



Review article

Potential effects of genetic polymorphism on anesthesia use for COVID-19 infected patients at intensive care unit

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Received: 17 December, 2021

Accepted: 05 January, 2022

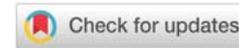
Published: 06 January, 2022

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Keywords: COVID-19; ICU ventilators; Cytokine storm; General anesthetics; Fentanyl; Sevoflurane

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Abstract

Background: New coronavirus disease is considered one of the most widely spreading viral infections all over the world. Increased numbers of severe COVID-19 cases are growing up. Severe cases require ICU mechanical ventilation and hence anesthesia requirement.

Aim: Reviewing of different genetic polymorphisms which might affect patient clinical response, safety and tolerability to different types of anesthesia used in severe COVID-19 patients requiring mechanical ventilation.

Main body of the abstract: Severity of COVID-19 infection resulted from cytokine storm that leads to Acute Respiratory Distress Syndrome (ARDS) contribute in ICUs mechanical ventilation and anesthesia. Genetic polymorphisms showed to contribute in wide variation in anesthetic responses. Different polymorphic genes of RYR1, CACNA1S, MTHFR, OPRM1, ABCB1, CYP2B6 and others, play a main role in such variations. Different types of anesthesia as sevoflurane, midazolam, suxamethonium, nitrous oxide, fentanyl, and propofol showed altered pharmacokinetics and/or dynamics leading to a lack of anesthetic effect and incidence of life-threatening adverse effects as malignant hyperthermia, myocardial infarction, dyspnea, and others.

Short conclusion: Genetic screening is a serious step to take into consideration to identify genetic polymorphic types that may alter the anesthetic effect in ICUs ventilation. Besides, it will avoid possible adverse effects and different sedation response variations. Sevoflurane, Fentanyl, and propofol can be taken into consideration as a safe choice for use in ICUs taking into consideration genetic polymorphic variants.

Abbreviations

COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; ARDS: Acute Respiratory Distress Syndrome; ICU: Intensive Care Unit; WHO: World Health Organization; AGMs: Anesthesia Gas Machines; CNS: Central Nervous System; RYR: Ryanodine Receptor; EHS: Exertional Heatstroke; MTHFR: Methylene tetrahydrofolate Reductase; SNP: Single Nucleotide Polymorphism; H-Hcy: Hyper-Homocysteinemia; MYLK: Myosin Light-chain Kinase; ALI: Acute Lung Injury; N₂O: Nitrous Oxide; O₂: Oxygen

Background

COVID-19 has become a threatening disease worldwide as coronaviruses are highly diverse single-stranded RNA viruses that evoke several disease conditions as respiratory diseases, enteric diseases, hepatic diseases, and neurological diseases. Traditionally, human coronaviruses infections cause a low annual percent of respiratory infections [1,2].

There were 177,866,160 confirmed COVID-19 cases worldwide with a death rate of 2.17% according to the situation report of WHO on June 22, 2021. Africa showed 3,791,054

confirmed cases with a death rate of 2.42%, Europe showed 55,325,145 confirmed cases with a death rate of 2.12%, the Americas showed 70,663,034 confirmed cases with a death rate of 2.63% till the 22nd of June 2021 [3].

SARS-CoV-2 is the 7th member of Coronaviruses family that infects humans. COVID-19 main symptoms are close to that of SARS-CoV and MERS-CoV infection which included fatigue, fever, and cough. Pathology of these coronaviruses are overlapping and diverse, thus, causing severe diseases [4].

Investigations indicated that SARS-CoV-2 (S-protein) binds ACE2 receptors 10 to 20 times higher than SARS-CoV (S-protein), that is how the spread of SARS-CoV-2 within human is facilitated [5].

SARS-CoV-2 provokes the secretion of different pro-inflammatory cytokines that can lead to Cytokine Storm and serious respiratory injury due to epithelial cell damage and continuous inflammation, showing Acute Respiratory Disease Syndrome (ARDS) in some patients. That is why it is required in critical cases to be admitted to ICU ventilators [6].

The reported clinical presentations of COVID-19 start from asymptomatic infection to pulmonary collapse. The main COVID-19 symptoms include fever, dry cough, tiredness, and dyspnea, while the less common symptoms include diarrhoea, sputum production, headache, and hemoptysis [7].

Severity of COVID-19 symptoms varies from mild symptoms showing no signs of pneumonia, passing through moderate symptoms as fever and respiratory pneumonia going through to severe symptoms characterized by dyspnea, respiratory rate more than or equal to 30/min, blood oxygen (O₂) saturation less than or equal to 93%, PaO₂/FiO₂ ratio less than 300, and lung infiltrates more than 50% within 24–48 hours, ending with critical cases that shows respiration failure, septic shock, and multiple organ failure [8].

Severe SARS-CoV-2 infection can lead to respiratory failure and severe hypoxia necessitate invasive ventilation to improve oxygen supply is required [9].

Tracheal intubation is considered a high risk for COVID-19 patients. Previously, before COVID-19, intubation was commonly done in controlled conditions, for example in ICUs, anesthesia and resuscitation rooms, as a consequence of the rapid increase in COVID-19 infections and high demand for such controlled areas, tracheal intubation is performed outside the ICUs by specially formed intubation teams [10,11].

To meet the increased demand of ICUs for critical COVID-19 cases, some healthcare facilities used anesthesia gas machines (AGMs) as ICU ventilators for ventilating critical cases which has many problems and precautions that must be considered [12].

According to current statistics, around 3.2 percent of patients infected with COVID-19 require intubation and invasive ventilation at some point during the disease's progression [13].

The patient's age, ethnicity, genetic mutations, and illness condition can all produce significant variances in anaesthetic responsiveness, making general anesthesia a very complicated procedure [14].

General anesthesia are among the most serious drugs used in clinical practice because of their unusual pharmacokinetic properties, narrow therapeutic window and various drug-unique adverse effects profile. The majority of adverse effects are dose or concentration-related, like hypotension, CNS depression and respiratory depression, or resulting from drug or formulation, like pain at the injection site. However, sometimes dangerous adverse effects, like malignant hyperthermia and many others cannot be predictable which have a genetic background [15,16].

Main text

Various genetic polymorphisms of molecular targets, as well as transporters and metabolic enzymes might change anesthetic drug pharmacodynamic or pharmacokinetic characteristics thereby affecting anesthesia clinical response. Differences in inhalational anesthetics' potency, speed of induction and recovery from anesthesia, as well as some specific side effects might contribute to selection of type of anesthesia used.

It is worthy to mention that, the effect both clinical and safety of the used anesthesia is greatly affected by human genetic polymorphism as well as their safety and tolerability, thus, it is important to present the correlation and association of patient clinical response, including adverse effects, and different types of consumed anesthesia in the intensive care unit.

Anesthesia and sedative drugs

Isoflurane is a volatile anesthetic that is used to induce and maintain general anesthesia [17]. It produces concentration-dependent intense pulmonary depression and hypotension due to reduced vascular resistance. Moreover, rapid changes in concentration can lead to transient tachycardia and hypertension as a result of sympathetic stimulation [18].

Sevoflurane can produce rapid initiation of anesthesia onset which is attributed to its lower solubility in blood and other tissues and is often used for outpatient anesthesia induction. It does not cause irritation to the respiratory airways and possess a strong bronchodilator effect. Moreover, in sick people at risk for myocardial infarction sevoflurane is considered as the anesthetic of choice, as it has no influence on heart rhythm [19].

Desflurane has the lowest potency and the least solubility in blood and other tissues, so it induces rapid anesthesia effect and fast recovery and can be used for outpatient surgical interventions. Besides, it possesses the lowest fat-to-blood solubility that makes it suitable for those patients suffering from obesity and undergoing prolonged surgery. Desflurane possesses a strong irritating effect on respiratory airways. Upper airway adverse events (moderate to severe events) may



be highly prevalent, so a choice for initiation of anesthesia desflurane is not appropriate [20].

Nitrous oxide (N_2O) is the only gas that has a significant positive impact on anesthesia outcomes. Although N_2O is unable to produce the required anesthetic depth during surgery, it is commonly applied as an auxiliary to halogenated anesthetics in order to reduce their effective concentrations and thus improve anesthesia safety. N_2O is the least soluble of all general anesthetics and it induces rapid anesthesia onset and fast emergence from anesthesia. Besides, N_2O produces a strong analgesic effect in comparison to morphine due to its stimulating action on the central opioidergic and adrenergic systems [21].

In addition to what is mentioned above, nitrous oxide (N_2O) is considered to be from the widely used general anesthetic. However, it causes acute plasma homocysteine elevation by irretrievable inactivation of vitamin B12 suggesting an elevated incidence of perioperative myocardial infarction. Hence, proposals for prophylactic use of folic acid and vitamin B12 resulted in a successful blunting of NO_2 induced elevation in plasma homocysteine [22].

Fentanyl and other related compounds like alfentanil, remifentanyl, and sufentanyl are synthetic opioids commonly used as parenteral anesthesia, either perioperative or postoperative owing to their fast and strong analgesic effect. Moreover, they relieve pain and minimize pain-evoked hemodynamic changes. Upon use, in combination with general anesthetics they aid in reduction of anesthetic required doses [23].

Propofol is considered from the most frequently used parenteral anesthetics for induction and maintenance of anesthesia. Propofol has a sedative-hypnotic effect, but also possess an anxiolytic effect, antiemetic, anticonvulsant, anti-oxidative, anti-inflammatory, and probably a neuroprotective effect [24].

Dexmedetomidine is an Alfa 2-adrenergic receptor agonist with high affinity. It has analgesic, anxiolytic, and sedative effects and used for patients admitted to ICUs post operations. Theoretically, *dexmedetomidine may have an advantage of changing the direction of immune response away from (T-helper cell 17) which has been correlated with severe COVID-19 pneumonia pathogenesis*. Although different studies support the anti-inflammatory and organoprotective effects of dexmedetomidine, its role in COVID-19 remains a proposal that is under investigation [25].

Midazolam is an imidazobenzodiazepine sedative having features that distinguish it from other benzodiazepines. In its acid formulation, it is water-soluble, but it is extremely fat-soluble in vivo. When compared to other benzodiazepines, midazolam has a relatively quick onset of action and a high metabolic clearance. When taken orally, intramuscularly, or intravenously, the medication induces consistent hypnosis and antianxiety effects. Midazolam has several perioperative applications, including premedication, anesthetic induction and maintenance, and sedation for diagnostic and therapeutic operations [26].

Suxamethonium is a short-acting depolarizing neuromuscular blocker that has been licensed for use as an adjunct to other sedatives or hypnotics. It inhibits the activity of Acetylcholine (ACh), causing all cholinergic receptors in the parasympathetic and sympathetic nervous systems to be disrupted. Its usage can speed up endotracheal intubation, make surgical operations easier, and help with mechanical breathing by relaxing skeletal muscles [27] Table 1.

Gene polymorphism association with the risk anesthetic effects

RYR1 and *CACNA1S* are the two main genes that encode the components of skeletal muscle Excitation-Contraction coupling (EC) complex localized in calcium channels [20]. *RYR1* and *CACNA1S* genetic defects are mainly associated with malignant hyperthermia and other myopathic diseases. Furthermore, variants in the *RYR1* and *CACNA1S* genes have recently been linked to Exertional Heat Stroke (EHS) [28].

RYR1 Multiple (48 variants) at 19q13.1, CACNA1S rs772226819 (c.520CT) genotypes showed to increase the risk of malignant hyperthermia resulting from Ca^{2+} leakage from the intracellular matrix for those individuals on sevoflurane, isoflurane, and desflurane anesthesia [29,30].

A clinical study indicated that after anesthesia with N_2O patients with 5,10-methylenetetrahydrofolic acid reductase (*MTHFR* 677C>T) or (1298A>C) mutation showed to be at a higher risk for developing abnormal plasma homocysteine concentrations [31].

Moreover, another study had reported that children with different Methylenetetrahydrofolate Reductase (*MTHFR*) gene polymorphisms had developed disastrous neurologic outcomes after N_2O anesthesia [32,33]. Methylenetetrahydrofolate Reductase (*MTHFR*) is from the most important enzymes that regulate fundamental processes in cell physiology such as DNA repair, membrane transport, and neurotransmitter functions [34]. There is a suggestion that T allele of the *MTHFR* C677T polymorphism, acts as contributing factor in protection against neoplastic diseases such as acute lymphatic leukemia and colon cancer [35].

It is important to mention that *MTHFR* C677T polymorphism is considered from the most prevalent Single Nucleotide Polymorphism (SNP) and the most common cause of hyper-homocysteinemia (H-Hcy) [34]. Moreover, investigations suggest that *MTHFR* C677T polymorphism can be associated with a significant elevated risk for coronary artery disease in homozygous men [36].

Also, hyper-homocysteinemia (H-Hcy) is correlated to the occurrence of vascular diseases like arterial hypertension and congestive heart failure [37]. *Suggestions during the COVID-19 pandemic is to undergo an early screen for patients by measurement of Hc-plasma levels to screen for possible presence of MTHFR C677T polymorphism and this seemed to be very promising* [38].

Studies have shown that *interleukin-10 polymorphism (IL10-1082GG) responsible for high interleukin-10 production* is linked to



Table 1: Summary table for different anesthetic agents and undesired or changes in anesthetic effect resulted from different genetic polymorphisms.

Anesthesia drug	Gene name	Gene polymorphism	Undesired or change in Anesthetic effect	Reference
Isoflurane	<i>RYR1</i> & <i>CACNA1S</i>	<i>RYR1</i> Multiple (48 variants) at 19q13.1, <i>CACNA1S</i> rs772226819 (c.520CT)	Increased risk of malignant hyperthermia	[29,30]
Sevoflurane	<i>RYR1</i> & <i>CACNA1S</i>	<i>RYR1</i> Multiple (48 variants) at 19q13.1, <i>CACNA1S</i> rs772226819 (c.520CT)	Increased risk of malignant hyperthermia	[29,30]
Desflurane	<i>RYR1</i> & <i>CACNA1S</i>	<i>RYR1</i> Multiple (48 variants) at 19q13.1, <i>CACNA1S</i> rs772226819 (c.520CT)	Increased risk of malignant hyperthermia	[29,30]
Nitrous oxide (N ₂ O)	<i>MTHFR</i>	<i>MTHFR</i> 677C>T or (1298A>C)	High risk for developing abnormal plasma homocysteine concentrations Disastrous neurologic outcomes in children	[31-33]
Fentanyl	<i>OPRM1</i>	<i>OPRM1</i> rs1799971 (AG)	Reduction in analgesic effect	[44,45]
	<i>ABCB1</i>	<i>ABCB1</i> rs1045642 (AG)	Decrease in drug excretion from CNS and plasma	
Propofol	<i>CYP2B6</i>	<i>CYP2B6</i> rs3745274 (G>T)	May result in a decrease in drug metabolism	[61,62]
		<i>CYP2B6</i> rs2279343 (A>G)	May result in a decreased drug elimination rate from the CNS	
Dexmedetomidine	<i>ADRA2A</i>	<i>ADRA2A</i> rs1800035, <i>ADRA2A</i> rs201376588, <i>ADRA2A</i> rs775887911	lowered analgesic and anesthetic effect	[66]
Midazolam	<i>CYP3A4</i> & <i>CYP3A5</i>	<i>CYP3A4</i> *22 & <i>CYP3A5</i> *3	Elevated levels of midazolam due to decreased metabolism resulting in high incidence of adverse effects or enhanced effect	[55-57]
	<i>POR</i>	<i>POR</i> *28	Increased midazolam receptor affinity and potentiated sedation	
	<i>GABRA1</i>	<i>GABRA1</i> 187+3553 (AG)		
Suxamethonium	<i>BChE</i>	<i>BChE</i> A-variant: rs1799807 (c.293TC), <i>BChE</i> K-variant: rs1803274 (c.1699CT), <i>BChE</i> F-variant: rs28933390 (c.1253CA), <i>BChE</i> S-variant: rs104893684 (c.1004AG).	Reduced suxamethonium metabolism leading to prolonged muscle relaxation and apnea	[58-60]

lower disease severity, lower death rates and lower age-related organ failure among ARDS patients [39]. Also, it was found that variabilities represented as single nucleotide polymorphisms in *Myosin Light-Chain Kinase (MYLK)* is correlated to Acute Lung Injury (ALI) development [40].

Mu-opioid receptor gene (*OPRM1*) is the gene responsible for encoding Mu-Opioid Receptor (MOR) that regulate analgesic response to pain and governs the rewarding effects of several substances of abuse, including opioids, alcohol, and nicotine [41].

The efflux pump P-glycoprotein (P-gp), a product of the *ABCB1* gene, is essential for the transport of different substances across the blood-brain barrier. P-gp protects the brain by selectively extruding its substrates, including antidepressants, restricting their absorption into the brain. In individuals suffering from major depression, *ABCB1* variants predicted remission to antidepressants with P-gp substrate characteristics [42].

Catabolizing catecholamines such as dopamine is catabolized by Catechol-O-Methyltransferase (COMT). These neurotransmitters appear to have a role in mood regulation, which can lead to aggressiveness [43].

Investigations showed that opioid analgesics like fentanyl are affected by the existence of *OPRM1* rs1799971 (AG) polymorphic gene, that leads to reduced analgesic effect. Moreover, it is affected with *ABCB1* rs1045642 (AG) causing a decrease in drug excretion from CNS and plasma as a result of reduced P-gp expression, requiring a careful dosage adjustment [44,45].

Evidence showed that variability of analgesic impact of fentanyl is affected by genetic variants in *OPRM1*, P-gp and

COMT, where, the SNP rs1799971 (118 A>G) is one of the most studied SNPs related to *OPRM1* and the opioid analgesic action. Additionally, a meta-analysis on morphine provided persuasive evidence supporting functional polymorphism of *OPRM1*, where, the finding showed that GG genotype was related to a reduced analgesic effect and higher opioid doses is required. This finding was confirmed by different studies to be applicable for fentanyl, sufentanil, and alfentanil as well [46].

A study that included 138 Japanese patients undergoing major abdominal surgery investigated the total opioid use (including epidural and rescue opioids) and monitored the use for 24 hours following surgery. Results indicated that when compared to heterozygous or homozygous wild-type carriers, homozygous c.118A.G carriers required considerably higher opioid analgesia [47].

The most common cytochrome in human body is cytochrome P450 3A4 (*CYP3A4*). It accounts for 30 to 50 percent of drugs metabolized by type I enzymes. Inhibitors, promoters, or substrates of *CYP3A4* activity and expression may induce some serious drug interactions [48].

Cytochrome P450 Oxidoreductase (POR) is an electron source for all cytochrome P450 enzymes. POR function is required for adequate control of Retinoic Acid (RA) levels and tissue distribution during early embryonic development, later morphogenesis and molecular patterning of the brain, abdominal/caudal region, and limbs [49].

Cytochrome P450 2B6 (*CYP2B6*) is a minor drug metabolizing enzyme found in the human liver. Non-genetic variables, inducibility, genetic polymorphisms, and irreversible inhibition by various substances all contribute to substantial variability in expression both across and within

people. Artemisinin, bupropion, cyclophosphamide, efavirenz, ketamine, and methadone are among the drugs mostly metabolized by *CYP2B6*. It is one among the most polymorphic CYP genes, with polymorphisms affecting transcriptional regulation, mRNA and protein expression, splicing, and catalytic activity. Some variations appear to influence many functional levels at the same time, resulting in haplotypes with complicated interactions between substrate-dependent and -independent processes [50].

GABRA1 (gamma-aminobutyric acid type A receptor subunit alpha1) is the gene that encodes a GABA (gamma-aminobutyric acid) receptor. GABA is the most important inhibitory neurotransmitter in brain, acting at GABA-A receptors, which are ligand-gated chloride channels. The chloride conductance of these channels can be altered by drugs that bind to the GABA-A receptor, such as benzodiazepines [51].

GABRA1 mutations have an important role in the genetic aetiology of both benign and severe epileptic disorders. Myoclonic and tonic-clonic seizures accompanied by a pathologic response to photic stimulation are prevalent and shared characteristics in both mild and severe phenotypes [52].

Butyrylcholinesterase (BChE) aids in the modulation of the cholinergic neurotransmitter's metabolism. BChE is primarily expressed in white matter and glia, as well as discrete populations of neurons in cognitive and behavior-related areas of the human brain [53].

Patients with pharmacological inhibition of Acetylcholinesterase (AChE) by cholinesterase inhibitors (ChEIs) and lower Butyrylcholinesterase (BChE) activity owing to single nucleotide polymorphisms have a negative effect on cognitive performance [54].

Sedatives like *midazolam* are affected by the presence of different genetic variations as *CYP3A4*22* which reduce the enzymatic metabolic activity leading to elevated levels of *midazolam* and high incidence of adverse effects. Besides, *POR*28* decreases *midazolam* metabolism and enhances its effect, finally, *GABRA1 187 + 3553 (AG)* increases *midazolam* receptor affinity and, thus, potentiates sedation [55,56].

Also, *CYP3A5*3* carriers showed a 22% lower average Clearance of *midazolam* than non-carriers in a study of 24 Asian patients with late stage gastrointestinal cancer [57].

Muscle relaxants including *suxamethonium* proved to be affected by different *BChE* variants like *A-variant: rs1799807 (c.293TC)*, *K-variant: rs1803274 (c.1699CT)*, *F-variant: rs28933390 (c.1253CA)*, *S-variant: rs104893684 (c.1004AG)*. The existence of these variants lead to enzymatic metabolic activity reduction and consequently reduced *suxamethonium* metabolism leading to prolonged muscle relaxation and apnea [58-60].

Pharmacokinetics of intravenous anesthetics like *propofol* is affected by genetic polymorphism as the existence of genotype *CYP2B6 rs3745274 (G>T)* might result in a decrease in drug metabolism. Also, *CYP2B6 rs2279343 (A>G)* genotype may result

in a decreased drug elimination rate from the CNS, and hence *propofol dosing adjustment should be taken in consideration* [61,62].

Genes polymorphisms for those ones coding for *CYP2B6* and *uridine 50-diphosphate (UDP) glucuronosyltransferase* metabolic enzymes might contribute in response variability to *propofol*. *Propofol* is mainly conjugated to glucuronide (70%) while (30%) undergoes hydroxylation via *CYP2B6*. The gene for *CYP2B6* is considered from the most polymorphic CYP genes (more than 100 SNPs) [63].

A model-based dosing simulations for *SNP rs2279343 in CYP2B6* propose a 50% reduction in *propofol* infusion dose in AA patient and AG patient genotypes during the maintenance of general anesthesia. A 250% higher exposure will occur within 1 hour from starting *propofol* infusion in these patients without dosage adjustments. Thereby, this particular polymorphism is important for dose adjustment to secure optimal anesthesia and avoid adverse effects [64].

The alpha 2A-adrenergic receptor (*ADRA2A*) is essential for the control of systemic sympathetic activity. *ADRA2A* functional deficiency has recently been linked to depression, attention deficit hyperactivity disorder, and Tourette syndrome [65].

A study that included Chinese women undergoing cesarean section concluded that the mutation of the *ADRA2A rs1800035*, *ADRA2A rs201376588* and *ADRA2A rs775887911* loci can lower the analgesic and anesthetic effect of *dexmedetomidine* for postoperative analgesia, without affecting drug safety [66].

Bradykinin and its metabolites work on G protein-coupled receptors B1 and B2 to cause vasodilation and enhanced vascular permeability [67]. *Bradykinin type 2 Receptor (BE1+9/+9)* polymorphism in 166 white Americans, and 62 black Americans patients showed an increased Systolic Blood Pressure (SBP) or vascular resistance that may contribute to the increased left ventricular mass [68]. Targeting the bradykinin system, either by suppressing or blocking bradykinin receptors, may provide novel treatment options for COVID-19-induced pulmonary edoema [69].

The human Angiotensin-Converting Enzyme II (*ACE2*) is responsible for viral cell entrance. *ACE2* and *ACE1* are now being studied as possible genes in which Single-Nucleotide Polymorphisms (SNPs) might modify SARS-CoV-2 binding or entrance and increase tissue damage in the lung or other organs. A study on 297 covid-19 positive and 253 covid-19 negative patients showed that the G-allele for *ACE2 rs2285666* was strongly related with a nearly two-fold increased risk of SARS-CoV-2 infection and a three-fold greater chance of developing severe illness or COVID-19 mortality. The *ACE1* polymorphism, on the other hand, was unrelated to infection risk or illness severity [70].

Serotonin (5-HT) is strongly linked to pain regulation. The promoter region (5-HTTLPR) of the human 5-HT Transporter (5-HTT) gene (*SLC6A4*) has many polymorphisms that alter 5-HTT expression. The S allele of 5-HTTLPR causes low 5-HT tone and may impact chronic pain regulation [71].



Individual risk of experiencing postoperative vomiting appears to be connected with genetic variants in the serotonin receptor subunits A and B (HTR3A and HTR3B) genes. This was investigated in a study that included 95 patients who had suffered from postoperative vomiting after general anesthesia. Results indicated that HTR3A variant c1377A>G was associated with a significantly higher risk for postoperative vomiting. On the other hand, HTR3B variant (c5+201_+202delCA) and HTR3B variant (c6-137C>T) were associated with a lower risk for postoperative vomiting [72].

Based on the previous findings, we suggest avoiding isoflurane in COVID-19 patients requiring ICUs mechanical ventilation to avoid risk of possible respiratory depression. From our point of view and based on the previously presented data, Sevoflurane is a good option for use in COVID-19 patients owing to its rapid onset, bronchodilator effect and its safety on the heart, furthermore, RYR1 variants and CACNA1S rs772226819 (c.520CT) genotypes should be considered in order to avoid possible occurrence of malignant hyperthermia.

Despite the advantages of N₂O as an adjunct in reducing the required concentrations needed of halogenated anesthetics and its strong analgesic effect, caution should be taken in consolation to avoid possible homocysteine elevation and myocardial infarction risk especially in those with MTHFR 677C>T or 1298A>C genetic mutations.

Fentanyl is a good choice in combination with general anesthetics, in COVID-19 patients admitted to intensive care unit, that contributes to reduction of anesthetic doses required and possess a strong analgesic effect that minimizes hemodynamic changes resulting from pain.

Also, propofol is considered a good choice, for COVID-19 patients, as a parenteral anesthetic due to its sedative-hypnotic characteristic, anxiolytic effect, antiemetic, anticonvulsant, anti-oxidative, anti-inflammatory, and neuroprotective effect.

Conclusion

Gene screening is an essential procedure that can stratify COVID-19 patients into different groups and provide healthcare professionals the chance for proper selection of appropriate anesthetic agents required in severe cases requiring ICU mechanical ventilation, especially those with ARDS.

Genetic screening must be implemented as one of the important procedures to be performed for all individuals, healthy before being infected or sick, to identify genetic polymorphic types that may alter the effect of anesthesia before using them in ICUs ventilation, when needed, in order to avoid possible adverse effects and different sedation response variations.

Sevoflurane, fentanyl, and propofol can be considered a safe and good choice for use in ICUs. Dexmedetomidine is, up to presenting this review, under evaluation for its role in COVID-19.

Other anesthetics should be investigated to assess its risk

versus benefit concerning its use on individualizing basics. Thus it is recommended to extend personalized medicine application and dose adjustment based on human genomics, including genetic polymorphism, to the different types of anesthesia used either pre-, peri-, or post-operation including the intensive care unit.

Authors' contributions

N.A.S contributed to the conception, design, reviewing the draft and revision of the manuscript. E.M.S and S.A.R contributed to the acquisition of the data and editing process. M.A.R contributed to the analysis and interpretation of the data. All authors have approved the submitted version.

Acknowledgement

The authors would like to present their deep gratitude and thankfulness to Drug Research Centre – Cairo / Egypt for giving plenty of time and support to the researchers to share and participate in this work.

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