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Total intravenous anesthesia vs inhalational anesthesia in patients undergoing surgery under general anesthesia. Cost-minimization study

Anestesia total endovenosa vs. anestesia basada en halogenados en pacientes llevados a cirugía bajo anestesia general. Estudio de minimización de costos

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What do we know about this topic?

· General anesthesia can be administered using two different techniques: balanced anesthesia with halogenated drugs, and total intravenous anesthesia.
· Both techniques provide adequate perioperative conditions and in non-cardiac and non-oncologic surgical models, clinically significant outcomes are similar.
· These techniques require resources, supplies and medical technologies, which points to a differential cost between the two types of techniques. This might result in decisions to use either of the techniques on the basis of the cost alone, without taking into account potential events associated with their use.

What is new about this study?

Although the cost of one technique may be higher, in particular when TCI technologies are used, compared to techniques based on anesthetic gases, this cost is offset by a shorter stay in the postanesthesia care unit (PACU) because of a lower risk of postoperative nausea and vomiting (PONV).

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Abstract

Introduction: The methods most frequently used at the present time in Colombia for the administration of general anesthesia are based on halogenated and intravenous drugs. However, in view of the lack of differential clinical outcomes, the existence of cost variations between the two is not clear.

Objective: To determine the expected cost of the use of both techniques in patients taken to surgery, within the framework of the Colombian national health system.

Methods: A cost minimization study was carried out using the decision tree as the analytical model. A time frame of 6 postoperative hours was used as the assumption. Only direct healthcare-related costs were included using a case study approach. An econometric model was used based on the frequency with which each technology is applied and the type of drug used, and a deterministic and probabilistic sensitivity analysis was performed.

Results: For the case study, total intravenous anesthesia (TIVA) is more costly than the inhalational technique, with an incremental cost of $102,718 per patient. The deterministic analysis shows that both the incidence of postoperative nausea and vomiting (PONV) as well as the use of target controlled infusion (TCI) techniques are the main cost determinants. The probabilistic analysis shows that the cost difference can even be nil in more than 50% of the simulated settings, when the difference in the risk of PONV is higher.

Conclusions: Although the total intravenous technique can be more costly than the inhalational technique, this difference is offset by a lower cost of the postanesthesia care unit, given the lower risk of postoperative nausea and vomiting.

Keywords: Total endovenous anesthesia; Halogenated-based anesthesia; Cost-minimization; Postoperative nausea; Postoperative vomiting; Anesthesiology.

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Resumen

Introducción: Actualmente, los métodos más usados en Colombia para la administración de anestesia general son las técnicas basadas en halogenados y en medicamentos intravenosos. No obstante, y ante la falta de desenlaces clínicos diferenciales, no es claro si existe una variación en los costos.

Objetivo: Determinar el costo esperado del uso de ambas técnicas en pacientes llevados a cirugía bajo la perspectiva del sistema nacional de salud colombiano.

Métodos: Se realizó un estudio de minimización de costos. Se empleó el árbol de decisión como modelo analítico. Se asumió un horizonte temporal de 6 horas postoperatorio. Se incluyeron solo los costos sanitarios directos mediante un caso tipo. Se empleó un modelo econométrico basado en la frecuencia de uso de cada tecnología y medicamento empleado y se realizó análisis de sensibilidad determinístico y probabilístico.

Resultados: Para el caso tipo, la técnica total endovenosa es más costosa que la técnica basada en halogenados, con un costo incremental de $102.718 por paciente. El análisis determinístico muestra que tanto la incidencia de náuseas y vómito postoperatorio como el uso de tecnologías TCI (*target controlled infution*) son los principales determinantes de estos costos. El análisis probabilístico muestra que la diferencia de costos puede ser incluso de cero pesos en más del 50 % de los escenarios simulados cuando se tiene una mayor diferencia del riesgo de náuseas y vómito postoperatorio.

Conclusiones: Aunque la técnica total endovenosa puede ser más costosa que la basada en halogenados, esto se compensa con un costo inferior en la unidad de recuperación postanestésica debido a un menor riesgo de náuseas y vómito postoperatorio.

Palabras clave: Anestesia total endovenosa; Halogenados; Costo-minimización; Náusea postoperatoria; Vómito postoperatorio; Anestesiología.

INTRODUCTION

Procedures that have had a significant impact in the setting of the perioperative care of patients taken to surgery have emerged in recent years, improving the quality of care and important clinical outcomes and, consequently, the cost of care (1,2).

It is estimated that close to 402 million procedures are performed under anesthesia every year. In 2015 in Colombia alone, 27,385 procedures were carried out under general anesthesia for every 100,000 inhabitants (3), with the techniques most widely used being inhalational and total intravenous anesthesia. Balanced anesthesia with halogenated drugs consists of the administration of anesthetic gases through a respiratory circuit plus the intravenous administration of an opioid drug during the entire procedure. In contrast, total intravenous anesthesia (TIVA) consists of the intravenous administration of only hypnotics (propofol) and opioids.

In Colombia, according to the latest national survey on anesthetic techniques conducted in 2017, the generalized use of inhalational anesthesia was placed at 58.1% as compared with TIVA which accounted for 30.9% of all general anesthesias administered in the country (4).

In general, multiple studies have documented the results of TIVA over those of inhalational techniques, with no consistent clinical outcomes found between the two techniques in the general, non-oncologic surgical population (5-14). In 2018, Schraang et al. (5) carried out the largest systematic review and meta-analysis ever conducted up to that date, which included more than 200 clinical trials comparing the two anesthetic techniques, and found no clinically or statistically significant differences for the most important outcomes in surgery, except for the lower impact on the risk of postoperative nausea and vomiting (PONV).

However, no strong literature is available on the topic of cost-effectiveness of these technologies in the different surgical settings; the few cost reduction studies were conducted more than 15 years ago and do not assess the impact of the implementation of these techniques on the health systems of the countries where they were conducted (6-14).

In Colombia, this absence of information and pressures for decision-making regarding the introduction of new anesthesia technologies, call for economic studies designed to identify which of the two anesthetic techniques can have the lowest impact on the cost of surgical patient care.

The objective of this study was to determine expected costs based on a case study on the use of an inhalational anesthetic technique versus intravenous anesthetic drugs in adult patients taken to non-cardiac and non-oncologic surgery under general anesthesia.

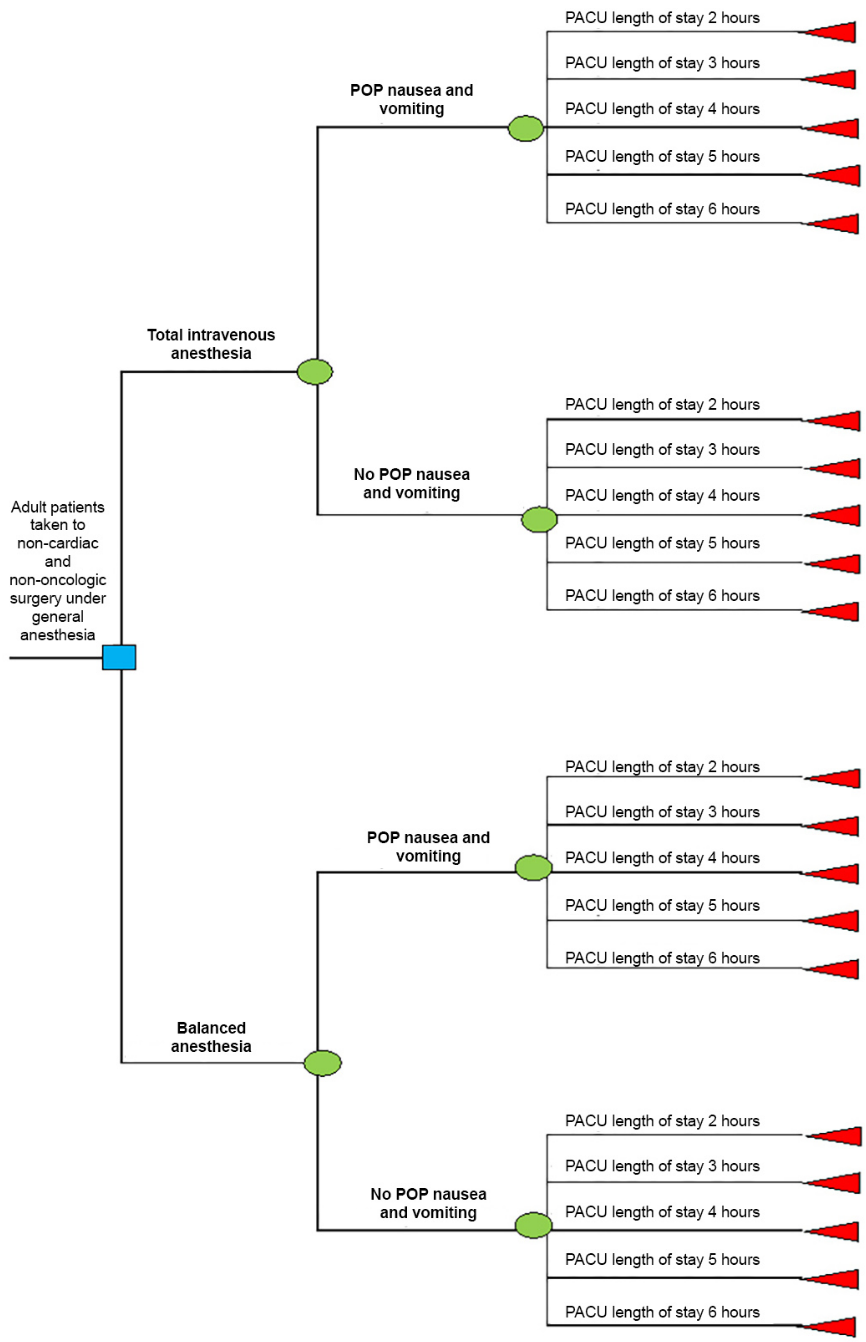
MATERIALS AND METHODS

Analytical model

A cost minimization analysis from the perspective of the Colombian health system was performed. The population included adult patients taken to non-cardiac and non-oncologic surgery under general anesthesia. The time horizon adopted was the length of stay in the post-anesthesia care unit (PACU) or 6 hours of the immediate postoperative period. This time frame was selected given that this study focused on anesthesia-related costs and not on secondary postoperative outcomes. The options considered were inhalational balanced anesthesia with opioids like remifentanil and total intravenous anesthesia with propofol and remifentanil. In view of this short time horizon, no discount rate was applied.

Given the lack of strong evidence in favor of one technique over the other in most surgical models, and given that primary clinical outcomes are not different between the two techniques, the study was designed to assess only the costs related to the use of both techniques. Consequently, for cost estimation, a decision tree was built of the potential pathways for a patient undergoing an anesthetic procedure, in accordance with differential events between both techniques: presence or absence of postoperative nausea and vomiting, and the length of stay in the PACU until discharge. This analysis option led to the creation of a logical structure to approach the problem and to incorporate the evidence of the options under assessment, in order to compare between them (Figure 1).

FIGURE 1. Decision tree.



PACU: postanesthesia care unit; POP: postoperative. **Source:** Author.

Transition probabilities

Transition probabilities were derived from a systematic literature review and meta-analysis carried out by the author of this study, analyzing clinical trials found in the most important databases: Medline, Embase and Cochrane Library. The study flowchart, bias analysis and meta-analysis for the risk of PONV are found in the supplemental content.

Based on this review and the meta-analysis that followed, it was found that the risk of PONV in TIVA and inhalational techniques was 0.61, 95% CI [0.52-0.72]. This means that the intravenous technique reduces the risk of this event by 39% as compared with the inhalational technique. The result was consistent regardless of the type of halogenated gases used, the type of surgical intervention or the setting (outpatient or inpatient) (supplemental content).

To determine length of stay in the PACU according to the presence or absence of PONV, the evidence of the clinical trials included in the aforementioned systematic review was analyzed. However, determining length of stay when the groups were divided according to the presence or absence of the PONV event was not possible. This led to a new literature review which found only one large cohort study that evaluated clinical outcomes according to the presence of PONV (15). This was a prospective cohort study that used matching techniques and different surgical models to evaluate not only the time to anesthetic recovery but also the economic costs associated with the presence or absence of PONV. Given that the study was methodologically well conducted and used prospective measurements and comparison with a low risk of bias to assess the economic impact of this event in particular, the PACU length of stay data from that study were used for this one.

Table 1 shows the probability of occurrence of the events modeled in the decision tree, based on the methodological recommendations contained in the economic evaluation manual of the Health Economic Evaluation Institute (IETS) (16) and the recommendations of Gidwai et al. (17) for converting event risks into probability of occurrence of an event based on the meta-analysis carried out by the author for the presence or absence of PONV. It also shows length of stay in the PACU, which was categorized by hours - between 2 and 6 hours of the time horizon. This choice was based on two factors: ease to determine probabilities in terms of 60-minute intervals, and cost of care for patients in the PACU estimated in terms of hours of stay and not in minutes.

Costs

Direct medical cost calculations for each intervention started with the identification, measurement and quantification of consumed expenditure-generating resources. Two costing strategies were used: construction of a case study, and microcosting. The case study was built on the basis of the most widely reported clinical characteristics and surgical model in the clinical studies assessed as part of this study: 40-year-old patient weighing 70 kg, 168 cm tall, taken to laparoscopic cholecystectomy and 2 hours of surgical time. The case was validated by consensus of the three anesthetists with expertise in both techniques. The case assumption was that anesthetic consumption is directly proportional to surgical time in both interventions and that fixed surgical costs are similar in both techniques.

Following their identification, costs were divided into two large groups. The first included fixed costs related to operating room fees, medical fees, surgical material and length of stay in the PACU. The recommendation of the IETS methodological manual was applied for cost quantification and measurement (16), leading to the use of the 2001 rates schedule of the Social Security Institute (ISS), applying a 30% adjustment for 2012; the average consumer price index (CPI) reported by the Colombian National Statistics Department (DANE) for the past 5 years was used to make the 2020 adjustment. A 25% and 45% of the ISS value were used as the minimum and maximum values, respectively.

The other group consisted of variable costs, represented by medications, supplies and technologies used. For identification and quantification, the consensus of three anesthetists with expertise in the management of these techniques, and anesthetic simulators were used: the Gasman® software for the halogenated group (18) and the Rugloop® for TIVA, with the clinical parameters of the case study and the recommendations of the World Federation of Societies of Anesthesiology 2019 (WFSA) (19) for the administration, monitoring and surveillance of the TIVA technique. Medication cost estimates were taken from the Medication Price Information System (SISMED) for the

Table 1. Parameters (probabilities) included in the decision tree.

Parameter	Expected value	Sensitivity analysis[a]	
		Minimum	Maximum
Inhalational anesthesia			
PONV	0.3315	0.3035	0.3595
No PONV	0.6685	0.6405	0.6965
Intravenous anesthesia			
PONV	0.1948	0.1745	0.2151
No PONV	0.8052	0.7849	0.8255
PACU Length of stay and PONV			
2 hours	0.0577	0.037	0.078
3 hours	0.1732	0.1412	0.2102
4 hours	0.3016	0.2622	0.3403
5 hours	0.2832	0.2434	0.3217
6 hours	0.1842	0.1535	0.2211
PACU Length of stay and no PONV			
2 hours	0.1663	0.1346	0.2018
3 hours	0.4016	0.3641	0.4436
4 hours	0.3372	0.303	0.3821
5 hours	0.0878	0.0616	0.1123
6 hours	0.0072	0.002	0.0233

a. Minimum and maximum probability data come from the different 95% confidence intervals for the different estimators. PONV: postoperative nausea and vomiting. **Source:** Author.

2020 period. Weightings of the prices for each medication were derived in accordance with the market share, and minimum and maximum prices were obtained for the doses used in the case study. The microcosting strategy was used for measurement and quantification of supplies and technologies for anesthesia administration, using market rates, in which two hospitals in Medellín were included: IPS Universitaria Universidad de Antioquia and Hospital Universitario San Vicente Fundacion. They were included because they are referral centers in the region and have experience with the techniques selected for the analysis.

Econometric model

Variable cost weightings for each technique (medications, supplies and technologies) were determined in accordance with the frequency of use of these resources. The frequency was queried and validated by the team of three expert anesthetists. The formula recommended by IETS was used for the final calculation (16):

$$Cost = \sum_{l=i}^{n} C_l Q_l f_l$$

Where, n is the number of resources used, Cl is the cost of the i-th procedure, Ql is the i-th quantity of consumed resources; and fi is the frequency of use of the i-th expenditure-generating resource.

Uncertainty analysis

Both deterministic as well as probabilistic sensitivity analyses were carried out. In the deterministic analysis, costs were modified according to the confidence intervals for PONV incidences and PACU length of stay probabilities, as well as the surgical intervention setting: medium and high complexity. Moreover, the setting where the intravenous technique was not carried out using TCI systems but conventional volumetric infusion equipment was also evaluated. The results are shown in a tornado diagram (Figure 2).

A β distribution was assumed for PONV probabilities, with n and N parameters for the construction of the probabilistic analysis. For costs, a ɣ distribution was generated taking the α and β values of the costs of each anesthetic intervention. The impact of PONV incidence on the cost of each intervention was analyzed by means of 1,000 Monte Carlo simulations.

Moreover, the incremental cost effectiveness ratio of the TIVA technique to reduce at least one PONV episode was determined by means of the difference ratios between the incidence of PONV and the net cost of both anesthetic techniques, without including the costs associated with the management of PONV and PACU length of stay.

The Microsoft® Excel 2020 software was used for the construction of the decision tree and costing of each intervention. All costs are in Colombian pesos. From the ethical point of view, this study did not use patient data directly and was classified as a low risk study in accordance with the current national regulations.

RESULTS

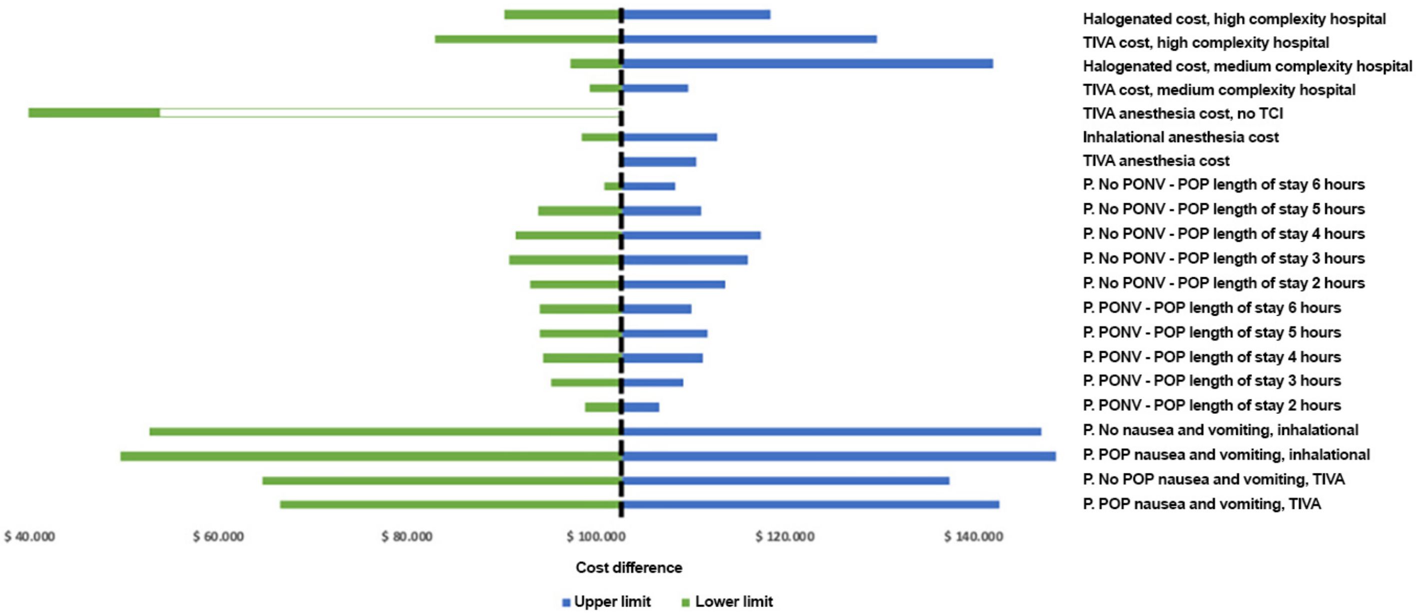
For the proposed case study, the cost of intravenous anesthesia is $1,811,218, whereas the cost of the inhalational technique is $1,708,500, with an incremental cost per patient receiving TIVA of $102,718. Table 2

TABLE 2. Costs of each intervention.

PACU length of stay	2 hours PACU ($)	3 hours PACU ($)	4 hours PACU ($)	5 hours PACU ($)	6 hours PACU ($)
Medium complexity hospitals					
Inhalational					
Minimum	1,405,731	1,468,542	1,531,353	1,594,164	1,656,974
Base Case	1,547,254	1,615,806	1,684,357	1,752,909	1,821,461
Maximum	1,619,992	1,692,075	1,764,159	1,836,242	1,908,325
TIVA					
Minimum	1,508,173	1,570,983	1,633,794	1,696,605	1,759,416
Base Case	1,654,879	1,723,430	1,791,982	1,860,534	1,929,085
Maximum	1,730,590	1,802,673	1,874,756	1,946,839	2,018,923
High complexity hospitals					
Inhalational					
Minimum	1,431,064	1,506,542	1,582,019	1,657,496	1,732,974
Base Case	1,574,903	1,657,278	1,739,654	1,822,030	1,904,406
Maximum	1,626,780	1,702,258	1,777,735	1,853,212	1,928,690
TIVA					
Minimum	1,533,506	1,608,983	1,684,460	1,759,938	1,835,415
Base Case	1,682,527	1,764,903	1,847,279	1,929,655	2,012,031
Maximum	1,759,663	1,846,282	1,932,902	2,019,522	2,106,141

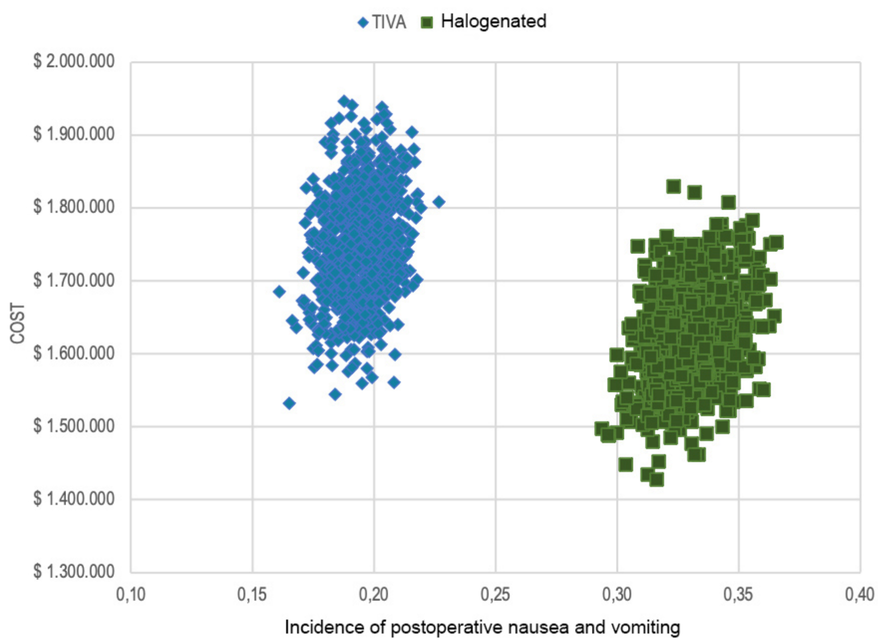
PACU: postanesthesia care unit; TIVA: total intravenous anesthesia. **SOURCE:** Author.

TABLE 2. Tornado diagram: deterministic analysis.



P: probability; PONV: postoperative nausea and vomiting; TCI: target controlled infution; TIVA: total intravenous anesthesia. **SOURCE:** Author.

FIGURE 3. Scatter diagram: cost vs. PONV incidence.



SOURCE: Author.

shows costs according to each intervention, length of stay in the PACU, and the care level where the procedure is performed.

For the deterministic analysis, it was found that the main variable than can impact cost differences between the two techniques is the risk of PONV; therefore, the increased incidence of PONV has a direct impact on the increased cost of care in both interventions. Additionally, it was found that more than 50% of the cost difference in favor of inhalational techniques is explained by the use of TCI technologies in TIVA interventions (Figure 2).

However, the probabilistic analyses found that, in the majority of the simulations, cost differences can be nil when the PONV risk difference between both techniques is large, as happens with the base case (Figure 3).

The incremental cost-effectiveness ratio between TIVA and balanced anesthesia for PONV was $7,687; this means that $7,687 are needed to avoid at least one additional PONV episode when TIVA is used, as compared with inhalational anesthesia.

DISCUSSION

Perioperative management of patients taken to surgery requires the administration of an anesthetic technique that allows to perform the surgical procedure. General anesthesia techniques are traditionally the most widely used to achieve this objective and, among them, inhalational and intravenous techniques are the most common. A recurrent concern among healthcare providers is how to reduce costs and improve efficiency in activities that have a high impact on the expenses of the healthcare organization and, therefore, on the health system itself, as is the case of surgical procedures. From this perspective, one of the most frequent questions in anesthetic practice is, precisely, which of the two anesthetic techniques can have a lower cost in perioperative care, given the belief that an intravenous drug-based technique can result in a higher cost because it requires a greater use of devices and technologies as compared to techniques based on anesthetic gases (4). In fact, this argument has been used to create a barrier to the implementation of a highly versatile anesthesia technique, particularly in elective outpatient procedures.

The aim of this study was to determine and compare the expected cost of administering these two anesthetic techniques, based on the fact that both are highly effective and are associated with a similar risk of anesthesia-related complications. This led to the performance of a cost minimization study.

The results of this study show that the mean incremental cost difference between the two anesthetic techniques is $102,718 for every patient taken to non-cardiac, non-oncologic surgery.

When uncertainty analyses are used to contextualize this result, cost differences for both techniques vary according to the risk of PONV occurrence, where the higher the risk of PONV the greater the cost difference between both techniques, while the lower the risk or probability of PONV in both groups, the more significant the reduction of the cost difference between the two.

However, the stochastic analysis found that, despite high consistency in the incidence of PONV, the variation of the costs associated with each anesthetic technique is very similar between the two. This even results in the cost difference of the interventions analyzed being nil in more than 50% of the simulations, and when the difference in the risk of PONV increases.

It is worth noting that though it is clear that the intravenous technique is potentially cost-effective for the prevention of PONV, with an incremental cost-effectiveness ratio of $7,787, the final cost of the intervention is determined by the time spent in the PACU as a result of this event. This finally explains why, although it is a more costly technique, the additional cost incurred with TIVA administration is offset, in the long run, by the cost savings from shorter length of stay in the PACU, as observed in the analytical model used in this study. Additionally, it was found that no major differences exist between the cost of the interventions when they are carried out in medium and high complexity centers.

Another relevant finding in this analysis was the ability of the target controlled infusion (TCI) systems to substantially affect the cost difference between the two techniques. If the cost of the TCI systems were to be eliminated in TIVA, the cost difference between both techniques would be almost 60% lower. In this regard, it is expected that as the cost of this type of system drops, not only would the use of this technique grow but the cost could be substantially lower than those of generic, inhalational anesthetic techniques.

These results are in stark contrast with the cost reduction studies nested in four clinical trials. To date, there are only four cost minimization studies published on this topic, all of them carried out more than a decade ago (10-13). The four studies not only specify the econometric models applied, but they also report high cost differences between the study techniques in favor of halogenated gases. This can be explained because the introduction of the technologies required for intravenous anesthesia administration and neuromonitoring became massively available only 20 years ago. This resulted in the substantially higher cost of intravenous techniques as compared to inhalational techniques. However, complete economic studies have not be conducted in other countries to allow for direct or indirect cost comparisons between anesthetic techniques or that can serve as a comparison reference with the results reported in these studies.

The probabilities on which the decision model was built are based on controlled clinical studies where the anesthetic techniques, the baseline risks and the prevention of PONV were completely controlled. Therefore, it is probable that this event could be under or overestimated according to individual patient characteristics and the surgical intervention.

There are no national studies to help determine with certainty the average time a patient remains in the PACU and how this time is impacted by the different events affecting recovery. This variable can eventually influence the final cost of one technique over the other.

The model on which the case study was built is based on the assumption that anesthetic administration occurs under the highest standards and in accordance with the relevant recommendations. In that regard, this model does not assess the variability caused by differential administration in terms of dosing, anesthetic drugs and technique used by the different anesthetists. Similarly, the anesthetic quantification for the case was derived from anesthetic simulators because they provided a better approximation of the anesthetic volumes used; however, they may lose accuracy when clinical and technical variables which are not controlled by those simulators are applied.

Costing of anesthetic procedures in Colombia poses a major challenge for several reasons: specific anesthetic rate schedules created by scientific societies (like the Schedule of the Anesthesiology Society of Antioquia) are not a regular part of the service agreements between Benefit Plan Management Organizations (EAPBs) and the various healthcare providers in the country; the vast majority of healthcare providers are unaware of the costs derived from anesthesia administration, other than staff fees. For this reason, the use of microcosting techniques, despite the fact that they can provide a good approximation to the actual cost of an anesthetic technique, can be very limited precisely due to the variability among different healthcare providers. In the case of this study, it may well be that microcosting techniques, based only on two healthcare institutions and market rates, could under or overestimate the total cost of anesthesia.

To conclude, from the perspective of the Colombian health system and under the premise that there are no significant perioperative clinical differences in patients taken to non-cardiac and non-oncologic surgery under general anesthesia, though there may be a slight difference in the average cost of total intravenous anesthesia when compared with inhalational anesthesia in favor of the latter, this difference can be of zero pesos when the difference in the risk of PONV is high and when the cost of the TCI technology is low.

ETHICAL RESPONSIBILITIES

Ethics Committee endorsement

This study was approved by the Ethics Committee of Hospital Universitario San Vicente Fundacion in a meeting held on January 15, 2021, as set forth in minutes No. 02-2021; and by the Ethics Committee of IPS Universitaria in a meeting held on December 15, 2020, as set forth in minutes No. 155.

Human and animal protection

The author declares that no experiments in humans or animals were conducted for this research. The author declares that the procedures applied complied with the ethical standards of the responsible human experimentation committee, the World Medical Association and the Declaration of Helsinki.

Data confidentiality

The author declares that they have followed their institutional protocols regarding patient data disclosure.

Right to privacy and informed consent

The author declares that no patient data appear in this study. This document is kept by the corresponding author.

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Author's contribution

FC: Study planning, data collection, data interpretation and initial drafting of the manuscript.

Assistance for the study

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Conflict of interest

None declared.

Submissions

None declared.

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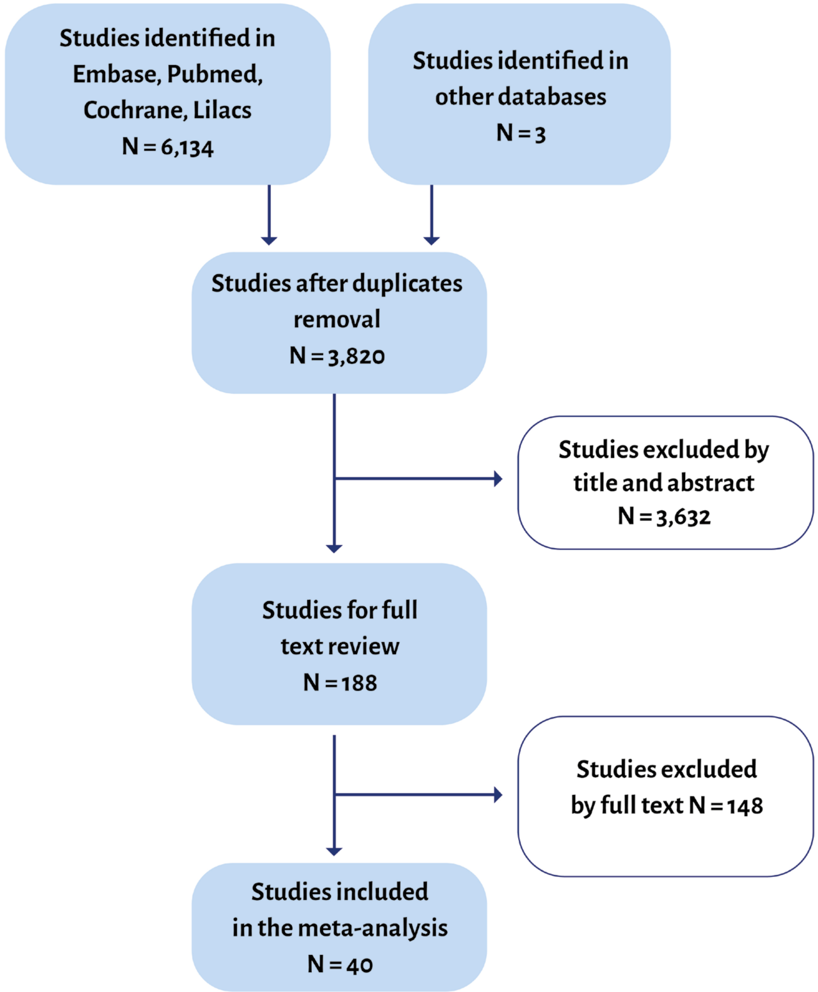
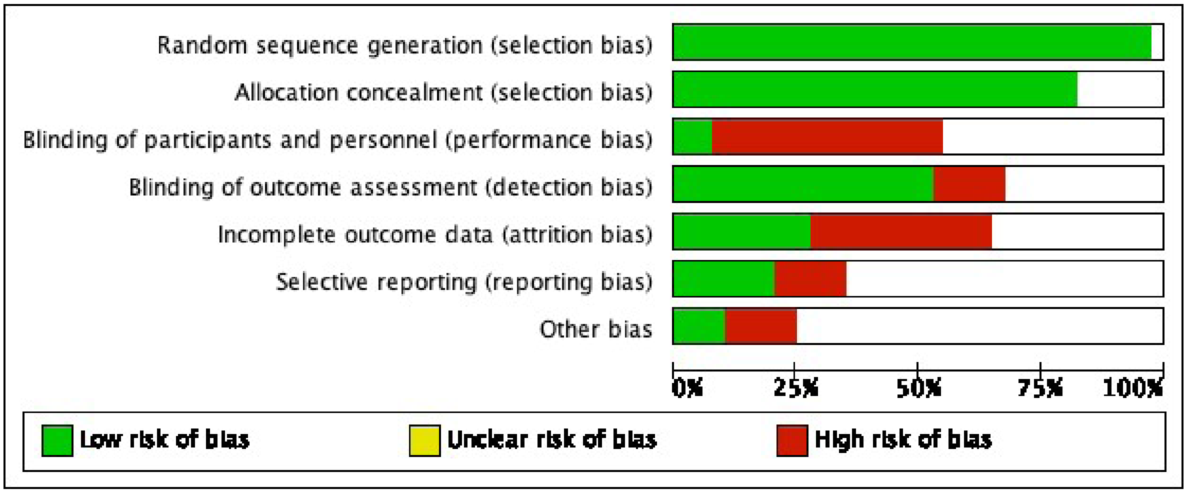
SUPPLEMENTAL MATERIAL

Supplemental material 1. PRISMA flow diagram of studies included in the meta-analysis for events considered in the decision tree.



Source: Author.

Supplemental material 2. Risk summary of the studies included in the review for modeled events.



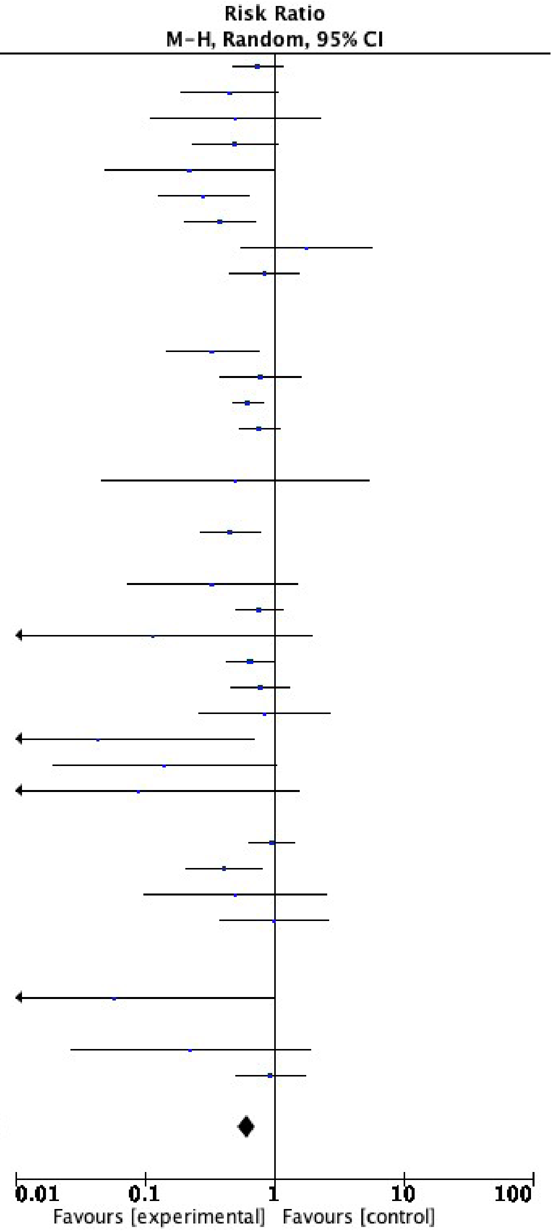
Source: Author.

SUPPLEMENTAL MATERIAL 3. Forest Plot for postoperative nausea and vomiting.

Study or Subgroup	Propofol Events	Propofol Total	Halogenados Events	Halogenados Total	Weight	Risk Ratio M-H, Random, 95% CI
Akkurt 2009	15	30	20	30	6.5%	0.75 [0.48, 1.16]
Braun 2005	5	20	11	20	2.8%	0.45 [0.19, 1.07]
Caverni 2005	2	40	8	80	1.1%	0.50 [0.11, 2.25]
Celik 2011	8	50	16	50	3.4%	0.50 [0.24, 1.06]
Cheng 2006	2	30	6	20	1.1%	0.22 [0.05, 0.99]
Cheng 2013	6	42	21	42	3.1%	0.29 [0.13, 0.64]
Citerio 2012	12	138	31	136	4.4%	0.38 [0.20, 0.71]
De Carli 2020	7	60	4	61	1.6%	1.78 [0.55, 5.76]
De Oliveira 2017	11	30	13	30	4.4%	0.85 [0.45, 1.58]
Demeere 2006	0	0	0	0		Not estimable
Epple 2001	0	0	0	0		Not estimable
Hernandez 2006	6	45	18	45	2.9%	0.33 [0.15, 0.76]
Hocker 2006	10	51	13	52	3.5%	0.78 [0.38, 1.62]
Hofer 2003	50	155	75	146	9.2%	0.63 [0.48, 0.83]
Horng 2008	17	30	44	60	7.9%	0.77 [0.55, 1.09]
Jelish 2003	0	0	0	0		Not estimable
Jiang 2016	1	50	2	50	0.4%	0.50 [0.05, 5.34]
Jones 2015	0	0	0	0		Not estimable
Kawano 2016	12	42	26	42	5.3%	0.46 [0.27, 0.79]
Kim 2015	0	0	0	0		Not estimable
Kumar 2016	2	30	6	30	1.0%	0.33 [0.07, 1.52]
Lauta 2010	30	153	38	149	6.7%	0.77 [0.50, 1.17]
Lee 2014	0	25	8	51	0.3%	0.12 [0.01, 1.96]
Lee 2015	17	38	26	38	6.9%	0.65 [0.43, 0.99]
Lindqvist 2014	13	30	16	29	5.4%	0.79 [0.46, 1.33]
Ortiz 2014	3	18	11	56	1.7%	0.85 [0.27, 2.71]
Ozbakis 2009	0	21	11	21	0.3%	0.04 [0.00, 0.69]
Pieters 2010	1	19	7	19	0.6%	0.14 [0.02, 1.05]
Prasana 2010	0	30	5	30	0.3%	0.09 [0.01, 1.57]
Rocha 2017	0	0	0	0		Not estimable
Shen 2014	22	60	46	120	7.0%	0.96 [0.64, 1.43]
Shin 2010	9	50	21	48	3.9%	0.41 [0.21, 0.81]
Stevanovic 2008	2	30	4	30	0.9%	0.50 [0.10, 2.53]
Tan 2010	7	40	7	40	2.3%	1.00 [0.39, 2.59]
Tang 2001	0	0	0	0		Not estimable
White 2007	0	0	0	0		Not estimable
Yoo 2012	0	31	8	31	0.3%	0.06 [0.00, 0.98]
Yoo 2014	0	0	0	0		Not estimable
Zaballo 2017	1	32	4	29	0.5%	0.23 [0.03, 1.91]
Zhang 2013	12	40	16	50	4.4%	0.94 [0.50, 1.75]
Total (95% CI)		1460		1635	100.0%	0.61 [0.52, 0.72]
Total events	283		542			

Heterogeneity: Tau² = 0.05; Chi² = 44.16, df = 30 (P = 0.05); I² = 32%

Test for overall effect: Z = 5.94 (P < 0.00001)



SOURCE: Author.

SUPPLEMENTAL MATERIAL 4. Table of subgroup analyses of included studies.

Outcome/subgroup	No. of studies	No. of patients	Effect mean (statistical model)	Effect estimation (95% CI)	Decision in favor
PONV	40	3,095	RR (M-H, RE)	0.61 [0.52, 0.72]	P
Sevoflurane	30	2,320	RR (M-H, RE)	0.55 [0.49, 0.61]	P
Desflurane	7	542	RR (M-H, RE)	0.53 [0.44, 0.64]	P
Isoflurane	3	233	RR (M-H, RE)	0.81 [0.72, 0.92]	P
Women	22	1,702	RR (M-H, RE)	0.56 [0.49, 0.65]	P
Mixed	18	1,393	RR (M-H, RE)	0.62 [0.53, 0.73]	P
Laparoscopic	25	1,935	RR (M-H, RE)	0.62 [0.53, 0.72]	P
Other types of surgeries	15	1,160	RR (M-H, RE)	0.60 [0.51, 0.71]	P
Outpatients	27	2,089	RR (M-H, RE)	0.82 [0.71, 0.94]	P
Inpatients	13	1,006	RR (M-H, RE)	0.72 [0.61, 0.96]	P
TCI	11	852	RR (M-H, RE)	0.65 [0.58, 0.72]	P
No TCI	29	2,243	RR (M-H, RE)	0.57 [0.52, 0.65]	P
EEG Monitoring	9	697	RR (M-H, RE)	0.72 [0.60, 0.81]	P
No EEG monitoring	31	2,398	RR (M-H, RE)	0.68 [0.56, 0.79]	P
Nausea	35	2,708	RR (M-H, FE)	0.64 [0.55, 0.75]	P
Vomiting	31	2,398	RR (M-H, FE)	0.64 [0.54, 0.75]	P
PACU length of stay (minutes)	21	2,653	MD (IV, RE)	-2.91 [-5.47, -0.35]	P
Sevoflurane	12	1,009	MD (IV, RE)	-4.99 [-8.81, -1.17]	P
TCI	8	920	MD (IV, RE)	-2.51 [-6.70, 1.68]	NS
No TCI	12	1,649	MD (IV, RE)	-2.64 [-7.30, 2.02]	NS
Outpatient	9	1,381	MD (IV, RE)	-4.75 [-11.43, 1.94]	NS
Inpatient	12	1,272	MD (IV, RE)	0.03 [-1.39, 1.44]	NS

CI: confidence interval; EEG: electroencephalogram; IV: inverse-variance; MD: mean differences; M-H: Mantel-Hanzel; NS: no significance; P: propofol; PACU: postanesthesia care unit; PONV: postoperative nausea and vomiting; RE: random effect; RR: relative risk; TCI: target controlled infution. **SOURCE:** Author.

SUPPLEMENTAL MATERIAL 5. Study included for the determination of PACU length of stay.

Authors	Design	Number	Comparators	Outcomes
Parra, I; Abdallah, R; Jing, Y. 2012 (15).	Prospective cohort	100	Patients with PONV, patients without PONV	- Incidence of PONV - Time of recovery in PACU - Direct care costs - Hospital readmission - POP satisfaction - Days of work lost

PACU: postanesthesia care unit; PONV: postoperative nausea and vomiting; POP: Postoperative. **SOURCE:** Author.

SUPPLEMENTAL MATERIAL 6. PACU length of stay of patients with PONV vs. No PONV (15).

Variable	No PONV (N = 51)	PONV (N = 49)	p Value
Length of stay and POP recovery, minutes; Med, (IQR).	171 min (141-212)	234 min (188-287)	< 0,001

a: Mann Whitney U test for two medians. IQR: Interquartile rank; PACU: post-anesthesia care unit; PONV: postoperative nausea and vomiting; POP: Postoperative. **SOURCE:** Author.