ABSTRACT

Objective: This study aimed to investigate the inhibitory effects of sedative, analgesic and anaesthetic drugs on SARS-CoV-2, human angiotensin converting enzyme-2 (ACE-2) and SARS-CoV-2-ACE-2 complex through molecular docking and their potential use for the treatment of coronavirus disease 2019 (COVID-19).

Materials and Methods: In this study, molecular docking was employed to investigate the molecular interaction between drugs under clinical tests (chloroquine, hydroxychloroquine and nelfinavir) and the most commonly used drugs for sedation, analgesia and anaesthesia, such as inhibitors (desflurane, dexmedetomidine, fentanyl, detamine, midazolam, propofol, remifentanil and sevoflurane) of three different enzymes (6LU7, 1R4L and 6LZG). Autodock 4.2 Lamarckian Genetic Algorithm was used to analyse the probability of the molecular docking. The evaluation was based on docking points calculated by Biovia Discovery Studio Visualizer 2020. As a result of the molecular docking, interaction types, such as hydrogen-electrostatic and van der Waals between enzymes and drugs, were determined and the results were compared.

Results: Among the drugs included in the study, fentanyl had a low binding energy (-8.75 to -7.64 kcal/mol) for SARS-CoV-2, ACE-2 and SARS-CoV-2-ACE-2 complex and can inhibit these proteins at low concentrations. Apart from fentanyl, midazolam, ketamine, propofol and remifentanil can also inhibit proteins; however, sevoflurane and desflurane were found to be ineffective.

Conclusion: Our findings suggest that fentanyl is preferable for sedation, analgesia and anaesthesia in COVID-19 patients and that total intravenous anaesthesia can be preferred for general anaesthesia. However, experimental and clinical studies are required to determine the efficacy of these substances in treatment.

Keywords: Anaesthesia, COVID-19, sedation, molecular docking
Introduction

A new coronavirus subtype called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in an acute respiratory disease outbreak and it posed a pandemic threat to global public health (1). World Health Organization (WHO) called this disease Coronavirus Disease 2019 (COVID-19). The potentially fatal virus caused a global public problem with its international rapid spread, increasing number of cases and deaths day by day (2). Although most COVID-19 patients have mild symptoms and good prognosis, 15% of patients develop pneumonia, acute respiratory distress syndrome (ARDS), heart damage, kidney damage, or multiorgan failure, 7 to 10 days after hospitalization (3).

Critically ill patients, including COVID-19 patients, will experience pain and distress due to their underlying respiratory disease and invasive procedures, primarily mechanical ventilation (4). Sedation and analgesia in critical patients are important in reducing inflammation and stress response (5). A mild sedation for most intensive care unit patients ensures patient comfort, maintaining a safe and effective strategy level, thereby achieving improved clinical results (6). Invasive mechanical ventilation (MV) is the main organ replacement therapy in ARDS patients. Although light sedation is the recommended goal for patients requiring mechanical ventilation, COVID-19 associated pneumonia and ARDS may require moderate to deep levels of sedation to optimize the patient’s respiratory status (4,7).

SARS-CoV-2 is a newly discovered pathogen, a specific drug has not been identified or is currently not available due to the inadequacy of research into its treatment. Due to the need for therapeutic intervention against COVID-19, several efforts have been made to identify appropriate targets to develop specific antivirals or to repurpose drugs against this newly emerging pathogen (8). One of the most current among these studies is molecular docking based on genomic sequence information combined with protein structure modeling; it was promised to enable the discovery of therapeutic agents by providing identification of drugs with targeting highly conserved proteins associated with SARS-CoV and SARS-CoV-2. (9-11). The molecular docking method can be used to model the atomic level interaction between a small molecule and a protein, which allows us to characterize the behavior of small molecules in the binding site of target proteins, and to illuminate basic biochemical processes. The purpose of molecular placement is to give an estimate of the ligand-receptor complex structure using computational methods (12).

In this study; we investigated the binding potentials of the most commonly used drugs for sedation, analgesia and anaesthesia (propofol, midazolam, dexmedetomidine, sevoflurane, desflurane, ketamine, fentanyl, remifentanil) to SARS-CoV-2, human angiotensin converting enzyme 2 (ACE-2), SARS-CoV-2- ACE-2 Complex proteins with Molecular Docking method. In this way, we aimed to determine which drugs are more advantageous in patients undergoing invasive mechanical ventilation in intensive care units where sedation is inevitable, or in other procedures that require sedation, analgesia and anaesthesia.

Materials and Methods

Proteins/Macromolecules

In this study, we chose COVID-19 (PDB ID: 6LU7 chain A) the crystal structure of SARS-CoV-2, human angiotensin converting enzyme ACE-2 (PDB ID: 1R4L chain A), and SARS-CoV-2- ACE-2 Complex (PDB ID: 6LZG chain A and B) novel coronavirus spike receptor-binding domain complexed with its receptor ACE2. The 6LU7 (13), the 1R4L (14) and the 6LZG (15) structures were obtained from the RCSB Protein Data Bank (PDB) (https://www.rcsb.org/), in .pdb format. The proteins target structures (with ligand and free) were presented in Table 1.
Table 1. Proteins target structures (with ligand and free) (BIOVIA Discovery Studio Visualizer 2020)

| No | PDB ID | Macromolecule (with ligand) | Macromolecule (free) |
|----|--------|------------------------------|----------------------|
| 1  | 1R4L   | ![Image](image1.png)         | ![Image](image2.png) |
| 2  | 6LU7   | ![Image](image3.png)         | ![Image](image4.png) |
| 3  | 6LZG   | ![Image](image5.png)         | ![Image](image6.png) |
**Ligand**

In this study, the interaction of compounds used for sedation, analgesia and anaesthesia was investigated. The dimensional structures of the compounds as described in Table 2 were obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov) in structure-data file (SDF) format. The compounds used in the present study were desflurane, dexmedetomidine, fentanyl, ketamine,

| No. | Compound Name | PubChem CID | 2D Structure |
|-----|---------------|-------------|--------------|
| 1   | Nelfinavir    | 64143       | ![Nelfinavir](image1) |
| 2   | Chloroquine   | 2719        | ![Chloroquine](image2) |
| 3   | Hydroxychloroquine | 3652 | ![Hydroxychloroquine](image3) |
| 4   | Desflurane    | 42113       | ![Desflurane](image4) |
| No. | Compound Name | PubChem CID | 2D Structure |
|-----|---------------|-------------|--------------|
| 5   | Dexmedetomidine | 5311068     | ![Image](image1.png) |
| 6   | Fentanyl      | 3345        | ![Image](image2.png) |
| 7   | Ketamine      | 3821        | ![Image](image3.png) |
| 8   | Midazolam     | 4192        | ![Image](image4.png) |
| No. | Compound Name | PubChem CID | 2D Structure |
|-----|---------------|-------------|--------------|
| 9   | Propofol      | 4943        | ![Propofol](image) |
| 10  | Remifentanil  | 60815       | ![Remifentanil](image) |
| 11  | Sevoflurane   | 5206        | ![Sevoflurane](image) |
midazolam, propofol, remifentanil and sevoflurane. However, Chloroquine, Hydroxychloroquine and Nelfinavir were used as standards for comparison.

**Molecular Docking**

Preparation of the ligands (Desflurane, Dexmedetomidine, Fentanyl, Ketamine, Midazolam, Propofol, Remifentanil and Sevoflurane) and the three different enzymes (6LU7, 1R4L, and 6LZG) for docking were performed by Autodock tools (16). The 3 dimensional structures of the ligands were optimized by MM3 and saved in .mol2 format (17). Autodock 4.2 was supported by Autodock tools, MGL tools. The docking analyses were performed by both Autodock 4.2, and BIOVIA Discovery Studio Visualizer 2020.

**Results**

The molecular docking analysis results for the drugs under clinical test (Chloroquine, Hydroxychloroquine and Nelfinavir) and the Sedatives, analgesics and anaesthetics drugs (desflurane, dexmedetomidine, fentanyl, ketamine, midazolam, propofol, remifentanil and sevoflurane) as inhibitors with the three different enzymes (6LU7, 1R4L, and 6LZG), including binding energy, inhibition constant, intermolecular energy, van der Waals (VDW)-H Bond desolvation energy, electrostatic energy, total internal energy, torsional free energy are presented in Table 3.

Table 3 shows the docking score values for 1R4L, 6LU7 and 6LZG. As reflected from the docking scores, the binding energies of the drugs changes as follows. The binding energies obtained from docking 1R4L with the Chloroquine, Hydroxychloroquine and Nelfinavir were -7.02, -6.41, and -8.77 kcal/mol, respectively. The binding energies of Desflurane, Dexmedetomidine, Fentanyl, Ketamine, Midazolam, Propofol, Remifentanil and Sevoflurane with 1R4L are in the range of (-1.79 kcal/mol) – (-7.44 kcal/mol), while Fentanyl has the highest value. The binding energies obtained from docking 6LU7 with the Chloroquine, Hydroxychloroquine and Nelfinavir were -7.19, -6.93, and -11.13 kcal/mol, respectively. The binding energies of Desflurane, Dexmedetomidine, Fentanyl, Ketamine, Midazolam, Propofol, Remifentanil and Sevoflurane with 6LU7 are in the range of (-1.75 kcal/mol) – (-7.97 kcal/mol), while Fentanyl has the highest value. The binding energies obtained from docking 6LZG with the Chloroquine, Hydroxychloroquine and Nelfinavir were -7.85, -6.56, and -7.97 kcal/mol, respectively. The binding energies of Desflurane, Dexmedetomidine, Fentanyl, Ketamine, Midazolam, Propofol, Remifentanil and Sevoflurane with 6LZG are in the range of (-2.31 kcal/mol) – (-8.11 kcal/mol), while Fentanyl has the highest value.

When the molecular structure and interactions of the Fentanyl with 1R4L are examined, it is seen that there are conventional hydrogen bond interactions with TYR255. Additionally, Fentanyl also exhibited Carbon Hydrogen Bond with MET49, Pi-Sigma interaction with PRO389, pi-alkyl interaction with HIS34, TYR495, PHE497, and TYR505. Docking analysis results, including the other interaction with 1R4L, 6LU7 and 6LZG can be observed in Table 4, 5 and 6, respectively.

**Discussion**

SARS-CoV-2 is an enveloped virus containing a single stranded RNA genome belonging to the betacoronavirus family (18). Betacoronavirus genome mediates host cell invasion by both SARS-CoV and SARS-CoV-2 by encoding the Spike protein, binding to the ACE-2 receptor protein located in the surface membrane of host cells. (19,20). The interaction between the viral S protein and ACE-2 on the host cell surface is an important consideration as it initiates the infection process. Cryo-EM structure analysis revealed that the binding affinity of the SARS-CoV-2 S protein to ACE-2 was approximately 10-20 times higher than that of the SARS-CoV S protein. (9,20). SARS-CoV-2 main protease enzyme is known to play an important role in virus replication and transcription (21). Therefore, these proteins are among the most attractive targets for the development of new drugs.
Table 3. Molecular docking analysis of drugs under clinical tests and the drugs examined in this study as inhibitors against 1R4L, 6LU7 and 6LZG.

| Protein | Compound          | Binding Energy (ΔG) | Inhibition Constant | Intermolecular Energy | VDW-H Bond Desolvation Energy | Electrostatic Energy | Total Internal Energy | Torsional Free Energy |
|---------|-------------------|---------------------|---------------------|-----------------------|--------------------------------|----------------------|----------------------|-----------------------|
|         |                   |                     |                     |                       |                                |                      |                      |                       |
| 1R4L    | Chloroquine       | -7.02               | 7.16 μM             | -9.41                 | -7.85                          | -1.55                | -0.73                | 2.39                  |
|         | Hydroxychloroquine| -6.41               | 20.02 μM            | -9.39                 | -7.62                          | -1.77                | -0.79                | 2.98                  |
|         | Nelfinavir        | -8.77               | 375.13 nM           | -12.35                | -10.73                         | -1.61                | -3.00                | 3.58                  |
|         | Desflurane        | -2.33               | 19.64 mM            | -3.22                 | -3.04                          | -0.18                | -0.15                | 0.89                  |
|         | Dexametomidine    | -4.97               | 228.85 μM           | -5.56                 | -5.52                          | -0.05                | -0.46                | 0.60                  |
|         | Fentanyl          | -7.44               | 3.54 μM             | -9.23                 | -7.79                          | -1.43                | -1.29                | 1.79                  |
|         | Ketamine          | -6.43               | 19.23 μM            | -7.03                 | -5.82                          | -1.21                | -0.02                | 0.60                  |
|         | Midazolam         | -6.04               | 37.13 μM            | -6.34                 | -5.98                          | -0.36                | -0.77                | 0.30                  |
|         | Propofol          | -4.86               | 272.22 μM           | -5.76                 | -5.71                          | -0.05                | -0.33                | 0.89                  |
|         | Dexmedetomidine   | -5.73               | 62.76 μM            | -8.42                 | -6.92                          | -1.50                | -2.30                | 2.68                  |
|         | Sevoflurane       | -1.79               | 48.36 mM            | -2.99                 | -2.83                          | -0.15                | -0.18                | 1.19                  |
| 6LU7    | Chloroquine       | -7.19               | 5.32 μM             | -9.38                 | -9.35                          | -0.23                | -0.94                | 2.39                  |
|         | Hydroxychloroquine| -6.93               | 8.31 μM             | -9.91                 | -9.39                          | -0.52                | -0.61                | 2.98                  |
|         | Nelfinavir        | -11.13              | 6.95 nM             | -14.71                | -14.29                         | -0.42                | -3.68                | 3.58                  |
|         | Desflurane        | -2.07               | 30.45 mM            | -2.96                 | -2.95                          | -0.02                | -0.22                | 0.89                  |
|         | Dexametomidine    | -5.91               | 46.53 μM            | -6.51                 | -6.48                          | -0.02                | -0.42                | 0.60                  |
|         | Fentanyl          | -7.97               | 1.43 μM             | -9.76                 | -9.49                          | -0.27                | -1.51                | 1.79                  |
|         | Ketamine          | -5.74               | 61.82 μM            | -6.34                 | -4.63                          | -1.71                | -0.08                | 0.60                  |
|         | Midazolam         | -7.57               | 2.83 μM             | -7.87                 | -7.82                          | -0.04                | -0.59                | 0.30                  |
|         | Propofol          | -5.39               | 112.27 μM           | -6.28                 | -6.25                          | -0.03                | -0.31                | 0.89                  |
|         | Remifentanil      | -6.15               | 31.27 μM            | -8.83                 | -8.50                          | -0.33                | -2.14                | 2.68                  |
|         | Sevoflurane       | -1.75               | 52.11 mM            | -2.94                 | -2.91                          | -0.03                | -0.19                | 1.19                  |
| 6LZG    | Chloroquine       | -7.85               | 1.76 μM             | -10.24                | -8.40                          | -1.83                | -0.53                | 2.39                  |
|         | Hydroxychloroquine| -6.56               | 15.49 μM            | -9.55                 | -8.18                          | -1.36                | -1.12                | 2.98                  |
|         | Nelfinavir        | -7.97               | 1.43 μM             | -11.55                | -10.55                         | -1.00                | -2.69                | 3.58                  |
|         | Desflurane        | -2.31               | 20.28 mM            | -3.20                 | -3.10                          | -0.11                | -0.15                | 0.89                  |
|         | Dexametomidine    | -5.91               | 46.87 μM            | -6.50                 | -6.60                          | 0.10                 | -0.05                | 0.60                  |
|         | Fentanyl          | -8.11               | 1.14 μM             | -9.90                 | -9.23                          | -0.67                | -1.31                | 1.79                  |
|         | Ketamine          | -6.90               | 8.72 μM             | -7.50                 | -6.47                          | -1.03                | -0.36                | 0.60                  |
|         | Midazolam         | -7.15               | 5.71 μM             | -7.45                 | -7.65                          | 0.20                 | -0.59                | 0.30                  |
|         | Propofol          | -5.97               | 41.74 μM            | -6.87                 | -6.82                          | -0.05                | -0.38                | 0.89                  |
|         | Remifentanil      | -6.75               | 11.34 μM            | -9.43                 | -8.01                          | -1.42                | -1.78                | 2.68                  |
|         | Sevoflurane       | -2.43               | 16.56 mM            | -3.62                 | -3.43                          | -0.20                | -0.22                | 1.19                  |

Energy unit: kcal/mol
| Protein | Compound      | Molecular structure and interactions |
|---------|---------------|---------------------------------------|
| 1R4L    | Chloroquine   | ![Chloroquine](image)                    |
|         | Hydroxychloroquine | ![Hydroxychloroquine](image)          |
|         | Nelfinavir    | ![Nelfinavir](image)                   |
|         | Desflurane    | ![Desflurane](image)                   |
|         | Dexmedetomidine | ![Dexmedetomidine](image)             |
|         | Fentanyl      | ![Fentanyl](image)                     |
| Protein | Compound | Molecular structure and interactions |
|---------|----------|--------------------------------------|
| 1R4L    | Ketamine | ![Molecular structure](image1) ![Interactions](image2) |
|         | Midazolam| ![Molecular structure](image3) ![Interactions](image4) |
|         | Propofol | ![Molecular structure](image5) ![Interactions](image6) |
|         | Remifentanil | ![Molecular structure](image7) ![Interactions](image8) |
|         | Sevoflurane | ![Molecular structure](image9) ![Interactions](image10) |
| Protein     | Compound     | Molecular structure and interactions |
|-------------|--------------|--------------------------------------|
| 6LU7        | Chloroquine  | ![Molecular structure](image1.png)   |
|             | Hydroxychloroquine | ![Molecular structure](image2.png) |
|             | Nelfinavir   | ![Molecular structure](image3.png)   |
|             | Desflurane   | ![Molecular structure](image4.png)   |
|             | Dexmedetomidine | ![Molecular structure](image5.png) |
|             | Fentanyl     | ![Molecular structure](image6.png)   |

Table 5. Molecular structure and interactions of the docked drugs under clinical test the drugs examined in this study as inhibitors with the 6LU7.
Table 5. Continued

| Protein | Compound       | Molecular structure and interactions |
|---------|----------------|--------------------------------------|
| 6LU7    | Ketamine       | ![Molecular structure of Ketamine](image1) |
|         | Midazolam      | ![Molecular structure of Midazolam](image2) |
|         | Propofol       | ![Molecular structure of Propofol](image3) |
|         | Remifentanil   | ![Molecular structure of Remifentanil](image4) |
|         | Sevoflurane    | ![Molecular structure of Sevoflurane](image5) |
| Protein   | Compound       | Molecular structure and interactions |
|-----------|----------------|--------------------------------------|
| Chloroquine | ![Molecular Structure](image1) | ![Interactions](image2) |
| Hydroxychloroquine | ![Molecular Structure](image3) | ![Interactions](image4) |
| Nelfinavir  | ![Molecular Structure](image5) | ![Interactions](image6) |
| Desflurane  | ![Molecular Structure](image7) | ![Interactions](image8) |
| Dexmedetomidine | ![Molecular Structure](image9) | ![Interactions](image10) |
| Fentanyl    | ![Molecular Structure](image11) | ![Interactions](image12) |
| Protein | Compound | Molecular structure and interactions |
|---------|----------|-------------------------------------|
| 6LZG    | Ketamine | ![Molecular structure](image1)        |
|         | Midazolam| ![Molecular structure](image2)       |
|         | Propofol | ![Molecular structure](image3)       |
|         | Remifentanil | ![Molecular structure](image4)   |
|         | Sevofturane | ![Molecular structure](image5)      |
against COVID-19. ACE-2 has been studied by different groups to find inhibitors that can stop the main protease enzyme activity and consequently the proliferation of the virus. Molecular docking methods are the basis of research for the detection of the most effective drugs against SARS-CoV-2 (22).

Different and new data were obtained from the researchers conducted with the molecular docking method for the treatment of COVID-19. Positive results obtained by silico screening of various molecules (23) and herbal medicines (24) for the treatment of COVID-19 using calculation methods have been reported. Some clinical studies also support this data. Hung et al reported that, the anti-viral drugs approved for human therapies such as Lopinavir, Ribavirin and Ritonavir, targeting the main protease enzyme (Mpro) structure of SARS-CoV-2, have potential effects against COVID-19, and reduced the length of hospital stay by triple combined therapy (25). Several published studies with inhibitors of viral proteases have supported the theory that the SARS-CoV-2 M pro could be a good target for therapeutic agents (8,26,27). In another study it was found that Nelfinavir, which is also used as an antiviral drug and protease inhibitor, prevents the membrane fusion by binding to the spike protein complex with low energy (-9.98 kcal/mol) by the molecular docking method. In the same study, it was found that Nelfinavir prevented the fusion of SARS CoV-2 by S protein in Vero cells in vitro. (28). In addition, the effectiveness of some drugs such as favipiravir, chloroquine and remdesivir has been shown in vitro. (29), The effectiveness of some drugs is still controversial. In the first clinical studies, it was reported that combination therapy with hydroxychloroquine and azithromycin reduced viral RNA detection compared to control (30). However, the results of ongoing clinical trials brought discussions about the use of Hydroxychloroquine and chloroquine (31). A multicenter, open-label, randomized controlled clinical trial did not show additional benefits in virus elimination by hydroxychloroquine in association with specifically standard of care in patients with mild to moderate COVID-19. It also promoted an increased frequency of adverse events (32).

With the rapid spread of COVID-19 disease, these patients are frequently encountered especially in intensive care units and operating theaters (4). All the possibilities of modern medicine against this global enemy must be used against this global enemy. Until clinical trials are concluded, it may be necessary to modify existing treatments. Being able to choose the most effective agent among drugs frequently used in anaesthesia and intensive care practice will contribute positively to the mortality and morbidity of the patients. Currently there are no guidelines available for managing sedation in COVID-19 patients requiring mechanical ventilation. However, the 2018 PADIS guidelines for sedation in critically ill patients still pertain (4,33). Although there are many studies on the clinical uses of these drugs, our aim in this study is to determine the possible advantageous drug for COVID-19 patients and lead clinical studies.

In our study, A chain for 6LU7, A chain for 1R4L and A and B chain for 6LZG protein were used for macromolecule preparation in molecular docking process. In other words, the interaction between the amino acids and the enzyme involved in the interaction between the functional groups of the indicated drugs on the compound molecules was observed in three dimensions. Molecular placement was made between compounds and protease with the ability to investigate the interaction between hydrogen-electrostatic and van der Waals reactions in the enzyme active region, and the results were compared.

According to the results of our study; when the binding score of drugs for 1R4L, 6LU7 and 6LZG was evaluated, binding energies were examined; the binding energies for 1R4L were -1.79 to -7.44 kcal/mol, while fentanyl has the lowest value, sevoflurane has the highest value. The binding energies for 6LU7 were -1.75 to -7.97 kcal/mol, while the lowest value was detected in fentanyl and the highest value in sevoflurane. The binding energies for 6LZG were -2.31 to -8.11 kcal/mol, while the lowest value was detected in fentanyl and the highest value in sevoflurane. While fentanyl has the lowest value in binding energies for all three proteins, the highest values were determined in volatile anesthetics, sevoflurane and desflurane. In addition, the drugs we examined in the study were compared with Chloroquine, Hydroxychloroquine and Nelfinavir, which previously detected good binding energy against the SARS CoV-2 virus using the molecular docking method. In particular, the drug with the closest binding energy to nelfinavir is fentanyl followed by remifentanil, ketamine, midazolam and propofol. As a result, we found that intravenous agents are superior to volatile agents. This is probably due to structural differences between the drugs. This shows that total intravenous anaesthesia can be preferred in general anaesthesia applications. Fentanyl’s potential to bind with the lowest energy can make it a priority choice for sedo-
analgesia procedures in COVID-19 patients. The results we obtained in this study may contribute to drug development. Our data are not at the level of recommendation for clinical decisions, and they should to be supported by clinical studies.

**Conclusion**

In this study, where we examined the effects of sedative, analgesic and anesthetic drugs on SARS-CoV-2 by molecular docking method, we found that fentanyl and then remifentanil, ketamine, midazolam and propofol inhibits proteins that have important functions in the spread and proliferation of SARS-CoV-2. However, sevoflurane and desflurane are found ineffective in this regard. The data we obtained with the molecular docking method will be a reference for further studies and should be supported by clinical studies.
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