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RESEARCH ARTICLE

Cost-Effectiveness Analysis of Inhaled Isoflurane Sedation in Critically Ill Patients: A Comparison with Intravenous Sedation

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ABSTRACT

Background: Sedation is a cornerstone of care for critically ill patients requiring invasive mechanical ventilation. Conventional intravenous sedation with agents such as midazolam, propofol, and opioids remains standard practice in most intensive care units (ICUs). Inhaled volatile anesthetics, including isoflurane, have emerged as alternative sedative strategies with potential clinical advantages, such as faster awakening, reduced opioid exposure, and shorter ICU length of stay. However, their economic impact remains insufficiently characterized, particularly in low- and middle-income healthcare settings.

Objective: To evaluate the cost-effectiveness of inhaled sedation with isoflurane compared with conventional intravenous sedation using midazolam and fentanyl in mechanically ventilated ICU patients, from the perspective of the Colombian healthcare system.

Methods: A decision tree–based economic model was developed using clinical effectiveness data from contemporary studies, including patients with and without COVID-19. Direct medical costs were obtained from national tariff manuals, institutional databases, and published literature. The model simulated a cohort of 1,000 patients (500 per group) and incorporated ICU length of stay, duration of mechanical ventilation, delirium incidence, and sedative and opioid consumption. Deterministic sensitivity analyses were performed under optimistic and pessimistic assumptions. Cost-effectiveness was assessed using the incremental cost-effectiveness ratio (ICER), with ICU length of stay as the primary effectiveness outcome.

Results: In the base-case analysis, inhaled sedation reduced ICU stay by 4.02 days per patient and resulted in total costs of USD 1,258,580 compared with USD 1,838,040 for intravenous sedation, yielding net savings of USD 579,460. The ICER was −USD 144,144, indicating that inhaled sedation was a dominant strategy. Sensitivity analyses confirmed cost savings across all scenarios.

Conclusions: Inhaled isoflurane sedation is a cost-effective strategy for mechanically ventilated critically ill patients, offering clinical benefits and net cost savings driven by reduced ICU length of stay.

Keywords: Inhaled sedation, isoflurane, ICU, mechanical ventilation, cost-effectiveness, decision tree, delirium, Colombia

Introduction

Sedation is a fundamental component of care for critically ill patients requiring invasive mechanical ventilation, as it ensures patient comfort, facilitates ventilator synchrony, and prevents agitation-related complications in the intensive care unit (ICU). For decades, intravenous (IV) sedation strategies—primarily using propofol, benzodiazepines, and opioids—have been the cornerstone of ICU practice. However, growing evidence has demonstrated that prolonged exposure to IV sedatives is associated with drug accumulation, tolerance, withdrawal syndromes, neuromuscular weakness, prolonged mechanical ventilation, ICU-acquired delirium, and long-term cognitive impairment, all of which adversely affect survival and functional outcomes.[1-4]

The association between deep or prolonged sedation and poor outcomes has been consistently demonstrated across large observational cohorts and randomized trials. Excessive sedation depth has been linked to increased duration of mechanical ventilation, longer ICU length of stay, higher incidence of delirium, and increased mortality.[5-7] These findings have led to a paradigm shift toward lighter sedation strategies and daily sedation interruption, yet implementation remains inconsistent, particularly in patients with severe respiratory failure requiring high ventilatory support.[8-10]

The COVID-19 pandemic further highlighted structural vulnerabilities in ICU sedation practices. Global shortages of IV sedatives during pandemic surges forced clinicians to reconsider alternative sedation strategies, accelerating the adoption of inhaled sedation in mechanically ventilated patients.[11,12] Volatile anesthetics such as isoflurane and sevoflurane, administered via anesthesia-conserving devices, offer unique pharmacological advantages, including rapid onset and offset, minimal systemic accumulation, and predominantly pulmonary elimination independent of hepatic or renal function.[13,14] These properties may be particularly advantageous in critically ill patients with multiorgan dysfunction.

Emerging clinical evidence suggests that inhaled sedation may improve clinically meaningful outcomes compared with IV sedation. Randomized trials and meta-analyses have shown that volatile anesthetic–based sedation is associated with faster awakening, improved sedation quality, shorter time to extubation, and reduced ICU length of stay.[15-18] Additionally, inhaled sedation has been associated with reduced cumulative opioid and neuromuscular blocker exposure, which may mitigate ICU-acquired weakness and facilitate earlier rehabilitation.[19,20]

Delirium remains one of the most prevalent and devastating complications of critical illness, affecting up to 80% of mechanically ventilated ICU patients and independently associated with increased mortality, prolonged hospitalization, long-term cognitive decline, and higher healthcare costs.[21,22] Several observational studies and propensity-matched analyses suggest that inhaled sedation may reduce the incidence and duration of ICU delirium compared with IV sedation, potentially through reduced γ-aminobutyric acid (GABA) receptor overstimulation and improved sleep architecture.[23-25] However, the available evidence remains heterogeneous, and uncertainty persists regarding long-term neurocognitive outcomes.[26]

Beyond clinical effectiveness, sedation strategies have substantial economic implications. Delirium, prolonged mechanical ventilation, and extended ICU stays are major drivers of ICU costs, accounting for a significant proportion of critical care expenditures.[21-27] Cost-minimization and cost-effectiveness analyses conducted during the COVID-19 pandemic suggest that inhaled sedation may offset higher upfront device and drug costs through reductions in ventilation duration, ICU length of stay, and sedation-related complications.[28,29] However, comprehensive economic evaluations integrating both clinical and resource utilization outcomes remain limited.

Therefore, rigorous cost-effectiveness modeling is essential to inform evidence-based decision-making regarding sedation strategies in the ICU.

Such evaluations must account not only for direct medication and device costs but also for downstream economic effects related to delirium prevention, reduced mechanical ventilation duration, ICU throughput, and long-term patient outcomes.[30,31]

The objective of this study is to develop a cost-effectiveness model comparing intravenous and inhaled sedation strategies in mechanically ventilated critically ill patients. Using contemporary clinical evidence and a resource optimization framework tailored to ICU practice, this analysis aims to determine whether inhaled sedation represents a cost-effective alternative to conventional intravenous sedation and whether its broader adoption could be justified within modern critical care systems.

Methods

To model an economic evaluation study comparing traditional intravenous (IV) sedation with inhaled sedation in critically ill patients, a series of assumptions were established based on the best available evidence. The decision problem was framed as an economic research question using the PICO strategy (see Table 1).

Table 1. PICO elements of the analysis

• **Population:** Adult ICU patients requiring sedation and mechanical ventilation.
• **Intervention:** Inhaled sedation with isoflurane administered via an anesthesia conserving vaporizer device (AnaConDa), with an average dose of 3 to 8 ml/hour via infusion pump, combined with continuous infusion of an opioid, typically fentanyl.
• **Comparator:** Conventional intravenous sedation using continuous infusion of midazolam combined with fentanyl.
• **Outcomes:** ICU length of stay, duration of mechanical ventilation, incidence of delirium, and consumption of fentanyl and midazolam.

Study Population

The population included adult ICU patients requiring invasive mechanical ventilation. Patients with contraindications to volatile agents or those on deep sedation protocols incompatible with inhaled sedation strategies were excluded.

Intervention

Although inhaled sedation can be administered using various halogenated agents including desflurane and sevoflurane, isoflurane was selected for this analysis due to its widespread clinical use, lower cost, and safety profile in prolonged sedation. Desflurane is not routinely used in ICU settings, and sevoflurane is limited to a maximum duration of five days and is significantly more expensive. Isoflurane administration was (carried out) administered using the AnaConDa device, enabling controlled delivery at 3 to 8 ml/hour via an infusion pump.

Comparator

The comparator consisted of conventional intravenous sedation with continuous infusion of midazolam and fentanyl. This standard sedation approach, along with mechanical ventilation support, is included in the bundled ICU care services in Colombia, which also covers noninvasive monitoring, room and board, nursing care, intensivist support, and specific procedures such as defibrillation and cardioversion.

Primary Outcomes

- ICU length of stay
- Duration of mechanical ventilation
- Incidence of delirium
- Fentanyl and midazolam consumption

Research Question

Is inhaled sedation with isoflurane cost-effective compared to conventional intravenous sedation with midazolam in adult patients undergoing invasive mechanical ventilation in intensive care units?

Time Horizon

The study time horizon was defined as the complete ICU stay, as this is one of the key clinical outcomes and iteration scenarios include extended ICU admissions. Costs and outcomes beyond the ICU setting were not considered.

Perspective

This study was conducted from the perspective of the Colombian healthcare system, including direct medical costs related to hospitalization, mechanical ventilation, medication, and medical devices.

Discount Rate

No discount rate was applied for to future costs and benefits, given that as the analysis was limited to a short time horizon less than one year, corresponding to the average ICU stay duration.

Modeling and Uncertainty Analysis

A decision tree was selected as the analytical model due to the characteristics of the intervention and the defined time horizon. Given that the analysis focuses on comparing sedation strategies during typical ICU stays, with clearly delineated clinical outcomes such as the incidence of delirium and fentanyl consumption, a decision tree effectively captures the differences in costs and effectiveness between both therapies across various clinical scenarios.

A sensitivity analysis was performed to demonstrate how changes in delirium incidence, ICU length of stay, and duration of mechanical ventilation affect the model's results.

Assumptions of the Pharmacoeconomic Model

PROBABILITIES OF THE CONSIDERED OUTCOMES

Delirium (D):

For the base-case scenario, we used data from Teinten et al. (2024) (4), which reported a delirium incidence of 16.1% in the group receiving inhaled isoflurane sedation and 32.2% in the group receiving conventional intravenous sedation. For the most favorable scenario, we incorporated data from Foudraine et al. (2021)[14], where 9 out of 85 patients in the inhaled sedation arm developed delirium, compared to 25 out of 85 in the conventional sedation group.

Fentanyl (F):

Fentanyl use was modeled as a cost-driving factor, since opioid consumption differs significantly between sedation modalities. To estimate the probabilities related to fentanyl consumption, we referenced data from Gómez et al. (2023)[3], calculating the proportion of patients who received ≥ 200 μg/hour of fentanyl (F≥) under each sedation strategy (I and V), and stratified by the presence (D+) or absence (D−) of delirium. These probabilities are detailed in Table 2.

Table 2. Estimated probabilities of fentanyl administration ≥ 200 μg/hour based on sedation modality and delirium incidence in the base-case scenario

Sedation Type	Delirium	Probability	Fentanyl ≥ 200 μg/h	Probability
Inhaled Sedation (I)	Yes (D+)	0.16	Yes (F≥)	0.42
			No (F<)	0.58
	No (D−)	0.84	Yes (F≥)	0.31
			No (F<)	0.69
Intravenous Sedation (V)	Yes (D+)	0.32	Yes (F≥)	0.62
			No (F<)	0.38
	No (D−)	0.68	Yes (F≥)	0.62
			No (F<)	0.38

These outcomes were incorporated into a decision tree model that included the probability of each clinical event, as derived from prior clinical studies and literature reviews. Figure 1.

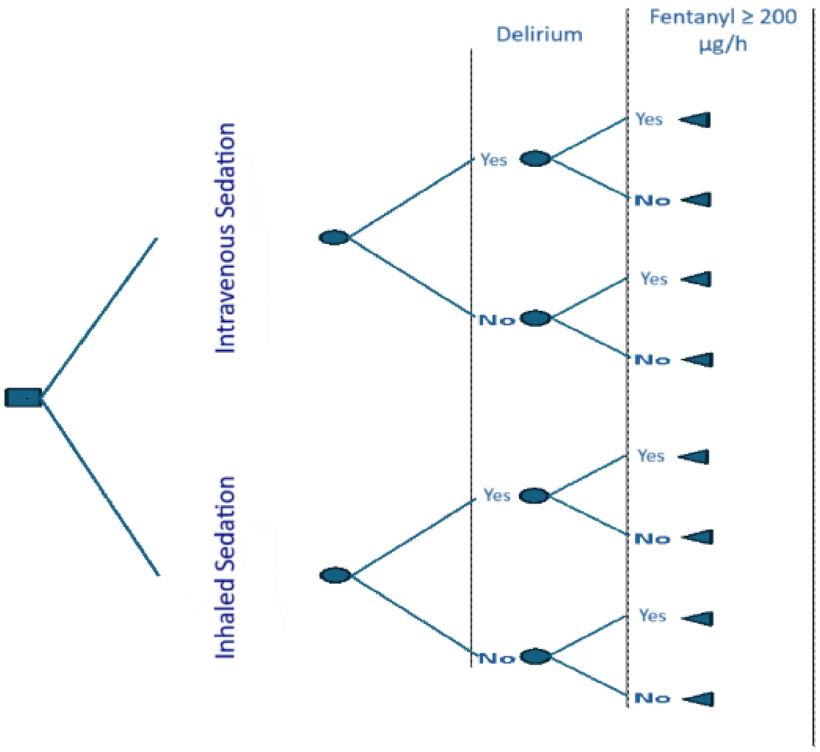


Figure 1. Decision tree comparing the two sedation strategies and the effectiveness outcomes

The probabilities associated with these two variables define eight terminal nodes:

1. **I/D+/F≥**: Patients who received inhaled sedation, developed delirium, and received ≥200 µg/h of fentanyl.
2. **I/D+/F<**: Patients who received inhaled sedation, developed delirium, and received <200 µg/h of fentanyl.
3. **I/D−/F≥**: Patients who received inhaled sedation, did not develop delirium, and received ≥200 µg/h of fentanyl.
4. **I/D−/F<**: Patients who received inhaled sedation, did not develop delirium, and received <200 µg/h of fentanyl.
5. **V/D+/F≥**: Patients who received intravenous sedation, developed delirium, and received ≥200 µg/h of fentanyl.
6. **V/D+/F<**: Patients who received intravenous sedation, developed delirium, and received <200 µg/h of fentanyl.
7. **V/D−/F≥**: Patients who received intravenous sedation, did not develop delirium, and received ≥200 µg/h of fentanyl.
8. **V/D−/F<**: Patients who received intravenous sedation, did not develop delirium, and received <200 µg/h of fentanyl.

ICU Length of Stay

The variables described above influence both treatment costs and ICU length of stay. To simplify the pharmacoeconomic model, we adopted the length of stay data reported in Teiten et al. (2024), which provides medians and ranges for both groups (I and V). The terminal nodes were assigned ICU length of stay values according to the following assumptions:

1. The upper bound of the reported ICU stay range was assigned to patients receiving higher fentanyl doses and who developed delirium: I/D+/F≥ and V/D+/F≥.
2. The lower bound was assigned to patients with no delirium and lower fentanyl doses: I/D−/F< and V/D−/F<.
3. The median value of ICU stay was assigned to all other terminal nodes, based on their respective group (inhaled or intravenous sedation).
4. These values were verified against the average increase in ICU stay associated with delirium, which has been reported to extend hospitalization by 4.77 days, according to the meta-analysis by Dziegielewski et al. (2021)[15]. Additionally, based on data from Gómez et al. (2023), patients receiving inhaled sedation had two fewer days of mechanical ventilation on average, and this difference was used as a proxy for mechanical ventilation costs in the model[3].

ICU length of stay was also the variable selected for iteration in the pessimistic simulation scenario, which assumes no difference in length of stay between the groups.

Duration of Mechanical Ventilation (MV)

Mechanical ventilation duration was considered a key outcome due to its relevance in patient morbidity and hospital costs. Prior studies have demonstrated that inhaled isoflurane sedation is associated with a mean reduction of approximately two days in MV compared to conventional intravenous sedation[3]. The following assumptions were applied to simplify this outcome:

1. In Colombia, MV costs are bundled into the ICU care package and cannot be itemized separately. Therefore, the model assumes that all patients received MV throughout their ICU stay. Hence, the number of sedation days for the inhaled group is considered equivalent to the total ICU stay.
2. MV duration was not used as a variable for iteration in the optimistic scenario (which favors the intervention under evaluation: I).
3. In the pessimistic scenario, MV duration was considered equal across both groups, and all incremental costs of inhaled therapy were included, representing the worst-case economic scenario.

Simulation Scenario

A simulated cohort size of 1,000 patients was established: 500 patients per arm (inhaled vs. intravenous sedation) for the base-case analysis and all scenario iterations.

Cost Identification, Measurement, and Valuation

For this economic evaluation comparing inhaled isoflurane sedation with intravenous midazolam sedation, only direct costs were included, from the perspective of the Colombian healthcare system. These encompassed ICU stay, therapies, and health technology use. See Table 3.

Cost Estimation Approach

The costs used in the model were obtained from tariff manuals, hospital cost databases, and previously published literature. Average values were selected to ensure that estimates are representative and aligned with real-world costs in the healthcare system. Daily consumption rates were calculated to derive cost per day, since one of the key variables in the model is ICU length of stay. No discount rate was applied, as the analysis covers a time horizon of less than one year, in accordance with standard methodological recommendations for economic evaluations in healthcare.

Since the cost of mechanical ventilation is bundled into the total ICU stay cost in Colombia, only the additional costs specific to inhaled sedation were considered. These include anesthesia vaporizers, isoflurane administration syringes, Flurabsorb filters (10-syringe pack), filling adapters, and Flurabsorb accessory kits.

Table 3. Costs Considered in the Pharmacoeconomic Model

Category	Unit Cost (USD)
AnaConDa device	$163
AnaConDa syringe	$8
Flurabsorb filter (10 syringes)	$109
Filling adapter	$14
Flurabsorb accessory kit	$27
Isoflurane 250 ml (vial)	$74
Fentanyl ampoule 500 mcg	$0,92
Midazolam ampoule 5 mg	$1,46
Respiratory therapy	$6,53
Physiotherapy	$6,29
ICU stay (per day)	$380
Mechanical ventilation (approx. per day)	$87

The AnaConDa device is typically replaced every 48 to 72 hours. The number of isoflurane vials was calculated based on a maximum dose of 8 ml/hour. Three physical therapy sessions and four respiratory therapy sessions were assumed per day.

Due to the heterogeneous data in the literature regarding fentanyl consumption (e.g., cumulative dose, number of administration days, average daily dose, and number of days with doses ≥200 μg/hour), the model used data from Gómez et al. (2023) (20). For midazolam, an average dose of 3 mg/hour was assumed

Results

BASE-CASE RESULTS:

The base-case scenario was constructed using the probabilities and assumptions derived from the literature informing the model. In a simulated cohort of 500 patients receiving inhaled sedation (I), the total cost of care was **$ 1.258.580 USD**. This includes:

- 14 days of sedation for patients in the I/D+/F≥ node,
- 7 days for those in I/D+/F< and I/D−/F≥, and
- 1 day for patients in I/D−/F<.

Of the total, **$381.149 USD** represents incremental costs directly attributed to inhaled sedation. In comparison, the total cost of care for patients receiving intravenous sedation (V) was **$ 1.838.040 USD.** (Thus, the difference (V − I) in the base-case scenario is a cost reduction of **$ 579.460 USD** in favor of inhaled sedation). In the base-case scenario, the cost difference (V − I) corresponded to a reduction of $579,460 USD in favor of inhaled sedation Table 4.

Iteration Scenario Results

OPTIMISTIC SCENARIO:

This scenario assumes improved efficiency of the intervention by adjusting the probability of delirium, with a greater difference in incidence based on the results reported by Foudraine et al. (2021). No modifications were made to ICU length of stay in this iteration.

Under this assumption, the cost difference between the intravenous (V) and inhaled (I) sedation groups was $ 609.920 USD in favor of inhaled sedation. Table 5.

Table 4. Base Case Probabilities and Costs

	Delirium		Fentanyl ≥ 200 μg/h		Probability	N	ICU Days	Resp. Therapy	Physiotherapy	Fentanyl (USD)	Midazolam (USD)	ICU Stay Cost (USD)	Therapy Cost (USD)	AnaConDa Cost (USD)	Total (USD)
Inhaled Sedation	YES	0,16	YES	0,42	0,067	33	14	1808	1356	$ 4.290		$ 171.900	$ 20.350	$ 85.230	$ 281.640
			NO	0,58	0,094	47	7	1360	1020	$ 2.025		$ 129.550	$ 15.290	$ 64.110	$ 210.660
	NO	0,84	YES	0,31	0,260	130	7	3765	2823	$ 9.680		$ 357.200	$ 42.360	$ 177.420	$ 588.930
			NO	0,69	0,579	289	1	1157	868	$ 1.660		$110.230	$ 13.0107	$ 54.600	$ 179.260
														Total	**$ 1.258.580**
Intravenous Sedation	SI	0,32	YES	0,62	0,200	100	17	6918	5189	$19.5200	$ 35.700	$ 656.030	$ 77.920	$ -	$ 790.400
			NO	0,38	0,122	61	8	1953	1465	$2910	$ 10.250	$185.400	$22.000	$ -	$ 220.650
	NO	0,68	YES	0,62	0,421	211	8	6736	5052	$18.260	$ 35.240	$ 640.120	$ 75.750	$ -	$ 771.400
			NO	0,38	0,257	128	1	514	385	$ 730	$ 2700	$ 48.880	$ 5780	$ -	$ 58.050
														Total	**$ 1.838.040**

Table 5. Cost difference between the intravenous (V) and inhaled (I) sedation

	Delirium		Fentanyl ≥ 200 μg/h		Probability	N	ICU Days	Resp. Therapy	Physiotherapy	Fentanyl (USD)	Midazolam (USD)	ICU Stay Cost (USD)	Therapy Cost (USD)	AnaConDa Cost (USD)	Total (USD)
Inhaled Sedation	YES	0,11	YES	0,42	0,044	22	14	1189	892	$ 2.820		$ 113.040	$ 13.370	$ 56.020	$185.140
			NO	0,58	0,062	31	7	894	671	$ 1.330		$84.900	$ 10.060	$42.120	$ 138.500
	NO	0,89	YES	0,31	0,277	139	7	4012	3009	$ 10.310		$381.140	$ 45.110	$ 189.050	$ 625.850
			NO	0,69	0,617	308	1	1233	925	$ 1.770		$ 117.180	$ 13.870	$ 58.160	$ 191.100
														Total	**$ 1.140.980**
Intravenous Sedation	YES	0,29	YES	0,62	0,183	91	17	6210	4657	$ 17.820	$ 32.5905	$ 590.370	$ 69.860	$ -	$ 711.620
			NO	0,38	0,111	56	8	1784	1338	$ 2.650	$ 9.370	$ 169.450	$ 20.050	$ -	$ 199.640
	NO	0,71	YES	0,62	0,438	219	8	7013	5260	$ 19.120	$ 36.830	$ 666.200	$ 78.880	$ -	$ 781.660
			NO	0,38	0,268	134	1	535	401	$ 760	$ 2.810	$ 50.790	$ 6.020	$ -	$59.650
														Total	**$ 1.750.900**

PESSIMISTIC SCENARIO:

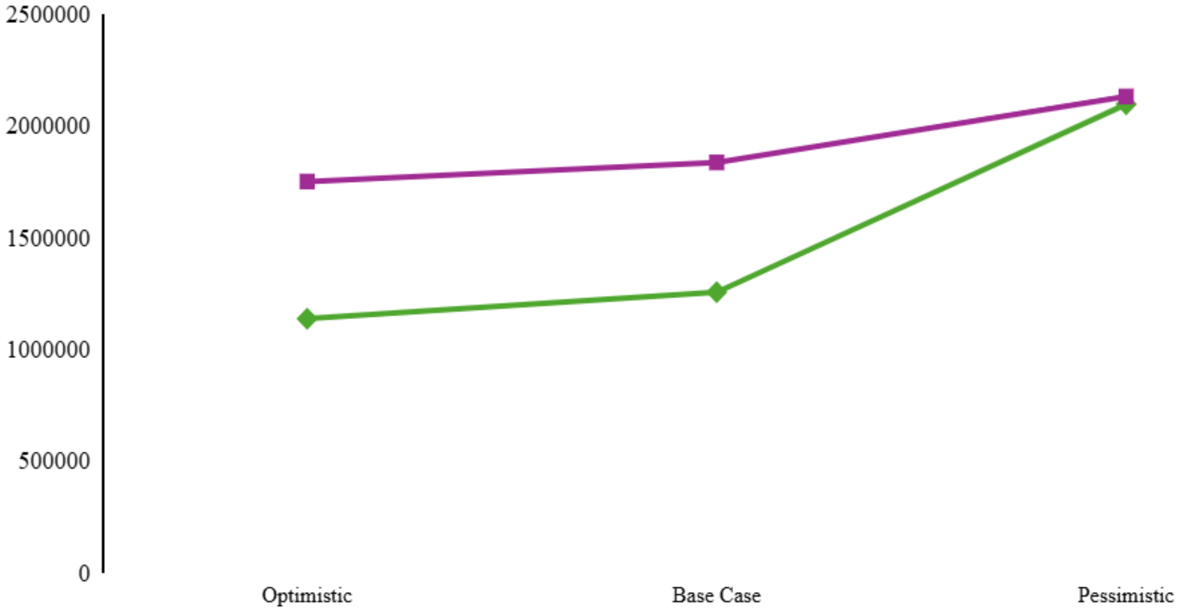
This iteration models the worst-case scenario, assuming no difference in ICU length of stay between the groups. This represents a low-probability scenario, but it was included for completeness.

Under this assumption, the cost difference between intravenous (V) and inhaled (I) sedation was $ 32.000 USD, still favoring inhaled sedation, though with a reduced margin.See **Table 6**.

Table 6. Probabilities and Costs of the Pessimistic Scenario

	Delirium		Fentanyl ≥ 200 µg/h		Probability	N	ICU Days	Resp. Therapy	Physiotherapy	Fentanyl (USD)	Midazolam (USD)	ICU Stay Cost (USD)	Therapy Cost (USD)	AnaConDa Cost (USD)	Total (USD)
Inhaled Sedation	YES	0,16	YES	0,42	0,067	33	16	2143	1607	$ 5.085		$ 203.598	$ 24.118	$ 100.785	$ 334.330
			NO	0,58	0,094	47	11	2069	1551	$ 3.079		$ 196.645	$ 23.264	$ 97.429	$ 320.111
	NO	0,84	YES	0,31	0,260	130	9	4686	3515	$ 12.048		$ 445.199	$ 52.785	$ 220.910	$ 730.620
			NO	0,69	0,579	289	4	4629	3472	$ 6.6431		$ 439.084	$ 52.682	$ 217.997	$ 716.362
														Total	**$ 2.101.200**
Intravenous Sedation	YES	0,32	YES	0,62	0,200	100	16	6398	4799	$ 18.335	$ 33.5908	$ 607.000	$ 72.000	$ -	$ 731.0008
			NO	0,38	0,122	61	11	2685	2014	$ 3.995	$ 14.100	$ 255.668	$ 30.200	$ -	$ 301.963
	NO	0,68	YES	0,62	0,421	211	9	7578	5684	$ 20.648	$39.780	$ 719.050	$ 85.240	$ -	$864.718
			NO	0,38	0,257	128	4	2056	1542	$ 2.924	$ 10.787	$ 195.290	$ 23.121	$ -	$ 231.1212
														Total	**$ 2.133.200**

Figure 2 Illustrates the difference in expenditure between the two sedation strategies across the three scenarios proposed in the analysis



Inhaled Sedation (green) Intravenous Sedation (purple)

Inhaled sedation, despite its better clinical outcomes, incurs additional costs compared to conventional ICU sedation. Therefore, it cannot be considered inherently dominant and warrants calculation… of the Incremental Cost-Effectiveness Ratio (ICER).

Incremental Cost-Effectiveness Ratio (ICER)

The Incremental Cost-Effectiveness Ratio represents the ratio between the difference in costs and the difference in effectiveness between two interventions. In the base-case scenario, effectiveness was defined as the weighted mean difference in ICU length of stay between the two groups. The incremental cost-effectiveness of inhaled sedation compared to conventional sedation was −**$ 144.144 USD**, indicating net savings in this scenario.

RICE = (Cost of Inhaled Intervention – Cost of Conventional Intervention) / (Weighted Average Length of Stay for Inhaled Intervention – Weighted Average Length of Stay for Conventional Intervention)

RICE = ($ 1.258.580 USD - $ 1.838.040 USD)/(4,04 − 8,06)= -$ 579.560/-4,02

RICE = -$ 144.144 USD

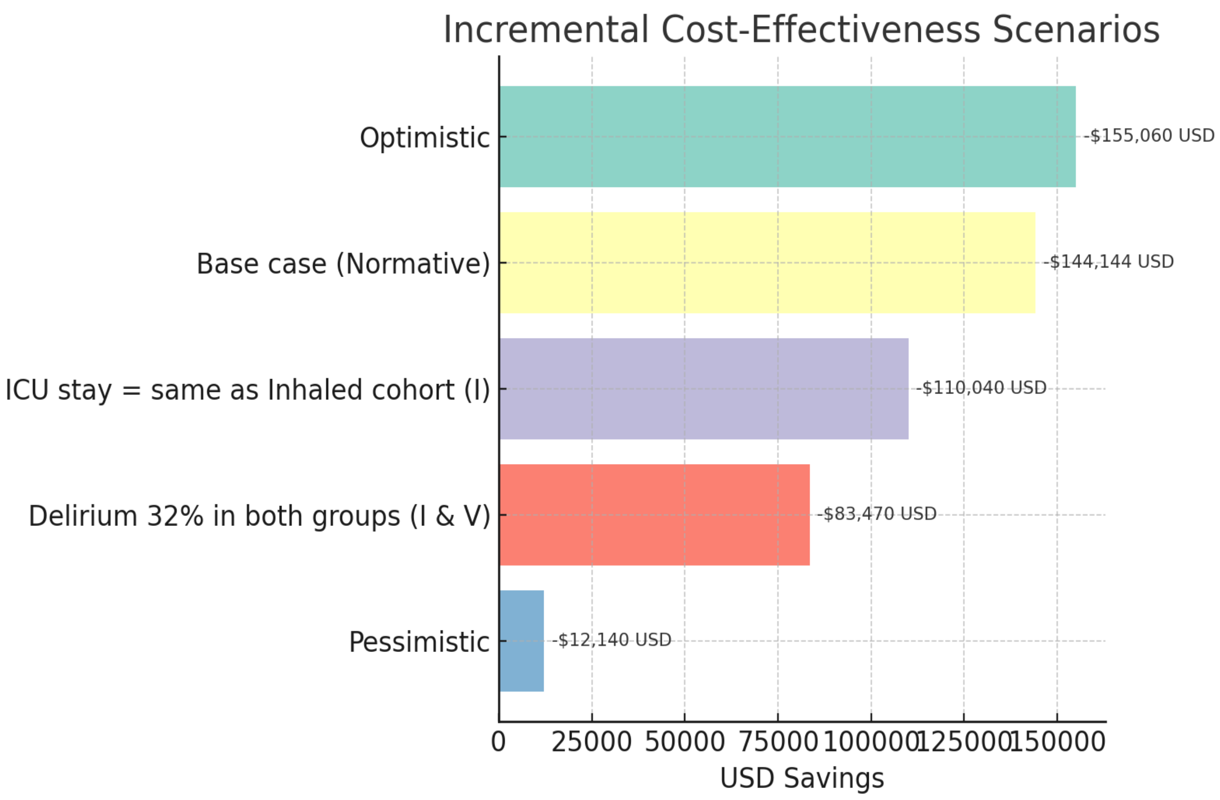
The effectiveness difference (−4.02 days) indicates that patients receiving inhaled sedation required, on average, 4.02 fewer days of mechanical ventilation compared to those who received conventional sedation. A negative ICER suggests that inhaled sedation is a dominant strategy, it is more effective (in reducing ICU/mechanical ventilation duration) and less costly than conventional sedation in the base-case analysis. Table 7.

Table 7. Incremental Cost-Effectiveness Ratio (ICER) of Inhaled Sedation versus Conventional Sedation

Technology	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Incremental Cost-Effectiveness Ratio
Inhalada	$1.258.580 USD	-$ 579.560	4,04	-4,02	-$ 144.144 USD

We also analyzed two additional scenarios: one where delirium incidence was assumed to be equal in both groups at 32% (Group V incidence), and another where ICU length of stay and mechanical ventilation days were assumed to be equal, using the days from Group I for both. The results from these two iterations weren't worse than those observed in the pessimistic scenario, so we classified them as intermediate scenarios. It's important to note that the willingness-to-pay analysis, which uses a threshold of 1 to 3 GDP per capita in Colombia, is typically focused on life-years gained; however, these outcomes weren't part of this study's analysis.

Figure 3 Incremental cost-effectiveness ratios across the scenarios considered



Discussion

This study represents a rigorous economic evaluation assessing the cost-effectiveness of inhaled sedation with isoflurane compared to conventional intravenous sedation with midazolam and fentanyl in critically ill, mechanically ventilated patients in the ICU. A decision tree analytical model was employed, informed by recent clinical data[3,4], and included patients with respiratory failure—with and without COVID-19—exhibiting variable delirium incidence and mechanical ventilation durations ranging from 3 to 12 days. The analysis considered direct healthcare costs from the perspective of the Colombian health system and simulated a cohort of 1,000 patients. Midazolam was selected as a comparator over propofol due to its stronger association with delirium in critically ill patients[16].

In the base-case scenario, inhaled sedation was associated with an average reduction of 4.02 ICU days, resulting in net savings of **$ 579.460 USD** and a negative incremental cost-effectiveness ratio (ICER) of –$144.144 USD , positioning inhaled sedation as a dominant strategy. These results are reproducible across different cohort sizes, provided the model assumptions remain constant.

The sensitivity analysis included various scenarios: in the optimistic scenario, characterized by a lower incidence of delirium in the inhaled sedation group, cost savings reached $ 609.920 USD; in the pessimistic scenario, which assumed equal ICU lengths of stay for both strategies, a modest saving of $ 32.000 USD was still observed. The robustness of the model is evident from its consistent favorable performance across all sensitivity scenarios.

A previous study by Álvarez et al. (2023) retrospectively analyzed costs and clinical outcomes of inhaled anesthetics versus intravenous sedatives in COVID-19 patients. That study calculated sedation costs during the first two ICU days, based on drug consumption recorded in clinical charts and acquisition prices from institutional procurement systems. Mean costs per drug and therapeutic group were compared. No significant differences were found in mortality, ventilation duration, ICU stay, or total hospital stay. However, significant reductions were noted in costs related to midazolam, propofol, and dexmedetomidine use ($p < 0.0001$), with an average difference of $4,108.42 (local currency) per patient/ day in favor of the inhaled sedation group[16]. While informative, this study does not constitute a formal economic evaluation.

In contrast, the present study constructed an explicit model with a defined time horizon and sensitivity analysis. A decision tree was selected due to the short-term perspective (ICU stay) and the clear identification of clinical outcomes. Although decision trees simplify clinical realities, this model is grounded in data relevant to the Colombian healthcare context. Costs—including medications, devices, and ICU care—were obtained from tariff manuals, institutional records, and national literature, ensuring local applicability.

It is important to highlight that the model was built on effectiveness data derived from real-world clinical settings. A key input was a retrospective observational study of ARDS patients during the COVID-19 pandemic, which reported an average reduction of approximately two days in ventilation duration for patients receiving inhaled sedation compared to intravenous sedation[3], with a range from 0.23 to 4.71 days. This difference is clinically and economically meaningful.

Reduced mechanical ventilation duration is associated with shorter hospital stays, decreased opioid and resource consumption, and lower risk of complications such as delirium or device-associated infections. Recently, the SESAR randomized clinical trial evaluated inhaled sedation using sevoflurane and found a reduction in ventilator-free days, potentially suggesting an adverse clinical effect. However, this contrasts with our findings, where isoflurane sedation was associated with reduced ventilation duration. This discrepancy may be attributed to the use of different agents: SESAR used sevoflurane, whereas our analysis focused on isoflurane, the agent internationally recommended for prolonged sedation and more widely used in intensive care settings.[32]

Although inhaled sedation involves higher upfront direct costs, it is not immediately considered a dominant strategy, thus necessitating the calculation of the Incremental Cost-Effectiveness Ratio (ICER) to quantify the additional cost per unit of effectiveness gained when compared to conventional intravenous sedation[18-20]. Such evaluations are essential to support rational clinical decision-making, balancing potential clinical benefits with the economic burden of the intervention.

The economic model demonstrated that isoflurane sedation is cost-effective. Despite the higher initial costs, net savings result from reductions in mechanical ventilation duration a key outcome linked to shorter ICU stays and fewer complications. The negative ICER indicates that inhaled sedation not only improves clinical effectiveness but also reduces total healthcare costs, making it both clinically and economically efficient.

While the model relies on cost and resource data specific to the Colombian health system, its methodological framework can be adapted to other healthcare settings. For implementation in different healthcare systems, local cost and outcome adjustments would be necessary to ensure external validity.

A recent meta-analysis deserves mention in light of our findings. Conducted by Yamamoto et al., it reported a potential increase in mortality associated with inhaled sedation. The Bayesian analysis used provided a complementary perspective to classical modeling, indicating a 92.8% posterior probability that inhaled sedation increased mortality, with an estimated relative risk (RR) of 1.16 (95% Bayesian credible interval: 0.94–1.42). This suggests a high probability of harm, though the credible interval includes the possibility of no effect or even mild benefit, reflecting statistical uncertainty. Additionally, the low heterogeneity (τ = 0.09) supports consistency, but warrants cautious interpretation of the results[19-25].

Importantly, subgroup analysis showed that the mortality effect was primarily driven by studies using sevoflurane. In contrast, the isoflurane-specific analysis showed no statistically significant results (RR 1.18; 95% CI 0.81–1.73), as the confidence interval crossed the null (RR=1), indicating no conclusive evidence. Moreover, in studies where both agents were used interchangeably, mortality events were not reported, making odds ratio estimation impossible and further limiting interpretability[19].

The main limitation of our model lies in its external validity, as the cost data reflect the Colombian healthcare context. Therefore, while the findings accurately represent local conditions, they may not be directly extrapolable to systems with different pricing structures or technological availability[20-24]. Nonetheless, the methodology used is reproducible and can be adapted for similar analyses in other health systems.

Key strengths of the model include the use of real-world national data, analytical robustness, a clear comparative framework, integration of relevant clinical and economic outcomes, and the inclusion of both optimistic and pessimistic scenarios. Furthermore, the model is enhanced with detailed tables and figures that support interpretation and transparency.

The analysis showed that inhaled sedation generated cost savings in the base case, and this finding was consistent across sensitivity analyses and simulated scenarios, reinforcing the model's reliability. The inclusion of variables such as delirium, ICU length of stay, mechanical ventilation duration, and concomitant sedative use allowed for a comprehensive representation of both the clinical and economic impact of each strategy.

Conclusion

This study provides robust evidence that inhaled sedation with isoflurane is a clinically effective and economically viable alternative for mechanically ventilated critically ill patients, from the perspective of the Colombian healthcare system. While broader applicability will require local cost and outcome adjustments, the proposed model offers a valuable tool for evidence-based decision-making in health policy.

Declaration of Competing Interest

Daniel Molano reports receiving honoraria as a speaker for Goba. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. All other authors declare no competing interests.

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