

Midazolam is a benzodiazepine medicine and is one of the basic medicines that induce pharmacological coma. Benzodiazepines induce retrograde amnesia, which in intensive care patients is an intended goal due to trauma and unpleasant sensations from the stay in the intensive care unit. On the other hand, these are medicines that are addictive, which is observed in older patients treated in primary care health or mental health clinics. The only laboratory tests currently performed in hospitals on benzodiazepines are qualitative or semi-quantitative toxicological studies to determine the cause of poisoning. However, quantitative research is not performed, especially in intensive care, where the consumption of medicine from this group is very high. An additional specificity of intensive care patients is the disturbed metabolism of medicines due to their severe condition and numerous medicine interactions. This issue requires further scientific research. Medicine monitoring in Poland is practically performed exclusively by transplant centers, due to the obligation to monitor the level of immunosuppressive medicines. COVID-19 is a new disease that was examined in December 2019 in Wuhan, China. It is a pathology that primarily causes extreme respiratory failure - ARDS (Acute Respiratory Distress Syndrome), but other disorders are also observed, including very dangerous microcirculation pathologies. Due to developing respiratory failure, these patients require ECMO (Extra Corporeal Membrane Oxygenation) therapy. It is one of the extracorporeal therapies. The oxygenator enables oxygenation outside the patient's lungs. The blood that flows through the oxygenator capillaries causes the deposition of drugs in the oxygenator, which reduces the concentration of medicines in the patient's blood.

The aim of this study is to monitor the level of midazolam in patients with COVID-19 hospitalized in the intensive care unit of the Silesian Center for Heart Diseases in Zabrze. The drug concentration will be compared in patients requiring pharmacological sedation, mechanically ventilated, and during ECMO therapy, compared to patients only ventilated mechanically.

Another issue of this study will be the bispectral analysis of the electroencephalogram (BIS - bispectral index) - it is a non-invasive method of sedation measurement used in the operating theater and in the ICU. The examination consists of placing electrodes on the forehead and non-invasive recording of waves originating from the brain. Additionally, for each patient, a scale will be calculated on the RASS scale (Richmond Agitation-Sedation Scale), which determines the degree of sedation. The score on this scale ranges from -5 (non-reactive patient) to +4 (agitated, delirious). The RASS score and the BIS test will correlate with the blood level of midazolam. The test will analyze blood drawn from the artery for the level of midazolam in COVID-19 patients requiring ECMO therapy and respiration therapy twice a week on working days (Tuesday and Thursday). On these days, kidneys and liver function level tests will be also taken. Kidneys function level will be assessed by the Cockcroft-Gault formula, while liver function level will be assessed by the MELD (Model of End-Stage Liver Disease) scale. Doses of midazolam will be calculated daily. Additionally, the level will be correlated with the amount of transfused red blood cells and albumin. After that, the correlation between the medicine level and possible complications will be assessed. The examination of the patient will be terminated in case of improvement of the patient's condition (discontinuation of the infusion of midazolam) or disqualification from continuing active treatment and starting the protocol of futile therapy.

The endpoints of the study will be to achieve a level of midazolam that is safe for patients hospitalized in the intensive care unit; obtaining information on the percentage of the medicine absorption in the oxygenator capillaries, prognosis of COVID positive patients in intensive care, as well as obtaining information on the annual survival of these patients.