Comparison of Cost-Effectiveness Analysis (CEA) between sevoflurane inhalation anesthetic and Propofol Total Intravenous Anesthesia (TIVA) in craniotomy surgery: a literature review

Petrus Devi Doko Rehi

ABSTRACT

Background: The common neuroaesthetics used for neurosurgery was inhalation of Sevoflurane and the newest, by continuous infusion of propofol called Total Intravenous Anesthetic (TIVA). Anesthesia procedures are one of the biggest healthcare expenditures in hospitals. Thus, finding the most effective and efficient anesthetic technique but in the same time can maintain patient safety is important. This literature review compares a cost-effective Sevoflurane and propofol TIVA analysis in craniotomy surgery.

Methods: This literature review was carried out by searching studies in three online databases consisted of PubMed, the Cochrane Library, and Google Scholar using the keywords “sevoflurane inhalation anesthetic”, “propofol total intravenous anesthesia”, “TIVA”, “craniotomy”, “cost-effective analysis”, and “pharmacoeconomic”. Appropriate studies were then carried out through a narrative synthesis analysis.

Results: The assessment of cost-effective analysis in anesthesia is broadly divided into fixed commodities and various commodities. The analysis found the highest use of costs in the TIVA group and the lowest in the isoflurane inhalation group. The high cost in the TIVA group was caused by propofol being the most expensive compared to other inhalation agents such as isoflurane and Sevoflurane. Based on the average intraoperative anesthetic cost, it was also found that the anesthetic cost per patient was Rp. 957,870,- for the TIVA propofol group and Rp. 1,318,130,- for the sevoflurane group. Sevoflurane use for induction and maintenance of anesthesia resulted in a further modest decrease in costs (especially if fresh gas flow was reduced early), primarily through less drug waste.

Conclusion: The cost-effective analysis showed that Sevoflurane was less expensive than propofol. Yet, in terms of pharmacoeconomics, using TIVA propofol results in much fewer PONV episodes, unplanned hospital admissions, and patient lengths of stay, all of which improve pharmacoeconomic benefits.

Keywords: Cost-effective analysis, pharmacoeconomic, propofol, sevoflurane inhalation anesthetic, TIVA.

INTRODUCTION

A craniotomy is a neurosurgical procedure in which a patient’s skull is opened or a portion of it is removed to conduct surgery with a specific goal. Craniotomy treatment options for cerebral mass lesions include a biopsy or resection, management of intracranial vascular disease and epilepsy, and trauma care. Neurosurgical procedures involving craniotomy and resection of brain tumors are usually performed under anesthesia. The goals of anesthesia during neurosurgical procedures are smooth induction, stable intraoperative hemodynamics, optimal surgical conditions, adequate brain relaxation, smooth and rapid recovery after surgery, and a rapid return to consciousness or rapid emergence that allows for a quick evaluation of the patient's neurological condition. In most neurological procedures, a quick recovery from anesthesia is preferred as it enables screening potential intracranial problems such as hematoma formation, cerebral herniation, and cerebrovascular ischemia. Also, wakefulness is crucial because lingering anesthesia may mask a developing intracranial issue or provide the wrong impression of a neurologic deficiency. Anesthesia used for neurosurgery may have a discernible impact on the results of neurologic testing. The most common technique for administering anesthesia for neurosurgery patients is total intravenous anesthesia (TIVA) or inhaled anesthesia. Almost all anesthetic agents have been employed, and for at least 15 years, the decision between intravenous and volatile anesthetics has been an important topic of dispute in neuroanesthesia. Propofol anesthesia results in a decrease in cerebral blood flow (CBF) as a result of flow metabolism coupling. Still, Sevoflurane and propofol have no effect on cerebral autoregulation and sensitivity to CO₂.
The effect of Sevoflurane on CBF is a balance between its direct vasodilatory and indirect vasoconstrictive effects, the latter being mediated through flow metabolic coupling. Sevoflurane does not uncouple flow and metabolism; it changes the flow/metabolism ratio. Propofol may lower intracranial volume more effectively in patients with impaired intracranial compliance, but Sevoflurane will likely improve CBF more than that drug.2,3

With the development of new and more sophisticated anesthetic techniques, there has also been a progressive increase in healthcare costs. One of the biggest hospital expenses is anesthesia procedures. This is why anesthesiologists are trying to find the most effective and efficient anesthetic technique in terms of cost while maintaining patient safety and kindness. The combination of drugs, including anesthesia, must be effective and cost-efficient. To assess the effectiveness of this financing, a cost-effectiveness analysis study can be carried out.2,3 According to WHO, cost-effectiveness analysis can provide decision-makers information to determine the action in certain health services. It can also provide general information about the costs and benefits of certain medical techniques. Propofol TIVA is more expensive than inhalational anesthesia with isoflurane and nitrous oxide (N₂O). However, some investigators have suggested that TIVA could be cost-effective because the costs of treating PONV and of increased recovery room stay after inhalational anesthesia offset the additional drug acquisition costs of propofol TIVA.2,8

Based on existing data at RSUD Dr. Soetomo Surabaya, it was found that the cost per 10 mL of Sevoflurane is Rp. 48,060, which requires 35 mL/hour of use every hour. The price of Sodalime at RSUD Dr. Soetomo is Rp. 55 per minute. For other anesthetic drugs, based on the price of the electronic catalog set by the government in 2021 and applies throughout Indonesia, namely: Propofol costs Rp. 13,167, Fentanyl costs Rp. 32,614, and Rocuronium costs Rp. 35,742. The limited funding ceiling and many patients are a reference for assessing the cost-effectiveness of a medical procedure.9 Based on this background, this literature review will discuss more the comparison of cost-effectiveness analysis (CEA) between sevoflurane inhalation anesthetic and propofol total intravenous anesthesia (TIVA) in craniotomy surgery.

METHODS

The literature review uses studies published online on three electronic data sources, namely PubMed, Cochrane Library, and Google Scholar, using the keywords “sevoflurane inhalation anesthetic”, “propofol total intravenous anesthesia”, “TIVA”, “craniotomy”, “cost-effective analysis”, and “pharmacoeconomic”. A study search was carried out using the following PICO criteria:

P (Population) = craniotomy patients
I (Intervention) = propofol total intravenous anesthesia
C (Comparison/Control) = sevoflurane inhalation anesthetic
O (Result) = cost-effective analysis.

The results of the studies that match the search criteria are then analyzed using a narrative synthesis to conclude.

CRANIOTOMY SURGERY

A craniotomy is a neurosurgical procedure performed by opening or removing a portion of the patient’s skull to perform an operative procedure with a specific purpose. Indications include a biopsy or resection of intracranial mass lesions, treatment of intracranial vascular pathology, treatment of epilepsy, and management of trauma. In 2007 in America, it was estimated that there were 70,849 tumor craniotomies, 2,237 vascular surgery craniotomies and 56,405 other craniotomies.1 Seotomo Surabaya in 2013, there were 1,411 people with brain injuries, 166 of them were sufferers of severe brain injuries, and craniotomy operations were performed around 18.87% - 25.27% of all brain injured patients.10

ANESTHESIA PRINCIPLE FOR CRANIOTOMY SURGERY

An ideal anesthetic agent in neurosurgery should have the following properties: rapid onset and rapid onset of action for neurologic assessment, hemodynamic stability, and reduction of ICP. Cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO2) are interdependent. Any increase or decrease in cerebral metabolic oxygen demand will respectively increase or decrease CBF, and this phenomenon is known as flow-metabolic coupling. The goals of anesthesia for intracranial procedures include hypnosis, amnesia, immobility, ICP and CPP control, and a “relaxed brain” (i.e., optimal for the surgical condition). Anesthetic plan with awake extubation should be chosen to evaluate the patient for neurological abnormalities at the end of the procedure. Anesthesia induction must be achieved without increasing intracranial pressure (ICP) or compromising cerebral blood flow (CBF).5,11 Hypertension, hypotension, hypoxia, hypercarbia and coughing should be avoided.

For neurosurgical patients having intracranial procedures, the anesthesia should ensure hemodynamic/instability, lower cerebral metabolism, preserve cerebral autoregulation, prevent rises in intracranial pressure, and ensure a quick recovery. Since these combinations allow for quick recovery and prompt neurological assessment, volatile anesthetics (isoflurane, Sevoflurane, and desflurane) in combination with synthetic opioids (remifentanil and fentanyl) have been utilized most commonly for neurosurgery procedures in recent years. However, volatile anesthetics have been demonstrated to influence intracranial pressure (ICP) and cerebral autoregulation, making surgery more challenging and risky and raising the risk of ischemic cerebral insults.2,3,12

SEVOFLURANE INHALATION ANESTHETIC

Sevoflurane is a halogenated inhalational anesthetic used to induce and sustain anesthesia. It is vaporized before usage. Sevoflurane has a sweet smell and is not irritating to the respiratory tract. It is even said to cause bronchodilation, so it is a volatile drug that can be used for inhalation induction. Compared with isoflurane, recovery with Sevoflurane can be 3 to 4 minutes faster. In the central nervous system, Sevoflurane causes an increase in cerebral blood flow and intracranial
pressure in normocarbia conditions. High concentrations of Sevoflurane (> 1.5 MAC) will interfere with brain autoregulation. If this occurs together with bleeding, the brain will fail to perform autoregulation and perfusion to the brain will decrease. Sevoflurane has a good relaxing effect on the musculoskeletal system, so that it can be relied upon as a muscle relaxant in infants induced by inhalation with Sevoflurane. Sevoflurane slightly reduces renal blood flow, and its metabolites, which are formed in large quantities, can be nephrotoxic. Sevoflurane reduces portal blood flow but increases hepatic arterial blood flow and so generally does not significantly affect hepatic blood flow and oxygenation. A 40-year-old adult's minimum alveolar concentration (MAC) in the oxygen mixture is 2.1%; MAC declines with age. Direct vasodilator effects of Sevoflurane reduce brain metabolic rate while increasing cerebral blood flow (CBF) (CMRO2). After the initial exposure to 1.3 MAC of anesthesia, CBF returns to normal in around 3 hours.

PROPOFOL TOTAL INTRAVENOUS ANESTHESIA (TIVA)

A sedative-hypnotic administered intravenously, propofol is used to induce and maintain anesthesia. Propofol is a selective GABA receptor modulator, the main inhibitory neurotransmitter in the central nervous system. When the GABAA receptor is activated, there will be an increase in transmembrane chloride conduction resulting in hyperpolarization of the postsynaptic cell membrane and inhibition of postsynaptic neuronal function. The interaction between propofol receptors and GABA reduces the rate of dissociation of an inhibitory neurotransmitter (GABA) from its receptors, thereby prolonging the effect of GABA. A therapeutic amount of propofol administered intravenously usually causes hypnosis 40 seconds after injection, the time needed for one arm’s circulation to reach the brain. Propofol blood concentrations at a steady state are often inversely correlated with infusion rates. With favorable cerebral hemodynamic effects that lower CBF, favorable pharmacokinetics, and a high-quality recovery profile despite a lengthy infusion time, propofol possesses many qualities of an excellent drug for neuroanesthesia. It decreases CMRO2 in a manner comparable to Sevoflurane. Propofol administered by continuous infusion is defined as total intravenous anesthesia (TIVA) propofol.

COST-EFFECTIVE ANALYSIS (CEA) BETWEEN SEVOFLURANE INHALATION ANESTHETIC AND PROPOFOL TIVA FOR CRANIOTOMY SURGERY

Assessment of cost-effective analysis in anesthesia is broadly divided into fixed commodities and various commodities. Fixed commodities consist of gas pipe installations, operating tables, anesthesia machines, and other equipment, which are one-time investments and have almost no impact on the daily expenses of each operation. In comparison, various commodities include drugs and anesthetic gases. Cost control and more efficient use of resources in terms of costs are priorities in health services. This can be achieved by modifying the cost variable, which the anesthetic technique can determine. Studies examining the cost-effectiveness comparison between inhalational anesthetic sevoflurane and TIVA propofol in craniotomy surgery are still limited. Lauta et al. conducted a randomized clinical trial study to compare the clinical outcomes of craniotomy patients who underwent surgery under inhalation anesthetic technique using Sevoflurane and TIVA propofol. The study involved 302 patients with SAS I-III who underwent elective craniotomy surgery. The clinical outcomes examined in this study were the Aldrete score which consisted of a time of eye-opening extubation, presence of adverse events, intraoperative hemodynamic conditions, brain relaxation score (BRS), use of opioids, and diuresis. They showed a significant difference between the inhalation sevoflurane and TIVA propofol groups regarding the Aldrete score. Likewise, there was no significant difference between the two groups regarding complaints of postoperative chills, nausea and vomiting and the pres within three hours postoperatively. Hypotensive conditions were more common in the sevoflurane group. Intraoperative diuresis and opioid use were greater in the propofol TIVA group.

The prospective cohort study by Malhotra et al. in 258 adult patients aged 18–60 with ASA I-II status compared the costs of using several anesthetic techniques such as isoflurane, Sevoflurane, and TIVA inhalation anesthesia. The analysis found the highest use of costs in the TIVA group and the lowest in the isoflurane inhalation group. The price of propofol caused the high cost in the TIVA group is the most expensive compared to other inhalation agents such as isoflurane and Sevoflurane. Sevoflurane's MAC can be easily obtained utilizing large flows because it is a rather insoluble agent. In contrast to low-flow anesthesia, high flows enable an early equilibrium and a subsequent reduction in dialed concentration. For MAC to remain constant when flows are reduced, a high initial flow and high concentration are needed to “charge” the circuit and saturate the soda lime. Higher fluxes must also facilitate the outflow of the anesthetic gases during the reversal phase. The maintenance phase is, therefore, what determines the overall cost of anesthesia, regardless of the technique. As a direct result of the reduced flows, low fresh gas flow cuts the cost by roughly 50%. The cost of nitrous oxide is reduced, which helps to offset the expense of soda lime, which is utilized in the low-flow technique. The main cause of greater costs with TIVA is propofol's higher unit cost than inhalational drugs.

Petersen et al. studied three groups of anesthetics propofol-fentanyl (TIVA), isoflurane-fentanyl, and sevoflurane-fentanyl to assess their effects on ICP and cerebral hemodynamics before and during hyperventilation in 117 patients undergoing elective craniotomy surgery for subdural ICP and venous oxygen saturation. Jugular pressure (SJVO2) was significantly lower in the TIVA group compared to patients in the inhalation agent group (p < 0.05), whereas mean arterial pressure and CPP were found to be higher in patients receiving propofol-fentanyl (TIVA) compared to patients who received isoflurane and Sevoflurane (p < 0.05). They concluded that the favorable cerebral hemodynamics of the propofol
group resulted in reduced cerebral swelling after dural dilatation.\(^3\)

In a meta-analysis by Prabhakar et al., TIVA and inhalation-based anesthetic techniques were compared to assess the rapid onset of anesthesia. They included 15 randomized controlled trials (RCTs) with 1,833 patients undergoing craniotomy for supratentorial tumor surgery. Emergence was faster in patients receiving propofol compared with isoflurane (mean difference [MD]: 3.29 minutes, 95% confidence interval [CI]: -1.18, low-quality evidence), whereas the emergence of similar anesthetics in the propofol and sevoflurane groups (MD: 0.28 min slower with Sevoflurane, 95% CI: -0.56 to 1.12, four studies, low-quality evidence). The overall risk of PONV was less in the propofol group. They also found that the propofol group's brain relaxation scores were better than with isoflurane (reference range [RR]: 0.88, 95% CI: 0.67 to 1.17 low-quality evidence). However, no difference in brain relaxation scores was seen when the propofol group was compared with Sevoflurane. The authors note that the evidence is of low quality and comment that the intravenous technique and the sevoflurane inhalation technique are comparable in terms of initial presentation and side effects of anesthesia. However, the use of isoflurane significantly delayed emergence. While these two techniques are similar in elective brain tumor surgery, things can be further complicated in emergency surgery. The risk of brain bulging increases in the presence of peritumoral edema, a midline shift of more than 5 mm, increased ICP features, and impending herniation.\(^5\)

In anesthesia, volatile anesthetic gases contribute up to 20-25% of the total cost of anesthesia. The cost of using anesthetic gas varies by institution and location. The biggest challenge for hospital pharmacies is budgeting drug costs. Designing a budget for intravenous drugs is much easier than for anesthetic gases because there is a direct relationship between the number of medications received and administered. The cost of anesthetic gas drugs is calculated based on the delivery method. Anesthetic gas is purchased in liquid form and administered via a vaporizer, making it difficult to measure directly how much anesthetic gas has been used per case without the aid of a vapor analyzer. Various delivery concentrations and techniques can increase or decrease total anesthetic gas consumption and significantly change acquisition costs.\(^5,9,10\) Seven cost analysis methods are found in the literature for professional anesthesiologists in determining anesthetic gas costs, namely: (1) Weight measurement, (2) Minimum alveolar concentration comparison, (3) Four-compartment model, (4) Volume percent equation, (5) Volume measurement, (6) Dion’s Formula, and (7) Loke’s Formula. It has been determined that Dion’s formula is the more reliable method for professional anesthesiologists to determine anesthetic gas costs. Calculating the amount of gas used using the Dion formula can make it easier to estimate costs. To determine the total anesthetic gas cost, it is necessary to resolve the percent concentration, amount of gaseous concentration, density, and molecular weight of the gas. Eger stated that although the unit cost of Sevoflurane is more expensive than desflurane, it takes approximately three times the amount of desflurane to create the depth of anesthesia as Sevoflurane at the same flow rate. This is due to the difference in potentiation, where it takes approximately 2% Sevoflurane to reach one MAC and 6% desflurane. The minimum alveolar concentration is defined as the minimum alveolar concentration of inhaled anesthetic gas that results in immobilization of 50% of the population undergoing surgical incisions.\(^14,16\)

Cost analysis of general anesthesia TIVA propofol compared with inhalation anesthetic sevoflurane was studied in patients undergoing major oncology surgery at Sanglah General Hospital 2013. (The results of this study found significant differences in the intraoperative costs of the two groups. The cost of intraoperative anesthesia in the total intravenous anesthesia group with TIVA averaged Rp. 957,870,- and a standard deviation of Rp. 73,910,-. In the control group, the cost of intraoperative anesthesia was an average of 1,318,130 with a standard deviation of Rp. 155,238,-. Based on statistics using the t test, it was found that the two groups had a significant difference (p = 0.001). Based on the average intraoperative anesthetic cost, it was also found that the anesthetic cost per patient was Rp. 957,870,- for the TIVA propofol group and Rp. 1,318,130,- for the sevoflurane group. Meanwhile, based on the minutes of anesthesia, the average intraoperative anesthetic cost is Rp. 5,999,- per minute of anesthesia in the TIVA propofol group and Rp. 8,170,- per minute of anesthesia in the sevoflurane group.\(^13,18\) Analysis of cost minimization of general anesthetic propofol TIVA and inhalational anesthesia with isoflurane in oncology surgery. In this study, the ratio of drug use per unit time for group A was 8.54 mg (±2.04 mg) per minute, and for group B, 0.42 ml (±0.09 ml) per minute. Cost of general anesthetic drugs in group A Rp. 800.85 (±Rp. 127.99) per minute. In group B Rp. 1,266.32 (±Rp. 248.26) per minute (p < 0.001). From the results of this study, it can be concluded that the analysis of minimizing the cost of general anesthetic drugs using TIVA propofol is significantly different, resulting in a lower cost than isoflurane inhalation anesthesia. The amount of drug used includes the remaining drug that is disposed of.\(^7,13,19\)

A meta-analysis by Kumar et al. stated that propofol had a lower incidence of postoperative nausea and vomiting than inhalational drugs (13.8% vs. 29.2%, respectively; p = 0.001). Post-discharge nausea and vomiting, however (23.9% vs. 20.8%, respectively; p = 0.26), showed no difference. Propofol made hospital stays shorter. However, the average reduction was only 14 minutes. With a mean (95% CI) difference of £6.72 (£5.13-£8.31; £8.16 (£6.23-£10.09); $11.29 ($8.62-$13.96)) each patient-anesthetic episode, the use of propofol was likewise more expensive (p=0.001). They concluded that maintaining anesthesia with propofol appeared to have no effect on the frequency of unexpected hospital admission and cost more money. However, it was associated with a lower incidence of early postoperative nausea and vomiting in ambulatory surgery patients than Sevoflurane or desflurane. The fact that PONV events were less frequent when TIVA was used; is consistent with the strong evidence that propofol is the best anesthetic for preventing PONV. PONV is particularly significant because it is the postoperative anesthetic complication
patients worry about the most. Also, the possible link to unplanned admissions, delayed discharge, and associated economic costs makes it relevant. Hospital admission rates were reduced with TIVA, which may support this.20

Although propofol is more expensive than Sevoflurane, a medication’s pharmacoeconomic benefits go far beyond lowering drug acquisition costs. The need for potentially costly antiemetics to combat the proemetic side effects of many anesthetics and the ability to deliver a predictable and quick awakening that facilitates neurological testing and reduces the need for unanticipated (and expensive) radiological evaluation all contribute to perioperative drug costs.5,7,18 This finding is also supported by a multicenter study by Smith et al. They found that TIVA propofol was more expensive than Sevoflurane but had minimal therapeutic advantages regarding recovery time or quality. Sevoflurane use for induction and maintenance of anesthesia resulted in a further modest decrease in costs (especially if fresh gas flow was reduced early), primarily through less drug waste. Still, it was linked to a significant rise in postoperative nausea and vomiting, a delay in ambulation (but not discharge), and a decline in patient satisfaction.7 Together with the superiority of propofol, we discovered several drawbacks. First, there is a risk of either delayed emergence due to propofol buildup or intraoperative consciousness due to insufficient propofol plasma concentrations for anesthesiologists who are new to propofol anesthetics. Another side effect of TIVA is the potential for a significant drop in cerebral blood volume. This becomes important because brain shift may occur during stereotactic-guided craniotomies. With intraoperative imaging at our disposal, this issue might be solved. According to previous studies, the average cerebral blood volume loss with standard balanced propofol anesthesia is only 25%.11,21-23

CONCLUSION

The objectives for the anesthetic administration during the craniotomy procedures included preserving hemodynamic stability, safeguarding the cerebral blood vessel’s autoregulation function, and ensuring favorable operating conditions and a speedy recovery. The common neuroaesthetics used for neurosurgery was inhalation of Sevoflurane and the newest, by continuous infusion of propofol called TIVA. Based on the cost-effective analysis, propofol was more expensive than Sevoflurane. But regarding pharmacoeconomics, using TIVA propofol has significantly lower PONV events, unplanned hospital admission, and patient length of stay, contributing to better pharmacoeconomic benefits.

CONFLICT OF INTEREST

The author declares no conflict of interest in writing this literature review.

ETHICAL CONSIDERATIONS

None.

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