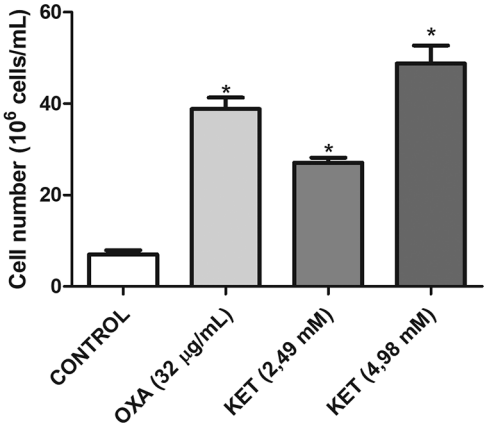
The selected fitting simulation showed affinity energy equal to −5.9 kcal/mol and RMSD of 1554 Å, binding at the same active site as the binder (PHQ)LPA(B27) complexed peptide in sortase A (Fig. 4). Ketamine was closer to Arg197 (2.6 Å) (Table 2). In addition, it was possible to identify a PI-cation interaction between the aromatic region of ketamine and the Arg197 residue of the A chain (Fig. 5), and the Val168 residue was located in the center of a hydrophobic region of sortase A (Fig. 6).

Table 1. Antibacterial effect of oxacillin (OXA) and ketamine (KET) against methicillin-resistant *Staphylococcus aureus* (MRSA).

	MIC value	
Strain	OXA (μg/mL) CIM 20 h	KET (mM) CIM 20 h
MRSA 1	32	2.49
MRSA 2	32	2.49
MRSA 3	24	3.73
MRSA 4	24	2.49
MRSA 5	24	2.49
MRSA 6	32	2.49
S. aureus (ATCC 6538p)	1.66	2.49

Note: Minimum inhibitory concentration (MIC) is defined as the lowest concentration that produced a 99% reduction in the growth of bacterial cells after 20 h of incubation. Microdilution in broth was performed according to CLSI protocol M07-A9. The OXA concentrations ranged from 0.125 to 64 μg/mL and the KET concentrations varied from 0.772 to 4.94 mM. The MICs represent the geometric means of at least three MICs determined on different days.

Fig. 1. Effect of ketamine in the number of viable cells in the representative strain of methicillin-resistant *Staphylococcus aureus* (MRSA) assessed using flow cytometry. MHCA was used as the negative control. *$p < 0.05$ compared to control by ANOVA followed by Newman–Keuls test.



4. Discussion

In the last year (2020), the pandemic caused by the new coronavirus (COVID-19) has generated several crises in the health system worldwide. One of the main difficulties encountered by doctors and the scientific community is to know what type of antimicrobial treatment would be ideal to combat this viral infection (Parveen et al. 2020). According to Punjabi et al. (2020), 71% of all patients hospitalized with COVID-19 receive antibiotic treatment. In addition, they claimed that almost all of these patients received anti-MRSA treatment, since staphylococcal superinfections are complications commonly associated with other viral pneumonias such as influenza A (Vardakas et al. 2009).

Fig. 2. TUNEL test against the representative strain of methicillin-resistant *Staphylococcus aureus* (MRSA) showing DNA fragmentation after incubation with ketamine (KET) (2.49 mM), 2× KET (4.98 mM), oxacillin (OXA) (32 μg/mL), and MHCA (Control) after 24 h. *$p < 0.05$ compared to control by ANOVA followed by Newman–Keuls test.

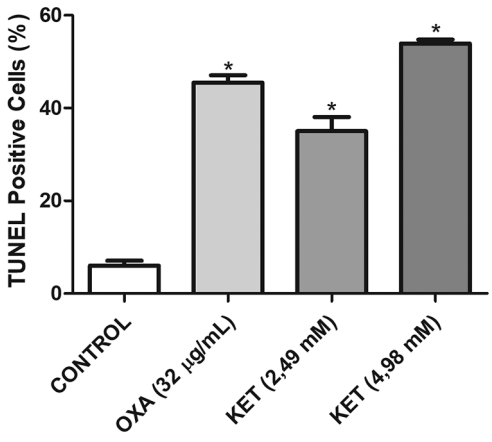
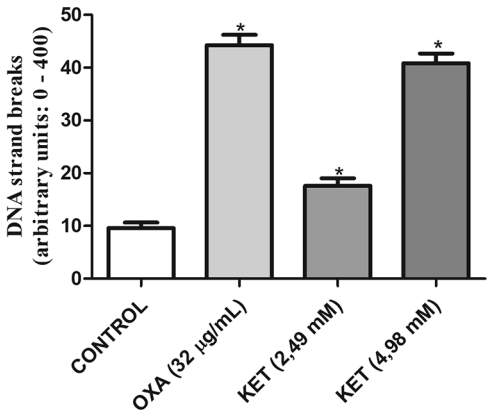


Fig. 3. Evaluation of the DNA damage in a representative strain of methicillin-resistant *Staphylococcus aureus* (MRSA). Effect of 24 h of incubation with ketamine (KET) (2.49 mM), 2× KET (4.98 mM), oxaxcillin (OXA) (32 μg/mL), and MHCA (Control). *$p < 0.05$ compared with the control according to ANOVA followed by Newman–Keuls test.



In this study, ketamine was shown to be effective against MRSA strains, a finding that is in line with the antimicrobial activity reported in other studies, such as the study by Gocmen et al. (2008), in which the in vitro antibacterial activity of ketamine against strains of *S. aureus* (ATCC 29213), *S. epidermidis* (ATCC 12228), *E. faecalis* (ATCC 29212), *S. pyogenes* (ATCC 19615), and *Pseudomonas aeruginosa* (ATCC 27853) was demonstrated. The antibacterial activity of ketamine isolated and associated with propofol was evaluated by Begec et al. (2013*a*) against strains of relevance in view of the paucity of studies evaluating their antimicrobial potential against methicillin-resistant strains.

With respect to its mechanism of action, we performed a membrane integrity test using PI as a marker, so that the impairment of the membrane and ketamine can enter the cell and bind to nucleic acids (Silva et al. 2011). MRSA cells exposed to ketamine showed increased PI absorption, presumably concentration-dependent damage, with the greatest change occurring at 2× the ketamine MIC. Damage to the cytoplasmic membrane may lead to changes in bacterial permeability, modifying the electrochemical balance; thus, failure to transport substances reflects the inability of the bacterial cell to self-regulate adequately, possibly leading to cell death (Das et al. 2016, 2017; Batista de Andrade Neto et al. 2019).

In a study of the antimicrobial activity of the local anesthetics lidocaine and procaine, Schmidt and Rosenkranz (1970) demonstrated that cells exposed to concentrations of up to 2% of these anesthetics inhibited proteins, DNA, and RNA, which can be explained by the damage caused to cell membranes. Another study reported that in addition to direct structural damage caused to the membrane by anesthetics, the permeability of the membrane is affected, causing, for example, efflux of K^+ and consequent enzymatic inhibition of the bacterial cell membrane (Silva et al. 1979). These mechanisms may be linked to affinity and interaction with phospholipids in bacterial cell membranes (Silva et al. 1979). This mechanism is particularly important considering the high solubility of ketamine in lipids (Gao et al. 2016).

Microorganisms such as bacteria use DNA repair mechanisms as a form of self-preservation, ranging from the protection of their genome and bacterial resistance to adaptation to oxidative stress (Žgur-Bertok 2013). In this context, tests were performed to analyze the state of DNA after exposure to ketamine, since the preservation of genetic material is important for the maintenance of bacterial metabolism. In the TUNEL test, increased DNA fragmentation was observed in MRSA cells after treatment with the drug. This assay identifies cells that undergo apoptosis triggered by DNA fragmentation, which was analyzed by this assay (Bayles 2014). In this sense, the fragmented DNA terminals were marked by the enzyme terminal deoxynucleotidyl transferase (TdT) (Bayles 2014; Batista de Andrade Neto et al. 2019).

From this perspective, we also performed the comet assay, in which the breakdown of the DNA strand at the individual level (Kim et al. 2015) was evaluated for a deeper analysis of this process. Our results showed a significant breakdown of DNA strands mediated by exposure to ketamine. These mechanisms may be involved in the process of bacterial cell death, possibly of apoptotic origin, since damage to membrane integrity and DNA is characteristic of programmed cell death (Bayles 2014). Hence, our results suggest that cell death mediated by exposure of MRSA strains to ketamine may occur through the mechanism of apoptosis. However, further studies are needed to elucidate the mechanisms involved in this process.

Fig. 4. Ketamine binding site compared to (PHQ)LPA(B27) peptide. [Colour online.]

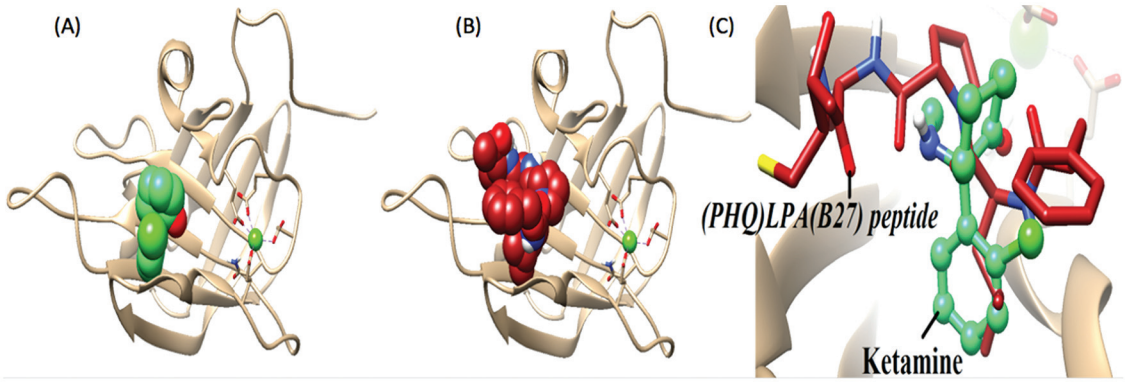


Fig. 5. Molecular interactions of ketamine with sortase A. [Colour online.]

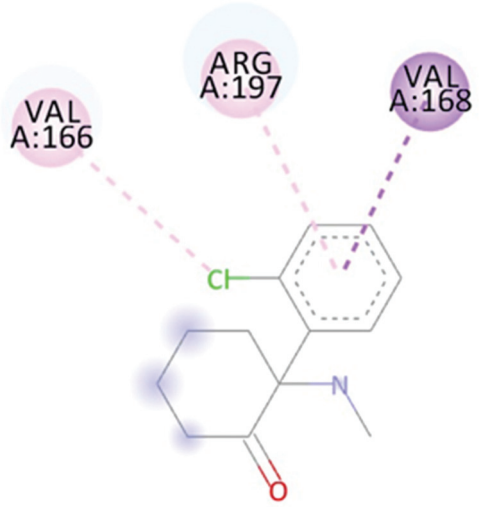


Table 2. Distances between the sortase A of *Staphylococcus aureus* residues and the ligand.

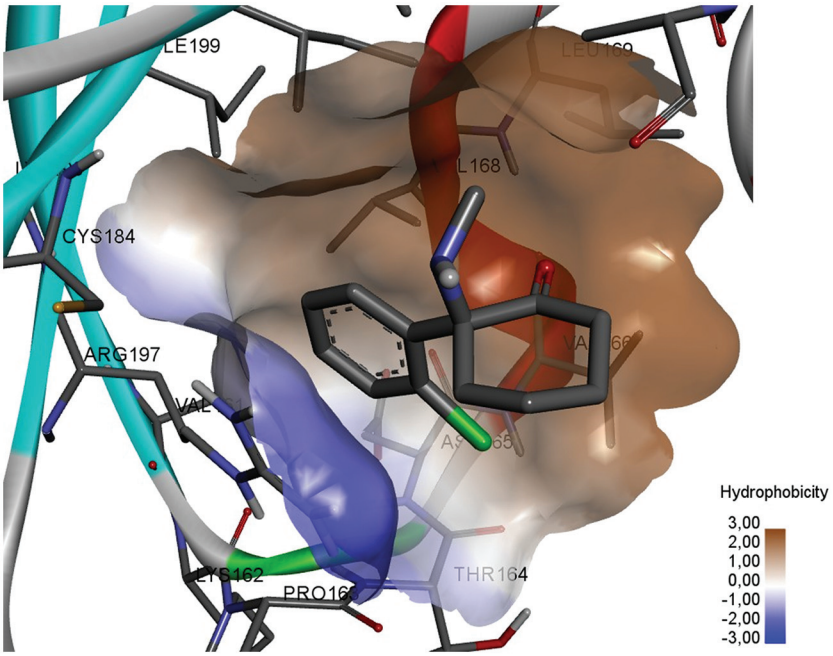
Sortase A residue	Ketamine (Å)	(PHQ)LPA(B27) peptide (Å)
Ala92	4.3	2.2
Leu97	5.3	2.5
Ala104	3.7	3.3
Ala118	3.5	2.7
His120	6.5	2.1
Val166	2.5	2.4
Val168	2.7	3.1
Leu169	2.9	3.1
Ile182	2.7	3.0
Cys184	5.5	2.0
Trp194	7.9	3.3
Arg197	2.6	1.7

In addition, the study of molecular targets is important for understanding the pathogenesis of microorganisms. An essential step during the infectious process is adherence to the host tissue, and this process occurs through the interaction of bacterial surface molecules and the host tissue (Schneewind and Missiakas 2019). In this respect, sortase A has been considered a molecular target for the development of new antimicrobial agents for the prevention or treatment of bacterial infections (Nitulescu et al. 2016). In the present study, we evaluated the possibility of ketamine interacting with sortase A, an important molecule in the pathogenesis of *S. aureus* (Cascioferro et al. 2014; Uddin and Saeed 2014; Bradshaw et al. 2015).

The sortases have a highly conserved arginine at the active site (Arg197) and two more conserved residues (His120 and Cys184). These three residues play an important role in catalysis (Ton-That et al. 2004; Suree et al. 2009). Thus, compared to the conserved residues, ketamine is closer to Arg197 (2.6 Å). The proximity of ketamine to the rest of the (PHQ)LPA(B27) peptide binding site can also be highlighted. The shortest distances were to Val166 (2.5 Å), Val168 (2.7 Å), Leu169 (2.9 Å), and Ile182 (2.7 Å). Hydrophobic interactions are essential for intermolecular recognition because they are involved in the early stages of binding to other molecules, where pi interactions involve an aromatic ring, Pi-Alkyl, which occurs when the alkyl (C-H) group of a hydrophobic residue interacts with the aromatic ring of another hydrophobic residue (Siles et al. 2013). With regard to pi-sigma type interactions, we identified two interactions with the VAL168 residue (chain A), with values of 3.56 and 3.50 Å, one interaction with ILE182 (chain A), a residue of 3.93 Å, and two interactions with the ILE182 (chain A) residue, of 3.93 and 3.77 Å.

With respect to the safety of ketamine use, a study by de Andrade Neto et al. (2020) did not find cytotoxicity when tested in L929 (IC50 $>$ 100) mammal cells at a concentration of 3.73 mM, for which the MICs found in our study of MRSA strains corresponded to 2.29 and 3.73 mM, showing non-cytotoxicity at these concentrations. In addition, Cavalcanti et al. (2020) analyzed the genotoxicity and mutagenicity of ketamine in human peripheral blood leukocytes (PBLs) and *Salmonella typhimurium* and

Fig. 6. Schematic of the hydrophobic surface of the interaction site of sortase A with ketamine. [Colour online.]



concluded that ketamine is devoid of mutagenic effects in eukaryotic and prokaryotic models and does not have aneugenic/clastogenic effects in PBLs. In view of this, the safety of this drug for cytotoxicity, genotoxicity, and mutagenicity (Cavalcanti et al. 2020; de Andrade Neto et al. 2020) should be emphasized.

Therefore, it is important to develop pharmaceutical formulations that enable the use of ketamine in MRSA infections. The reported concentrations of ketamine in the present study can be obtained locally. Studies with ketamine in some formulations have already been conducted, such as by Russo and Santarelli (2016), in which the use of a topical formulation containing 10% ketamine combined with other compounds was evaluated in patients with complex regional pain syndrome, and by Han et al. (2018), who encapsulated ketamine in biodegradable microparticles with sustained intrathecal release after injection. Both studies achieved promising results. Bassani and Banov (2015) evaluated the in vitro percutaneous absorption capacity of 5% ketamine and obtained a high rate of absorption by this administration route. Thus, the variety of formulations and routes that can be studied for ketamine use is noteworthy.

5. Conclusion

In the present study, ketamine was shown to have antibacterial activity against MRSA strains, damage to the cell membrane, and increased permeability, consequently leading to a change in the electrochemical balance. The results of the molecular docking showed that ketamine has affinity with sortase A. Ketamine thus has potential for use in the treatment of MRSA infections, so further studies should be conducted for evaluation in an in vivo model. We hope that the deeper knowledge gained from this study will strengthen the scientific community's experience in devising innovative strategies to reduce antimicrobial resistance.

Declarations

Authors' contributions

All authors contributed to the conception of the project and drafting, revising, and final approval of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest concerning this article.

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