Special Article

Re-emergence of TIVA in COVID times

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ABSTRACT

Total intravenous anaesthesia (TIVA) is a technique of general anaesthesia (GA) given via intravenous route exclusively. In perspective of COVID-19, TIVA is far more advantageous than inhalational anaesthesia. It avoids the deleterious effects of immunosuppression and lacks any respiratory irritation, thus providing an edge in the current situation. Many peripheral surgeries can be done with the patient breathing spontaneously without any airway device, thus avoiding airway instrumentation leading to droplet and aerosol generation. Intravenous agents can be utilized to provide sedation during regional anaesthesia (RA), which can easily be escalated to contain pain due to sparing of blocks or receding neuraxial anaesthesia. The present narrative review focuses on the merits of adopting TIVA technique during this pandemic so as to decrease the risk and morbidity arising from anaesthetizing COVID-19 patients.

Key words: Anaesthesia, COVID-19, etomidate, propofol, total intravenous anaesthesia

INTRODUCTION

Anaesthesiologists and intensivists across the globe are struggling in a fight against COVID-19 as frontline warriors and beyond no doubt we have to win this war. The world may have stopped for majority during this global lockdown to combat corona, but the clinical work has increased tremendously for these masked warriors. They are battling daily against the invisible enemy, subconsciously knowing that they may be the next victim of this deadly pandemic. Apart from managing COVID-19 patients, they also have to conduct emergency surgeries, admit critically ill patients in intensive care unit and at the same time teach residents besides taking care of other professional and social duties. In a race against time, when new innovations, techniques, drugs, vaccines, equipment and other measures are being developed for prevention against COVID-19, anaesthesia techniques and drugs are also undergoing critical observation and re-evaluation for providing better and safe mode of anaesthesia. Being Anaesthesiologists and critical care experts, they would be required to provide anaesthesia and sedation to COVID-19 proven positive, suspected and non COVID-19 patients either in emergency, operation theaters or intensive care units.[1] During these circumstances, TIVA, a General Anaesthesia (GA) technique, which uses a combination of intravenous agents without the use of inhalation agents, is emerging as a preferred choice for nearly all type of surgical procedures.[2]

SEARCH STRATEGIES

Keeping these words (Anaesthesia; COVID-19; Etomidate; Propofol; TIVA; Total Intra Venous Anaesthesia) as the main keys either single or in various combinations a systematic search was made

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on internet exploring various databases including PubMed, Cochrane Databases of Systematic Reviews, Scopus, EMBASE, Google and Google Scholar from the year 1990 to 2020. The references of relevant articles were cross-checked and the review was imbibed from the articles which elaborated on these keywords.

Types of TIVA

TIVA may be provided either with insertion of endotracheal tube or supra glottic airway device, nasal or oral airway or oxygen alone without insertion of any airway device, as summarized in [Figure 1].

Challenges in anaesthesia during COVID era

Use of inhalational anaesthesia in present situation is associated with numerous risks and difficulties. During present pandemic, the main focus of any anaesthesia procedure is to minimize the generation of aerosols. Inhalation induction in certain subset of patients can sometimes be claustrophobic, prolonged, frightening, may cause cognitive deficit[3] and may be associated with more than anticipated risk of infection through aerosol generation and transmission, especially in paediatric population. Smooth and rapid induction with intravenous anaesthetic agents is always a better alternative. Using high concentration and high flow of oxygen for prolonged ventilation can lead to oxidative damage and is not recommended in routine practice.[4] These techniques can possible flare up the pathology in surgical COVID patients where respiratory involvement is commonly seen. Air-oxygen mixture can be used and if facility to ventilate with air is not available, nitrous oxide may be best utilized to reduce the oxygen concentration along with its added analgesic effects, even though it is out of the purview of TIVA. Though it is recommended that anaesthesiologists inside the Operation Theatre don full airborne Personal Protective Equipment (PPE) and all precautions described for airway management in a COVID patient must be taken.[1]

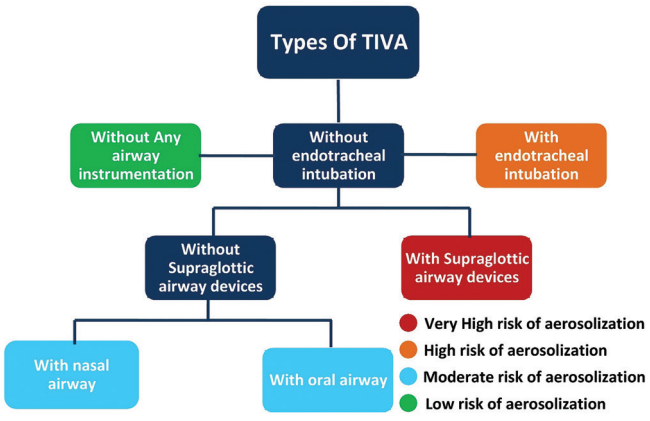

Figure 1: Types of TIVA

TIVA indications in COVID-19 pandemic

Present advisories recommend use of regional anaesthesia in COVID positive patients, wherever possible. However, to allay anxiety and fear in such population, TIVA can be combined with regional and neuraxial anaesthesia in individualized varying doses. In this pandemic, TIVA is definitely making its dominance felt in almost all type of surgical and airway procedures, anaesthesia at remote locations, patients at high risk of post-operative nausea and vomiting, day care surgeries, Malignant hyperthermia susceptible patients, neurosurgical procedures, short procedures such Computed Tomography, Magnetic Resonance Imaging, other radiological procedures, Cardiac catheterization and anaesthesia in non-operative locations where inhalational anaesthetics are difficult to administer. TIVA will definitely emerge as the anaesthetic technique of choice in all aerosol generating or triggering procedures.

Advantages of TIVA over inhalational agents in COVID-19 patients

The major exceptional advantage of TIVA over inhalational anaesthetic agents is minimal aerosol generation and can be provided by means of extension lines or infusion pumps, which are no doubt away from the patients, thus keeping recommended distance. There is minimal or no effect on immune system. On the contrary, *in vitro* studies have revealed immune suppressive effects of volatile anaesthetics on mononuclear cells and monocytes. Sevoflurane and isoflurane in 1.5-2.5 MAC are known to suppress TNF-alpha and IL-1 beta from peripheral mononuclear cells stimulated by NK cells.[5,6] Patients are usually not aware of placement of mask over face during induction of TIVA anaesthesia, which can be claustrophobic in many subsets especially children. There is no chance of sudden increase in concentration of any gas or vapor, which can cause sudden haemodynamic changes.[7] Except for a small prick in hand, experts find it very safe to titrate TIVA as maintenance anaesthesia. There is no risk of malignant hyperthermia with TIVA, less chances of emergence delirium, as is associated with sevoflurane or desflurane, which may add to aerosolization. TIVA avoids distension of air filed spaces in body as may be associated with the use of nitrous oxide, thus providing better surgical conditions. There is less operation room (OR) pollution and overall greenhouse effect is minimized with TIVA.

Stress response is reduced and there is better cerebral auto regulation, infect neuro surgeons find better surgical conditions with TIVA.[8]

With Non-touch or One-touch technique we can avoid cross contamination making TIVA an advantageous option in COVID-19 patients. So, TIVA with spontaneous breathing avoids airway instrumentation which leads to minimal risk of COVID-19 spread by droplets and aerosol. The various advantages of TIVA during COVID-19 pandemic can be summarized as in [Figure 2 and Table 1].

Merits of TIVA drugs in current pandemic

Majority of drugs used for TIVA including benzodiazepines, narcotics, propofol, ketamine, etomidate, dexmedetomidine, muscle relaxants, and other drugs are easily available in almost all the Operation theatre's across the nation. In addition, all these drugs can be given to any subset of population suffering from COVID-19 disease in easily titratable doses.

Table 1: Advantages of TIVA over Inhalation in COVID-1

Patient is unaware
Minimal aerosol generation
No mask over face
Can be given from a distance
Minimal effect on immune system
No sudden concentration of gas or vapor
No risk of Malignant Hyperthermia
Less post-operative delirium and emergence phenomena,
Better operating conditions
Less operating room pollution
Reduced stress response
Better preservation of cerebral auto regulation
Decreased Post-Operative Nausea and Vomiting
Avoidance of cross infection
Minimal intervention to airway in many surgeries
Widely acceptable across age groups
Definite advantage in remote locations

Propofol

Propofol is a commonly used intravenous agent for anaesthesia and procedural sedation. Propofol enhances innate immunity through Natural killer cells (NK) and cytotoxic T cell which is considered to be an essential first line of defense against novel corona virus which weakens the innate immunity associated with rapid progression and increased severity of illness.[9,10] Propofol also has a potent anti-inflammatory effect through adaptive immunity and decrease release of pro-inflammatory cytokines which may possibly benefit in decreasing cytokine storm in severe COVID19 sepsis.[10] TIVA with propofol is associated with decreased postoperative cough, postoperative nausea and vomiting (PONV) and a decreased need of airway instrumentation which in fact minimizes the aerosol generation and contamination of operation theatre.[11] Propofol is also a potent free radical scavenger and antioxidant which may have beneficial effect in reducing ischemic and reperfusion injury to vital organs.[10] TIVA with propofol has 30% decreased incidence of postoperative acute kidney injury (AKI) as compared to inhalational anesthesia, and a reduced need of renal replacement therapy when used as sedation during mechanical ventilation.[12] These beneficial effects of propofol may possibly reduce the incidence of AKI in critically ill COVID-19 patients. Decreased postoperative delirium and agitation in elderly patients, rapid recovery from anaesthesia and decreased duration of in-patient care associated with use of propofol, most likely can reduce the exposure of health care workers to COVID-19 patients. As a component of TIVA, propofol can be administered as intermittent manual infusion, continuous manual

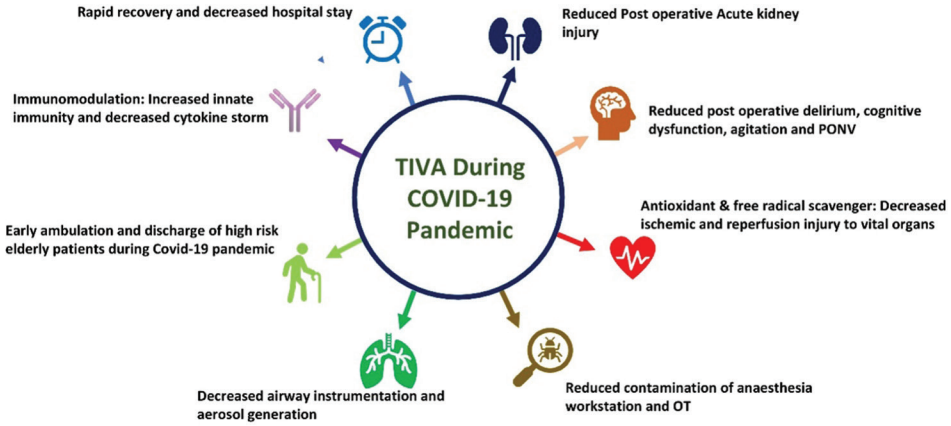

Figure 2: Merits of TIVA during COVID-19 Pandemic

infusion, and open loop target controlled infusion (TCI) or as closed loop target controlled infusion. Target controlled sedation with propofol allows the optimum titration of target site concentration. If TCI is combined with depth of anaesthesia monitoring either with Entropy or Bi-spectral index (BIS), target depth can be set around 60-80 for sedation and 40-60 for anaesthesia. This facilitates early recovery and precise titration of drug among individual patients with different phenotypes and co-morbidities.

TCI/TIVA with intubation

TCI TIVA for general anaesthesia allows smoother induction and less haemodynamic instability as compared to manual infusion, when using a TCI propofol for rapid sequence induction (RSI) in suspected or positive COVID-19 patients. Co-administration of remi-fentanyl, fentanyl or alfentanyl hastens the induction. Alternatively this can be achieved by setting an initial high target concentration or use of different inducing agents such as thiopentone or Etomidate and then TCI propofol can be used for maintenance.[13] TCI TIVA decreases the time required for recovery and decreases postoperative cough and thereby minimizes aerosol generation.

TIVA with manual infusion

Propofol can be used for general anaesthesia through normal syringe pumps. Commonly used regimen is Bristol regimen, which involves a loading bolus of 1 mg kg^{-1} followed by a step-down infusion of propofol (10-8-6 protocol).[14] Adequate monitoring of respiration and depth of anaesthesia is critical in prevention of desaturation and airway management during manual infusion of propofol.

Ketamine

Ketamine is a versatile anaesthetic agent with unique profile that allows it to be used in multitude of situations.[15] It can be used for induction or maintenance of anaesthesia and as analgesic, sedative and in Non-Operating Room Anaesthesia (NORA). Ketamine provides good haemodynamic profile and preserves airway reflexes and respiratory tone which makes it very useful in critically ill COVID-19 sepsis patients, as requirement of invasive ventilation is minimal and it reduces aerosol generation. Ketamine can be used alone or along with other agents like propofol, dexmeditomidine and opioids.[16] Though a word of caution for possible ketamine emergence pheomenon and aerosolization potential be taken.

Etomidate and thiopentone sodium

Etomidate is a derivative of the imidazoles, with minimal respiratory depression, and maintain haemodynamic stability which definitely can provide a certain advantage in COVID-19 sepsis patients. It can be used in severe sepsis COVID-19 patients with haemodynamic instability either alone or along with ketamine; it can also be combined with propofol for sedation and anaesthesia. On comparison, recovery from etomidate anaesthesia is similar to propofol and allows early discharge from healthcare facility thus minimizing risk of exposure to COVID-19 patients/carriers.[17] Thiopentone sodium can be used to augment induction during rapid sequence induction, while using TCI TIVA propofol can be used for maintenance. This reduces requirement of mask ventilation and aerosol generation after induction, but one must not forget the chances of histamine release, thus adding to inflammation or coughing during induction.

TIVA for remote locations

In spite of numerous evolving consensus guidelines which advocate minimization of elective surgeries during this pandemic, anaesthesiology services are still required at many places which further add to the challenges thrown by COVID-19. TCI TIVA for non-operating room anaesthesia or sedation in settings like radiology suite, radiotherapy unit and endoscopy suite allows optimum titration of intravenous agents, which minimizes airway obstruction, oxygen desaturation, unplanned airway instrumentation and aerosol generation. In MRI suite, TCI pumps are not allowed within 50 Gauss field. A long infusion line is required and it is preferable to have a single long infusion line with proper luer-lock connections keeping in consideration the possibility of line disconnection. Alternatively, TCI pumps can be kept inside aluminum case or radiofrequency shield enclosure (faraday cage).[13]

General anaesthesia in the COVID-19 intensive care unit (ICU)

TIVA is most appropriate to provide anesthesia for surgical and diagnostic procedures inside COVID-19 ICU. TIVA can be administered with manual or TCI pumps and when administering through TCI Pumps, target concentration should be titrated based on patient's present general condition. Most of the patients in Intensive Care unit (ICU) require lower target drug concentration. In critically ill patients with organ dysfunction, TCI models are unlikely to accurately predict the plasma or effect site concentration.

Processed EEG or depth of anaesthesia monitoring may be useful in titrating anaesthetic drugs.[13]

Methods of administering TIVA in COVID-19 patients

There are Joint Guidelines from the Association of Anaesthetists and the Society for Intravenous Anaesthesia, which has provided safe practice of TIVA.[13] TIVA offers many flexible approaches as it can be administered either with a single drug or combination of drugs, by single syringe technique with mixture of drugs or with only one drug, as continuous intravenous (IV) infusion through drips or with syringe infusion pumps, as well as through TCI machines and closed loop systems. These flexible approaches allows ease in formulation of policies for designing and setting up of COVID OT and ICU.

Non-operating room procedures such as MRI, CT, Cardiac Catheterization and surgeries under anaesthesia for short duration can be easily undertaken under spontaneous breathing without airway intervention with TIVA. Those surgeries like upper and lower limb procedures, breast lump excision, simple mastectomy and others can be managed with TIVA. Dexmedetomidine, ketamine, lignocaine and magnesium sulphate are agents that can be used to achieve the required anaesthetic depth while maintaining airway during spontaneous breathing. Use of narcotic analgesics and hypnotic agents alone will lead to airway collapse and respiratory depression demanding airway instrumentation and ventilatory support. Continuous administration of the intravenous agents by intermittent boluses or infusion titrated to the anaesthetic demand is desired so as to maintain adequate anaesthetic planes with the patient breathing spontaneously. Unnecessarily deeper plane may necessitate airway instrumentation and/or positive pressure ventilation.

Apart from taking all the precautions meant for surgical COVID-19 patients, N95 mask has to be worn by the patient throughout the surgery and post operatively to prevent contamination.[1] Supplemental oxygen can be administered with a simple mask or the N-95 mask. For surgical procedures that last more than an hour, safeguarding the airway with an endotracheal tube or a supra-glottic device is preferable. Thoracic or abdominal cavity surgeries need good muscle relaxation provided by non-depolarizing agents warranting intermittent positive pressure ventilation. When intravenous agents alone are used for anaesthesia, patient may be ventilated with air oxygen mixture. Generally with TIVA, emergence is smooth without cough or laryngospasm.

Many patients desire to be asleep during a surgical procedure. When regional anaesthesia is chosen for these patients, midazolam, dexmedetomidine or propofol are good options for procedural sedation administered in boluses or by infusion.

TIVA in special populations

Paediatric patients

In paediatric patients who are COVID 19 suspected or positive, TIVA in premedication or during induction is beneficial over inhalation agents. Inhalational induction may increase exposure to respiratory droplets and aerosols. PeDI-C (Paediatric Difficult Intubation Collaborative of Society for Paediatric Anesthesia) members recommended that IV induction is preferred in paediatric patients for TIVA.[18] TIVA in paediatric patients facilitates surgery, minimize the risk of emergence agitation and reduce airway inflammation, at the same time reduced risk of post-operative nausea and vomiting. Manual infusion form an important part in clinical practice due to variability of dosing regimen, therefore TCI Models such as Kataria and Paedfusior can be used. Kataria model is designed for children weighing 15-60 kg and aged 3-16 years, while Paedfusior Model is used in children 1-16 years weighing 5-60 kg. Propofol, ketamine, remifentanil and dexmedetomidine are important drugs in TIVA for pediatric population. For dose calculation, Total body weight (TBW) is used to calculate infusion rate in obese children.

TIVA in geriatric patients

TIVA is more beneficial in elderly subset of patients, as it preserves cognitive function in old age after surgery and anaesthesia. Compared to inhalational agents, TIVA helps preserves lung blood flow and avoids risk of cardiac depression. Inhalational agents reduce cardiac output and can potentially lead to lethal increase in alveolar concentration. These merits of TIVA may possibly be of greater benefits in COVID patients but presently there is no such clinical evidence. Start slow with low dose and titrate slowly to avoid hypotension.

TIVA in ASA III patients

TIVA can be provided to seriously ill and very sick COVID-19 patients in whom systemic disease is not a threat to life, as stated in ASA III classification. Though there is no specific protocol devised for ASA

III patients, we suggest using dosage recommended for elderly patients be adopted, as they require lower concentration of drug to achieve anesthesia. Choose the most appropriate TIVA drugs, according to the patient's physical condition, irrespective of age and obesity status.

TIVA in obese patients

TIVA will prove an excellent method of general anaesthesia to obese COVID positive patients. The recommended drug dose in obese patients is always lower than in non-obese patients, as the actual blood concentration is higher than the calculated target dose of drugs. In obese patients, it is always recommended to secure airway, so as to avoid respiratory depression. The faster acting muscle relaxant is advisable for obese patients and suxamethonium is an ideal choice for intubation using TIVA, keeping in consideration all the precautions to avoid aerosol generation.

TIVA checklist in COVID-19 OT

All anaesthesia drugs, airway equipment, oxygen supply, and multipara monitors and other essentials must be checked thoroughly before administering TIVA. It is emphasized to follow all personal protection protocols during any instrumentation in OT area. We suggest to place intravenous line with sterile drapes and gloves which will avoid any spillage. There should be no leakages from cannula and ensure that patient's intravenous cannula should always be visible during the surgery whenever possible. Syringes should be labeled with the drug name, date and concentration. Infusion lines should be checked every 15 minutes during surgery. The infusion set through which TIVA is delivered should have a Luer-lock connector at each end. If BIS is used, check placement before and after surgical draping. At the end of procedure, ensure all tubings and intravenous cannulas which had TIVA drugs by any method are flushed to prevent inadvertent boluses in the ward. Syringe pumps should be disinfected with 1% hypochlorite solution after each use and use of long small bore infusion line with luer lock system decreases contamination of pumps. All the disposables and wastes should be managed after the completion of surgery as advised by institutional policy for COVID surgeries.

Technology and TIVA

Anaesthesiologist is the best monitor for COVID-19 patient undergoing TIVA. Multipara monitoring, Bispectral Index Monitor, Evoked Potentials and EEG monitor is recommended, when a neuromuscular blocking drug is used with TIVA. Whenever we as anaesthesiologists have faced new challenges, we have always come up with newer innovative ideas or resurgence of previous neglected techniques with newer methods. TIVA will become more practical and popular in times to come, because of many reasons. Newer advancements in technology like infusion pumps, target controlled infusion, closed loop system, newer concepts in pharmacokinetic modelling, coupled with use of short acting opioids, advanced vast knowledge about pharmacokinetic and pharmacodynamics properties of drugs such as propofol, dexmedetomidine, ketamine make TIVA a unique and dominating concept in times to come, and may reduce inhalational anaesthesia technique. Propofol and remifentanil combination presently seems to be the dominating TIVA technique all over world, delivered either by conventional pumps or by target control systems or by close loop systems.

TIVA will be a norm in COVID pandemic as it is not only friendly for the patient, surgeon, anaesthesiologist, operation theatre, equipment and environment, but is also economical. Total intravenous anaesthesia is viable and safer alternative to the Inhalation Anaesthesia and will be the preferred mode over the latter in this pandemic. Newer advancement in monitors and TCI pumps have made administration of TIVA easy and precise. Manual Controlled Infusions using regular syringe pump can be used to deliver pre-calculated doses. The newer intravenous hypnotics and analgesic agents with favorable pharmacokinetic properties have made TIVA feasible in a wide array of varying clinical scenarios including COVID-19 pandemic.[19]

Limitations of TIVA

The major limitation with TIVA include pain on injection, especially true with propofol, though that limitation is reduced with administration of agents such as lidocaine/opioids and using wide bore cannula. The other challenging situation may arise in cases of difficult cannulation, though this will be equally challenging in cases of providing anaesthetic agents via maintenance with inhalational agents. The major limitation is costly equipment used in TIVA including disposables. Other limitations include the risk of bacterial contamination, especially when there is frequent misconnections in line. Environmental effects of plastic waste remains, though that is also true for greenhouse effect of inhalational anesthetics and nitrous oxide. Caution is advisable in prolonged procedures and obese subsets.

CONCLUSION

To conclude, Total Intravenous anaesthesia is a viable and safer alternative to the volatile anaesthesia, with added benefits. Inhalation agents may lead to immunosuppression, and can be deleterious during COVID pandemic, especially in severe cases. Respiratory irritation and increased secretions may lead to coughing and straining, as is common with volatile anaesthetic agents. The newer intravenous hypnotics and analgesic agents with favorable pharmacokinetic properties have made TIVA feasible in a wide array of varying clinical scenarios and anaesthetic demands. Manual Controlled Infusions using regular syringe pump can be used to deliver pre-calculated doses. TCI pumps and depth of anaesthesia monitors have made administration of TIVA very easy, safe and precise technique. In the COVID-19 scenario, TIVA offers anaesthesia for NORA and peripheral surgeries with the patient breathing spontaneously without the need for airway instrumentation avoiding droplet and aerosol risk, which will serve as a boon to the Anaesthesiologists in times to come. TIVA offers a smooth extubation with attenuated emergence phenomenon, in those who require intermittent positive pressure ventilation. In recent times of COVID-19 pandemic, less aerosolization, concept of rapid discharge, day care procedures, and green environment have created the *Re Emergence of TIVA*.

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Conflicts of interest

There are no conflicts of interest.

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