REMUNOM
ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
Vol: 13.09
DOI: 10.66104/f7w0py51
Pages: 1-34

FENTANIL E REMIFENTANIL NA PRÁTICA ANESTÉSICA: REVISÃO INTEGRATIVA DE EVIDÊNCIAS DIRETAS E INDIRETAS DE ENSAIOS CLÍNICOS RANDOMIZADOS

FENTANYL AND REMIFENTANIL IN ANESTHETIC PRACTICE: AN INTEGRATIVE REVIEW OF DIRECT AND INDIRECT EVIDENCE FROM RANDOMIZED CLINICAL TRIALS

FENTANILO Y REMIFENTANILO EN LA PRÁCTICA ANESTÉSICA: REVISIÓN INTEGRADORA DE EVIDENCIAS DIRECTAS E INDIRECTAS DE ENSAYOS CLÍNICOS ALEATORIZADOS

Lucas Stêvão Oliveira Crêspo
Estudante de Medicina, Afya Faculdade de Medicina de Garanhuns, Brasil
E-mail: stevao.oc@gmail.com
José Ferreira de Sousa Netto
Mestre em Educação para o Ensino na área da Saúde, Afya Faculdade de Medicina de Garanhuns, Brasil
E-mail: ferreira.netto@hotmail.com
Wenno de Melo Cadete
Estudante de Medicina, Afya Faculdade de Medicina de Garanhuns, Brasil
E-mail: wennokdt@hotmail.com
Antonio Fernando de Souza Leão Neto
Estudante de Medicina, Afya Faculdade de Medicina de Garanhuns, Brasil
E-mail: antoniofernandoxv@gmail.com
Wagner Breitner de Araujo Pinheiro Filho
Estudante de Medicina, Afya Faculdade de Medicina de Garanhuns, Brasil
E-mail: wagnerbpfilho@gmail.com

REMUNOM
ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
Vol: 13.09
DOI: 10.66104/f7w0py51
Pages: 1-34

João Gabriel Lucena Silva

Estudante de Medicina, Afya Faculdade de Medicina de Garanhuns, Brasil

E-mail: gabriellucena.suport@gmail.com

Resumo

A escolha racional entre fentanil e remifentanil na prática anestésica permanece controversa, dadas as diferenças farmacocinéticas que impactam eficácia analgésica e segurança perioperatória. O estudo objetivou analisar comparativamente eficácia e segurança desses opioides por meio de revisão integrativa da literatura. A busca foi conduzida em PubMed e EBSCO Host (com MEDLINE acessado via PubMed), em 25 de novembro de 2025, aplicando-se a estratégia *Population, Intervention, Comparison, Outcome* (PICO) e o fluxograma *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA), contemplando ensaios clínicos randomizados publicados entre 2015 e 2025, em português ou inglês. A seleção foi conduzida por três revisores em etapas independentes. Foram identificados 407 registros, dos quais 15 estudos atenderam aos critérios de elegibilidade — quatro com comparação direta entre fentanil e remifentanil (Grupo A) e onze com evidência indireta (Grupo B) —, todos com nível 2 de evidência segundo a *Agency for Healthcare Research and Quality* (AHRQ). Realizou-se avaliação semiestruturada de risco de viés contemplando seis domínios metodológicos. Em doses sedativas tituladas sob anestesia geral balanceada, fentanil e remifentanil apresentaram eficácia analgésica e estabilidade hemodinâmica equivalentes em pacientes hígidos. O remifentanil associou-se a maior instabilidade cardiovascular nas transições farmacológicas e a elevada incidência de depressão respiratória (25%) em geriátricos sob sedação consciente, evidência derivada de comparação com dexmedetomidina. O remifentanil apresentou vantagem contextual em procedimentos ambulatoriais de curta duração, condicionada à analgesia multimodal de transição. As evidências indiretas favorecem o fentanil em cirurgias de grande porte, neurocirurgia e como adjuvante neuraxial obstétrico, embora a ausência de comparações diretas limite inferências definitivas. Limitações incluíram escassez de comparações diretas, heterogeneidade dos comparadores e seguimento restrito à recuperação imediata. Conclui-se que fentanil e remifentanil constituem ferramentas farmacológicas complementares, cuja seleção exige individualização contextualizada ao paciente e ao procedimento.

Palavras-chave: Fentanil; Remifentanil; Anestesia; Analgesia perioperatória

Abstract

The rational choice between fentanyl and remifentanil in anesthetic practice remains controversial, given the pharmacokinetic differences impacting analgesic efficacy and perioperative safety. The study aimed to comparatively analyze the efficacy and safety of these opioids through an integrative literature review. The search was conducted in PubMed and EBSCO Host (with MEDLINE accessed through PubMed), on November 25, 2025, applying the *Population, Intervention, Comparison,*

REMUNOM
ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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Outcome (PICO) strategy and the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) flowchart, including randomized clinical trials published between 2015 and 2025, in Portuguese or English. Selection was conducted by three reviewers in independent stages. A total of 407 records were identified, of which 15 studies met the eligibility criteria — four with direct comparison between fentanyl and remifentanil (Group A) and eleven with indirect evidence (Group B) — all with level 2 evidence according to the *Agency for Healthcare Research and Quality* (AHRQ). A semi-structured risk-of-bias assessment was performed covering six methodological domains. At titrated sedative doses under balanced general anesthesia, fentanyl and remifentanil presented equivalent analgesic efficacy and hemodynamic stability in healthy adult patients. Remifentanil was associated with greater cardiovascular instability during pharmacological transitions and a high incidence of respiratory depression (25%) in geriatric patients under conscious sedation, evidence derived from comparison with dexmedetomidine. Remifentanil presented contextual advantage in short-duration outpatient procedures, conditioned upon multimodal transition analgesia. Indirect evidence favors fentanyl in major surgeries, neurosurgery, and as an obstetric neuraxial adjuvant, although the absence of direct comparisons limits definitive inferences. Limitations included the scarcity of direct comparisons, heterogeneity of comparators, and follow-up restricted to immediate recovery. It is concluded that fentanyl and remifentanil constitute complementary pharmacological tools, whose selection requires individualization contextualized to the patient and the procedure.
Keywords: Fentanyl; Remifentanil; Anesthesia; Perioperative analgesia

Resumen

La elección racional entre fentanilo y remifentanilo en la práctica anestésica sigue siendo controvertida, dadas las diferencias farmacocinéticas que impactan la eficacia analgésica y la seguridad perioperatoria. El estudio tuvo como objetivo analizar comparativamente la eficacia y seguridad de estos opioides mediante una revisión integradora de la literatura. La búsqueda se realizó en PubMed y EBSCO Host (con MEDLINE accedido a través de PubMed), el 25 de noviembre de 2025, aplicando la estrategia *Population, Intervention, Comparison, Outcome* (PICO) y el diagrama *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA), incluyendo ensayos clínicos aleatorizados publicados entre 2015 y 2025, en portugués o inglés. La selección fue conducida por tres revisores en etapas independientes. Se identificaron 407 registros, de los cuales 15 estudios cumplieron los criterios de elegibilidad, cuatro con comparación directa entre fentanilo y remifentanilo (Grupo A) y once con evidencia indirecta (Grupo B), todos con nivel 2 de evidencia según la *Agency for Healthcare Research and Quality* (AHRQ). Se realizó una evaluación semiestructurada del riesgo de sesgo contemplando seis dominios metodológicos. En dosis sedantes tituladas bajo anestesia general balanceada, fentanilo y remifentanilo presentaron eficacia analgésica y estabilidad hemodinámica equivalentes en pacientes adultos sanos. El remifentanilo se asoció a mayor inestabilidad cardiovascular en las transiciones farmacológicas y a

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elevada incidencia de depresión respiratoria (25%) en geriátricos bajo sedación consciente, evidencia derivada de comparación con dexmedetomidina. El remifentanilo presentó ventaja contextual en procedimientos ambulatorios de corta duración, condicionada a una analgesia multimodal de transición. Las evidencias indirectas favorecen al fentanilo en cirugías de gran porte, neurocirugía y como adyuvante neuroaxial obstétrico, aunque la ausencia de comparaciones directas limita inferencias definitivas. Las limitaciones incluyeron escasez de comparaciones directas, heterogeneidad de los comparadores y seguimiento restringido a la recuperación inmediata. Se concluye que fentanilo y remifentanilo constituyen herramientas farmacológicas complementarias, cuya selección exige individualización contextualizada al paciente y al procedimiento.

Palabras clave: Fentanilo; Remifentanilo; Anestesia; Analgesia perioperatoria

1. Introduction

The evolution of modern anesthesiology has consolidated through the development of drugs capable of precisely modulating the anesthetic triad: hypnosis, muscle relaxation, and analgesia. In this scenario, opioids have assumed a central role in the control of perioperative nociception. Pharmacologically, synthetic opioids exert their analgesic and sympatholytic effects predominantly through binding to mu receptors coupled to G protein, modulating ion channels and inhibiting the release of excitatory neurotransmitters in the ascending pain pathways (Beers; Camporesi, 2004).

In contemporary anesthetic practice, fentanyl and remifentanil are among the main agents used for the maintenance of perioperative autonomic stability, as highlighted by Asakura, Mihara, and Goto (2018), who characterize them as the main analgesic choices across a wide spectrum of surgical procedures. However, although they share the same molecular mechanism of action, these drugs possess distinct pharmacokinetic profiles, which directly influence efficacy and safety outcomes in the intra- and postoperative periods, as extensively investigated in contemporary clinical trials.

Fentanyl is a highly lipophilic synthetic opioid, characterized by rapid onset of action and intermediate clinical duration. Its metabolism occurs predominantly in the liver via the cytochrome P450 system, phase I, through the CYP3A4 enzyme,

REMUNOM
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conferring a longer elimination half-life and an increasing context-sensitive half-life with infusion duration (Beers; Camporesi, 2004). This pharmacokinetic feature provides relevant residual analgesia during the transition period to post-anesthetic recovery, reducing the immediate need for analgesic rescue. On the other hand, the literature demonstrates that fentanyl accumulation in peripheral tissues during prolonged continuous infusions may hinder timely titration and prolong respiratory depression, delaying awakening, extubation, and discharge from the post-anesthesia care unit. Furthermore, the versatility of the drug extends beyond the intravenous route, being widely used as a neuraxial adjuvant in obstetric contexts, in which its lipophilicity favors rapid onset of spinal analgesia with an acceptable maternal-fetal safety profile.

In contrast, remifentanil presents a unique pharmacokinetic profile in total intravenous anesthesia (TIVA) and in target-controlled infusion (TCI) systems. This drug has a constant context-sensitive half-life of approximately three to ten minutes, which does not substantially change with infusion duration. This characteristic results from its rapid hydrolysis by nonspecific plasma and tissue esterases, which prevents systemic accumulation (Glass et al., 1999). Such a profile confers advantages to remifentanil in procedures demanding fine control of nociceptive analgesia and rapid awakening, although its abrupt termination of action (offset) imposes challenges to postoperative safety and comfort. Clinical trials and recent reviews indicate that the intraoperative use of remifentanil requires careful planning of transitional analgesia in order to prevent acute rebound pain and opioid-induced hyperalgesia (OIH), a paradoxical phenomenon that may increase the consumption of rescue analgesics and compromise recovery quality (Fletcher; Martinez, 2014; Santonocito et al., 2018).

The pharmacokinetic differences between the two agents translate, in clinical practice, into distinct applications ranging from short-duration outpatient procedures to major surgeries, including vulnerable populations such as elderly patients under conscious sedation, patients with morbid obesity, and neurosurgical patients. Each context imposes particular requirements regarding hemodynamic stability, respiratory safety, postoperative pain control, and recovery time, making the choice

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between fentanyl and remifentanil a complex decision dependent on multiple clinical and logistical variables (Hemantkumar et al., 2024).

Despite the wide use of both drugs, the literature still presents divergences regarding their relative superiority when evaluated through the efficacy-safety binomial, with persistent uncertainties about which opioid strategy minimizes postoperative complications and optimizes recovery. Given this gap, the present study aims to comparatively analyze the efficacy and safety of fentanyl and remifentanil in anesthetic practice, through an integrative review of Randomized Clinical Trials (RCTs), offering an updated overview to guide the rational choice between the two opioids.

2. Materials and Methods

This research consisted of an integrative literature review aimed at comparatively analyzing the efficacy and safety of fentanyl and remifentanil in anesthetic practice, based on evidence derived predominantly from randomized clinical trials. The choice of the integrative modality, rather than systematic review *stricto sensu*, was grounded in three considerations: the integrative review is the broadest method of evidence synthesis, allowing the inclusion of studies with heterogeneous designs and the combination of experimental, quasi-experimental, and observational evidence under unified qualitative analysis (Mendes; Silveira; Galvão, 2008; Whittemore; Knafl, 2005); the topic presents a particularity in which only part of the RCTs compare fentanyl and remifentanil in parallel arms under identical anesthetic technique, while the majority evaluates one of the opioids versus agents from other pharmacological classes, requiring qualitative synthesis of direct and indirect evidence; and, unlike the systematic review — focused on quantitative aggregation of homogeneous studies —, the integrative approach enables the construction of the state of the art on a given topic (Botelho; Cunha; Macedo, 2011; Souza; Silva; Carvalho, 2010).

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was adopted as a tool for transparency and traceability of the

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selection process, due to its international recognition as a reporting standard and its transversal applicability to different review modalities (Galvão; Pansani; Harrad, 2015; Page et al., 2021), without claiming the status of a full systematic review. Similarly, the PICO strategy was adopted for organizational purposes, being recommended for integrative reviews in healthcare (Santos; Pimenta; Nobre, 2007). The combination of these elements does not constitute methodological inconsistency, but rather the adoption of contemporary best practices in evidence synthesis reporting.

The review was conducted in six stages: (1) identification of the topic and formulation of the guiding question; (2) definition of inclusion and exclusion criteria; (3) systematized literature search; (4) selection, extraction, and categorization of information; (5) critical appraisal and interpretation of results; and (6) synthesis of the produced knowledge (Botelho; Cunha; Macedo, 2011).

Under the PICO strategy, P corresponded to patients undergoing general anesthesia; I, to the use of remifentanil; C, to the use of fentanyl; and O, to parameters of analgesic efficacy and safety. The following guiding question was formulated: "In patients undergoing anesthetic-surgical procedures, what is the analgesic efficacy and the hemodynamic and respiratory safety profile of remifentanil compared to fentanyl, as evidenced by randomized clinical trials?". Descriptors registered in the Medical Subject Headings (MeSH) and Health Sciences Descriptors (DeCS) were used, in English (fentanyl, remifentanil, anesthesia, hemodynamics, postoperative pain, analgesia, randomized controlled trials) and in Portuguese (fentanil, remifentanil, anestesia, hemodinâmica, dor pós-operatória, analgesia, ensaios clínicos controlados aleatórios), with the latter yielding no additional results. The combination was performed using the Boolean operator AND, resulting in the strategy: fentanyl AND remifentanil AND anesthesia AND hemodynamics AND postoperative pain AND analgesia AND randomized controlled trials. Data collection was conducted in the PubMed and EBSCO Host databases, with MEDLINE accessed through the PubMed interface to avoid duplication. The last search was conducted on November 25, 2025.

As inclusion criteria, original articles with RCT methodological design were

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selected, published between 2015 and 2025, in Portuguese or English, evaluating the use of fentanyl or remifentanil in humans within the anesthetic-surgical context. Excluded were articles with distinct design, literature reviews, academic works (undergraduate theses, master's dissertations, doctoral theses), abstracts, book chapters, conference proceedings, and exclusively animal studies. Classic references prior to the search period, related to the pharmacokinetics and pharmacodynamics of fentanyl and remifentanil, were consulted only as supporting literature. Filters were applied for study type (RCT), language (Portuguese and English), and date (2015–2025). Although the search window was 2015–2025, the 15 eligible studies were published between 2016 and 2024, reflecting the actual temporal distribution of the production on the topic.

The selection followed the PRISMA flowchart (Figure 1), conducted by three reviewers in two independent stages: the main author performed the complete screening of all records; subsequently, two additional reviewers independently evaluated half of the records each, repeating the screening by title, abstract, and full text. The ten identified divergences were resolved by the main author through direct reapplication of the eligibility criteria. The final sample of 15 studies was categorized by author, year of publication, journal, objective, study type, methodological approach, and level of evidence.

The level of evidence was classified according to the Agency for Healthcare Research and Quality (AHRQ), which establishes seven levels. Due to the inclusion criteria, the findings of this review were based predominantly on level 2 (randomized clinical trials), ensuring robustness to the analysis.

Complementarily to the level of evidence classification, a semi-structured risk-of-bias assessment was conducted for the included randomized clinical trials, contemplating six critical methodological domains: (i) randomization method; (ii) allocation concealment; (iii) blinding of participants, personnel, and outcome assessors; (iv) reported losses and exclusions; (v) intention-to-treat analysis; and (vi) overall risk of bias. Each domain was qualitatively judged in three categories — low risk, some concerns, or high risk — according to the methodological detail reported by the authors in each study. This assessment was conducted by the main author

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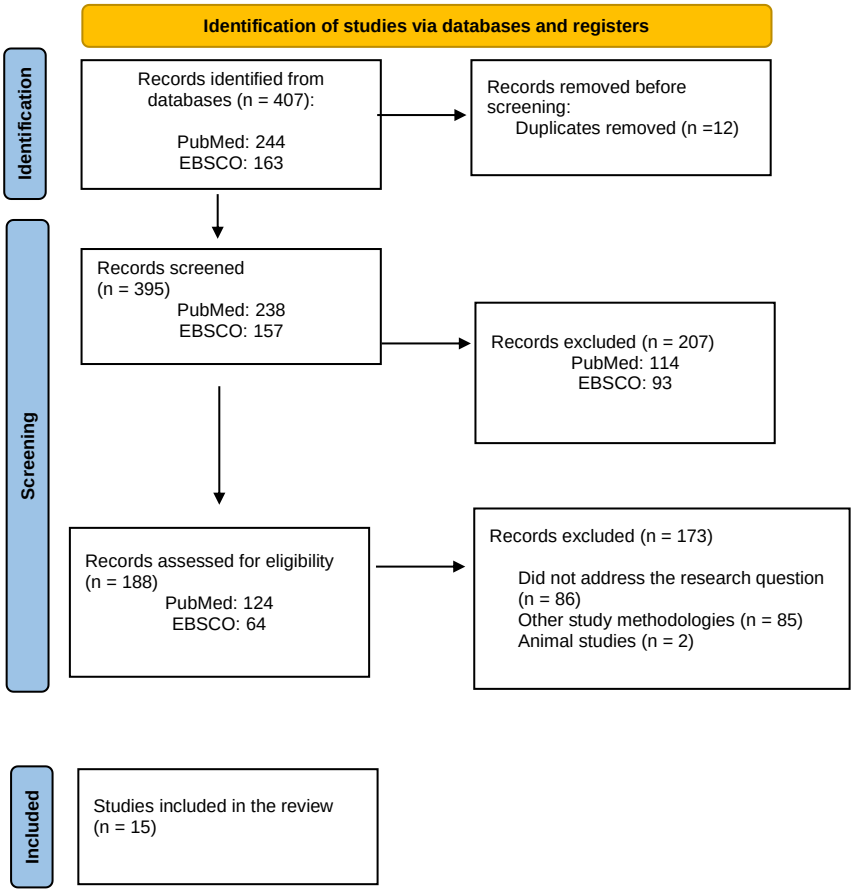
and reviewed by a second reviewer, with disagreements resolved by consensus. The synthesis of this assessment is presented in Chart 3, complementing the AHRQ level of evidence classification.

As this is bibliographic research without direct human participation, submission to the Research Ethics Committee (REC) was not required, in accordance with Resolution No. 466/2012 of the National Health Council, observing the ethical principles related to the reliability of citations and the correct attribution of authorship.

Figure 1. PRISMA Flowchart



Source: Prepared by the authors.

Figure 1 illustrates the process of search, identification, selection, eligibility, and inclusion of studies in the PubMed and EBSCO databases, in accordance with the PRISMA guidelines. A total of 407 records were identified (PubMed: 244; EBSCO: 163), of which 12 duplicates were removed, leaving 395 for screening. After reading

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titles and abstracts, 207 records were excluded for not meeting the eligibility criteria, totaling 188 studies assessed in full. Of these, 173 were excluded for the following reasons: did not address the research question (n = 86), presented methodology distinct from RCTs (n = 85), and were conducted in animals (n = 2). At the end, 15 studies composed the sample of this integrative review.

3. Results and Discussion

In accordance with the heterogeneous nature of the comparators employed in the eligible randomized clinical trials, the sample was structured into two distinct categories according to the direct relation with the guiding question of this review. Chart 1 brings together the studies that compared fentanyl and remifentanil in parallel arms under equivalent anesthetic technique (direct evidence), while Chart 2 presents the studies that evaluated one of the opioids in comparison with agents from other pharmacological classes, distinct doses of the same drug, or alternative technical strategies (indirect or contextual evidence). Such organization allows calibration of the strength of comparative inferences and differentiation of conclusions supported by direct experimental comparison from those based on contextual interpretation.

Chart 1 – Studies with direct comparison between fentanyl and remifentanil (Group A).

STUDY	POPULATION /PROCEDURE	INTERVENTION × COMPARATOR (DOSE/ROUTE)	PRIMARY OUTCOME	MAIN FINDINGS	LIMITATIONS
Choi et al., 2016	90 adult women (ASA I-II); total laparoscopic hysterectomy	F (1.0 µg/kg + 0.4 µg/kg/h IV) vs R (1.0 µg/kg + 0.08 µg/kg/min IV) vs Dexmedetomidine	Hemodynamic stability and postoperative pain (VAS)	Analgesic (VAS p>0.05) and hemodynamic (SBP, DBP, HR p>0.05) equivalence between F and R; comparable adverse events	Follow-up limited to 30 min post-extubation; insufficient to capture late OIHFollow-up limited to 30 min post-extubation; insufficient to capture late OIH

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STUDY	POPULATION /PROCEDURE	INTERVENTION × COMPARATOR (DOSE/ROUTE)	PRIMARY OUTCOME	MAIN FINDINGS	LIMITATIONS
Palumbo et al., 2017	960 adult patients; inguinal hernia repair (day surgery)	F (intermittent IV bolus) vs R (continuous IV infusion) under MAC	Intraoperative analgesic efficacy and postoperative pain	Absence of significant difference in intra- and postoperative pain control; R with favorable profile for early discharge	Low-complexity procedure; not generalizable to larger surgeries
Farzi et al., 2019	84 women of reproductive age; oocyte retrieval for IVF84 women of reproductive age; oocyte retrieval for IVF	F vs R vs Alfentanil (sedative IV doses under general anesthesia)	Hemodynamic parameters and reproductive outcomes	Comparable analgesic quality between F and R; no differences in post-procedural pain scores or recovery time	Short-duration procedure; reproductive outcomes as primary focus
Ding et al., 2019	154 adult patients; laparoscopic surgery for colon cancer	F vs R in combined anesthesia (IV)	Serum cytokines and oxidative stress markers	Lower incidence of nausea, vomiting, shivering, agitation, and cough with R ($p<0.05$); significant reduction of IL-6, IL-8, TNF-α, and CRP with R ($p<0.001$)	Secondary immunoinflammatory outcomes; results specific to oncologic surgery

Source: Prepared by the authors (2026).

Legend: ASA – American Society of Anesthesiologists; F – Fentanyl; IVF – In vitro fertilization; OIH – Opioid-induced hyperalgesia; IV – Intravenous; MAC – Monitored Anesthesia Care; DBP – Diastolic blood pressure; SBP – Systolic blood pressure; HR – Heart rate; R – Remifentanil; VAS – Visual Analogue Scale.

Chart 1 presents the four studies that constitute the core of direct evidence in this review, totaling approximately 1,288 patients evaluated in experimental comparisons between fentanyl and remifentanil under equivalent anesthetic conditions. The findings converge toward analgesic equivalence between the two opioids at sedative doses and in procedures of low to intermediate complexity, supporting robust comparative inferences, although limited by the heterogeneity of

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the surgical contexts evaluated and by the temporal follow-up predominantly restricted to the immediate post-anesthesia recovery period.

Chart 2 – Studies with indirect or contextual evidence (Group B).

STUDY	POPULATION /PROCEDURE	INTERVENTION × COMPARATOR (DOSE/ROUTE)	PRIMARY OUTCOME	MAIN FINDINGS	LIMITATIONS
Weigl et al., 2016	60 parturients; elective cesarean section	Intrathecal F 25 µg vs Bupivacaine alone	Analgesic demand in the first 12 postoperative hours	Significant reduction in rescue opioid consumption and prolongation of effective analgesia	Intra-class comparison (spinal); absence of R arm
Kim S.Y. et al., 2016	64 adult patients; craniotomy for aneurysm clipping	R (TCI 1.5 ng/mL IV) vs Dexmedetomidine	Airway reflex and hemodynamic changes during recovery	Higher MAP (p=0.01) and HR (p=0.04) in PACU with R; lower RR with R at 2 and 5 min post-extubation (p<0.01)	Non-opioid comparator; findings not directly extrapolable to F
Gaszyński et al., 2016	33 morbidly obese patients; bariatric surgery	F (standard IV induction) vs Dexmedetomidine (low-opioid dose)	Hemodynamic response to intubation	No differences in ΔSBP (+11.6 vs +0.4 mmHg; p=0.15), ΔMAP, or ΔHR between groups	Reduced sample size; focus restricted to intubation
Kim N.S. et al., 2018	116 adult patients; thyroidectomy	R high dose (0.32 µg/kg/min IV) vs R moderate dose	Postoperative F consumption in the first 24h	Significant increase in rescue F consumption with high-dose R (973.3 ± 252.5 vs 682.8 ± 212.9 µg)	Intra-class comparison; no intraoperative F arm
Jain et al., 2019	133 adult patients; laparoscopic cholecystectomy	F guided by SPI vs F conventional titration	Intraoperative consumption and postoperative pain	Greater intraop consumption with SPI (169 ± 47.2 vs 151 ± 39.3 µg; p=0.017), lower postop VAS (2.8 ± 2.1 vs 3.4 ± 2.0; p=0.04), and less rescue (p=0.01)	Intra-class comparison (titration technique); no R arm
Pan et al., 2019	84 adult patients; radiofrequency ablation of HCC	R + sevoflurane vs Dexmedetomidine + sevoflurane	Intraoperative hemodynamic stability	Lower HR with D at multiple time points (p<0.05); MAP and hypotension with dopamine without	Non-opioid comparator; findings specific to hepatic

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STUDY	POPULATION /PROCEDURE	INTERVENTION × COMPARATOR (DOSE/ROUTE)	PRIMARY OUTCOME	MAIN FINDINGS	LIMITATIONS
				difference (23.4% vs 34%; p=0.362)	oncologic population
Dolsan et al., 2020	70 adult patients; ambulatory dental surgery	R without muscle relaxant vs SufentanilR without muscle relaxant vs Sufentanil	Intubation conditions and early recovery profile	Aldrete = 10 faster with R (4650 vs 5310 s; p=0.029); MAP drop >20% in 62.2% (R) vs 27.8% (S) (p=0.006)	Distinct opioid comparator; absence of F arm
Lai et al., 2021	82 adult patients; percutaneous transluminal angioplasty (MAC)	R 1.0 ng/mL + midazolam vs R 2.0 ng/mL + midazolam (TCI)	Effective target concentration and respiratory safety	Higher concentration provided better comfort, with greater incidence of adverse respiratory events	Intra-class comparison (concentrations); no F arm
Kaya et al., 2022	80 geriatric patients (65–80 years); ambulatory cataract surgery	R (continuous IV infusion) vs Dexmedetomidine under conscious sedation	Adverse respiratory events and hemodynamic stability	RD 25% (R) vs 0% (D) (p=0.02); SpO_2 and RR lower with R (p<0.05); esmolol in 27.5% (R) vs 5% (D) (p=0.015)	Non-opioid comparator; specific geriatric population
Won et al., 2023	Adult patients; general surgical procedure	R guided by SPI vs R conventional titrationR guided by SPI vs R conventional titration	Perioperative dose and postoperative pain	Significant reduction in intraoperative consumption and incidence of adverse respiratory events with SPI	Intra-class comparison (titration technique); no F arm
Moghadam et al., 2024	62 adult patients; total knee arthroplasty	R (IV PCA) vs IV Acetaminophen (Apotel) (PCA) R (IV PCA) vs IV Acetaminophen (Apotel) (PCA)	Pain control in 24h postop (VAS) and rescue opioid consumption	Lower VAS with R (p<0.001); longer time to first rescue (p<0.001); lower cumulative consumption (4.68 ± 2.87 vs 8.71 ± 3.64 mg; p<0.001)	Non-opioid comparator; absence of F arm

Source: Prepared by the authors (2026).

Legend: HCC – Hepatocellular carcinoma; D – Dexmedetomidine; RD – Respiratory depression; F – Fentanyl; HR – Heart rate; RR – Respiratory rate; OIH – Opioid-induced hyperalgesia; IV – Intravenous; MAC – Monitored Anesthesia Care; MAP – Mean arterial pressure; SBP – Systolic blood pressure; PCA – Patient-controlled analgesia; R – Remifentanil; S – Sufentanil; SPI – Surgical Pleth Index; SpO_2 – Peripheral oxygen saturation; PACU – Post-anesthesia care unit; TCI – Target-controlled infusion; VAS – Visual Analogue Scale.

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Chart 2 gathers eleven studies that, although not performing direct comparison between fentanyl and remifentanil, offer relevant contextual evidence through three modalities of comparison: studies with remifentanil or fentanyl against non-opioid agents, especially dexmedetomidine (five trials); studies with intra-class comparison evaluating different doses or titration techniques of the same opioid (four trials); and studies with comparison against other opioids or non-conventional agents (two trials). Such studies do not allow direct inferences regarding the relative superiority between fentanyl and remifentanil, but illuminate pharmacological, safety, and clinical application aspects that enrich the interpretation of the Group A findings. Conclusions derived from these studies are presented, throughout the subsequent subsections, with cautious formulations that distinguish indirect inference from direct experimental evidence.

The rational choice of opioids in anesthetic practice remains a topic of continuous debate, considering the multiplicity of surgical scenarios, population profiles, and perioperative objectives. Fentanyl and remifentanil constitute the most widely used representatives of rapid-acting synthetic opioids, fundamentally differing in their pharmacokinetic properties. While fentanyl presents a context-sensitive half-life that progressively increases with infusion duration, reaching approximately 260 minutes after 8 hours of continuous infusion in humans — conferring postoperative residual analgesia mediated by tissue redistribution —, remifentanil is characterized by extracellular metabolism via nonspecific esterases present in plasma and tissues, resulting in a constant context-sensitive half-life of 3 to 4 minutes regardless of infusion duration, with consequent rapid and predictable dissipation of effect after interruption (Beers; Camporesi, 2004; Kim et al., 2018).

Such pharmacokinetic distinctions directly imply the choice of the most appropriate opioid for each clinical context, considering both analgesic efficacy and the safety profile. The present integrative review analyzed 15 randomized clinical trials, published between 2016 and 2024, retrieved through the search strategy described in the previous section (window 2015–2025), aiming to compare fentanyl and remifentanil regarding efficacy in perioperative pain control and hemodynamic and respiratory safety. Publications prior to 2015 were used exclusively as

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ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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theoretical reference supporting pharmacological contextualization and discussion of findings, not composing the sample submitted to comparative analysis.

The analysis of the included studies was organized into four thematic axes — analgesic efficacy, hemodynamic profile, respiratory safety, and specific clinical applications — presented in the subsequent subsections, with careful weighing of direct evidence (Group A) and indirect evidence (Group B) in supporting comparative inferences.

Chart 3 – Semi-structured risk-of-bias assessment of the included randomized clinical trials.

STUDY	Randomization	Allocation Concealment	Blinding	Losses/Exclusions	ITT	Selective Reporting	OVERALL RISK
Choi et al., 2016	L	SC	L	L	L	L	Low
Palumbo et al., 2017	SC	SC	SC	SC	SC	L	Some concerns
Farzi et al., 2019	L	L	L	L	L	L	Low
Ding et al., 2019	L	SC	SC	L	SC	L	Some concerns
Weigl et al., 2016	L	L	L	L	L	L	Low
Kim S.Y. et al., 2016	L	SC	SC	L	L	L	Some concerns
Gaszyński et al., 2016	SC	SC	H	SC	SC	SC	High
Kim N.S. et al., 2018	L	L	L	L	L	L	Low
Jain et al., 2019	L	L	L	L	L	L	Low
Pan et al., 2019	L	SC	SC	L	L	L	Some concerns

REMUNOM
ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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STUDY	Randomization	Allocation Concealment	Blinding	Losses/Exclusions	ITT	Selective Reporting	OVERALL RISK
Dolsan et al., 2020	L	L	SC	L	L	L	Some concerns
Lai et al., 2021	L	SC	SC	L	SC	L	Some concerns
Kaya et al., 2022	L	SC	L	L	L	L	Some concerns
Won et al., 2023	L	SC	SC	L	L	L	Some concerns
Moghadam et al., 2024	L	L	L	L	L	L	Low

Source: Prepared by the authors (2026)

Legend: L – Low risk; SC – Some concerns; H – High risk; ITT – Intention-to-treat analysis. Domains assessed: randomization, allocation concealment, blinding of participants/personnel/assessors, reported losses and exclusions, intention-to-treat analysis, and selective outcome reporting.

The semi-structured risk-of-bias assessment revealed that the majority of included randomized clinical trials present adequately described randomization and minimal blinding of assessors, conferring moderate robustness to the findings. However, recurrent methodological concerns are observed in three main domains: allocation concealment not explicitly reported in a significant portion of the studies; incomplete blinding of personnel and participants, particularly in studies under conscious sedation, in which integral blinding is technically challenging; and absence of description of intention-to-treat analysis in some trials. The overall assessment classified five studies as low risk of bias (Choi et al., 2016; Kim N.S. et al., 2018; Farzi et al., 2019; Jain et al., 2019; Moghadam et al., 2024), nine with some methodological concerns, and one with high risk of bias (Gaszyński et al., 2016, due to the reduced sample size and absence of adequate blinding). Such limitations reinforce the need for caution in weighing the findings and justify the qualitative interpretation adopted in this integrative review, with special attention to studies classified as low risk to support more robust comparative inferences.

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ISSN 2178-6925

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3.1 Comparative Analgesic Efficacy

The interpretation of postoperative opioid consumption following intraoperative exposure to remifentanil requires distinction between four pharmacologically distinct phenomena, although frequently coexistent (Yu; Cope; Pinto, 2016; Santonocito et al., 2018). Opioid-induced hyperalgesia (OIH) consists of paradoxical pro-nociceptive sensitization mediated by glutamatergic activation of NMDA receptors and plasticity of the spinal dorsal horn, manifesting as expansion of the painful area and paradoxical worsening of pain with dose increase. Acute tolerance corresponds to pharmacodynamic reduction of analgesic response during infusion, being compensable by dose increment, and also affects adverse effects such as respiratory depression and sedation. Rebound pain by abrupt offset is a pharmacokinetic phenomenon resulting from the sudden dissipation of effect after remifentanil cessation. Failure of multimodal transition analgesia translates inadequacy of perioperative planning, configuring a logistical deficiency rather than a biological phenomenon of the opioid. Increased postoperative consumption following remifentanil may reflect these mechanisms in isolation or in combination, and the literature rarely discriminates them, limiting causal inferences (Kim et al., 2018).

Choi et al. (2016), in a double-blind trial with 90 patients undergoing laparoscopic hysterectomy, compared fentanyl (1.0 µg/kg bolus + 0.4 µg/kg/h) versus remifentanil (1.0 µg/kg bolus + 0.08 µg/kg/min) versus dexmedetomidine. VAS scores did not differ between fentanyl and remifentanil at any of the time points evaluated in the post-anesthesia care unit (5, 10, 20, and 30 minutes; $p > 0.05$), evidencing analgesic equivalence at sedative doses. Farzi et al. (2019) corroborated these findings in 84 patients undergoing oocyte retrieval, without significant differences in post-procedural pain scores. Palumbo et al. (2017), in a series of 960 patients in day surgery for inguinal hernia under MAC, also documented absence of significant difference between fentanyl and remifentanil in intra- and postoperative pain control.

Discordant findings emerge in scenarios of prolonged analgesia or intense inflammatory stimulus. Moghadam et al. (2024), in 62 patients undergoing total knee

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ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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arthroplasty, demonstrated that patient-controlled analgesia with remifentanil was superior to intravenous acetaminophen (Apotel) in pain control over 24 hours, with lower VAS ($p < 0.001$), longer time to first rescue ($p < 0.001$), and lower cumulative consumption (4.68 ± 2.87 vs 8.71 ± 3.64 mg; $p < 0.001$). Weigl et al. (2016), in 60 parturients undergoing elective cesarean section, demonstrated that the addition of intrathecal fentanyl (25 µg) to bupivacaine reduced rescue opioid consumption during the first 12 postoperative hours, illustrating the clinical value of fentanyl's residual analgesia in obstetric contexts.

Studies with high doses of remifentanil suggest important nuances. Kim et al. (2018), in 116 patients undergoing thyroidectomy, observed that high intraoperative infusion (mean 0.32 µg/kg/min; total 973.3 ± 252.5 µg) was associated with greater fentanyl consumption in the first 24 postoperative hours compared to moderate doses (682.8 ± 212.9 µg), a phenomenon attributed to OIH. Jain et al. (2019) demonstrated in 133 patients undergoing laparoscopic cholecystectomy that fentanyl titration guided by Surgical Pleth Index (SPI) resulted in greater intraoperative consumption (169 ± 47.2 vs 151 ± 39.3 µg; $p = 0.017$), yet with lower VAS in recovery (2.8 ± 2.1 vs 3.4 ± 2.0; $p = 0.04$) and reduced need for rescue (36.0 ± 16.7 vs 43.0 ± 15.3 µg; $p = 0.01$), evidencing a dose-dependent relationship between intraoperative analgesic adequacy and postoperative analgesia quality.

The scarcity of direct comparisons between the two opioids under equivalent conditions constitutes a relevant methodological limitation. The Choi et al. (2016) study, although solid, presents follow-up limited to 30 minutes, a period insufficient to capture phenomena such as OIH, which typically manifests hours after interruption (Kim et al., 2018). Therefore, the equivalence observed should be interpreted within the context of sedative doses, short periods, and specific populations, not authorizing indiscriminate generalization.

3.2 Hemodynamic Profile

Perioperative hemodynamic stability constitutes a critical safety parameter in the selection of opioids for general anesthesia, particularly in vulnerable populations or neurosurgical procedures in which pressure fluctuations

REMUNOM
ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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represent elevated risk of complications. In the study with direct comparison between fentanyl and remifentanil at sedative doses, Choi et al. (2016) did not identify statistically significant differences in systolic blood pressure, diastolic blood pressure, or heart rate values at any of the time points evaluated during laparoscopic hysterectomy ($p > 0.05$ for all comparisons), demonstrating hemodynamic equivalence between the two opioids in the context of continuous infusions during intermediate-complexity procedures. Such a finding contradicts the initial hypothesis that remifentanil would offer systematic advantage in intraoperative autonomic stability compared to fentanyl, suggesting that both opioids, when adequately titrated, provide comparable control of the sympathetic response to surgical stimuli. The incidence of cardiovascular adverse events was comparable between groups, with arterial hypotension (SBP < 80 mmHg) occurring in 3.3% of patients in the fentanyl group versus 6.7% in the remifentanil group, and bradycardia (HR < 40 bpm) in 3.3% versus 10%, respectively, without reaching statistical significance in any of the comparisons.

Gaszyński et al. (2016), in a randomized clinical trial with 42 morbidly obese patients undergoing bariatric surgery (with 33 patients included in the final analysis), compared the hemodynamic response to intubation between induction with fentanyl and induction with low-dose opioid associated with dexmedetomidine, finding no significant differences between groups in deltas of systolic blood pressure (+11.6 mmHg in the fentanyl group versus +0.4 mmHg in the dexmedetomidine group; $p = 0.15$), mean arterial pressure, or heart rate, evidencing that fentanyl did not offer advantage over strategies with reduced opioid use in attenuating the sympathetic response to laryngoscopy in this population.

However, studies that compared remifentanil with other sedatives evidenced distinct hemodynamic patterns suggesting specific vulnerabilities of remifentanil in the transition period between intraoperative and post-anesthesia recovery. Kim et al. (2016), evaluating 64 patients undergoing craniotomy for cerebral aneurysm clipping, observed that the remifentanil group presented significantly higher mean arterial pressure ($p = 0.01$) and heart rate ($p = 0.04$) values upon PACU admission compared to the dexmedetomidine group, a phenomenon interpreted by the authors

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ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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as a hypertensive rebound effect secondary to the abrupt cessation of remifentanil infusion — a finding of particular clinical relevance in neurosurgical patients, in whom hypertensive peaks in the immediate postoperative period increase the risk of intracranial rebleeding.

Corroborating these findings, Kaya et al. (2022) documented in geriatric patients undergoing ambulatory ophthalmologic surgery that the need for pharmacological intervention to control arterial hypertension (esmolol administration) was significantly higher in the remifentanil group compared to the dexmedetomidine group (27.5% versus 5%; p = 0.015), reinforcing the hypothesis of greater pressure instability associated with the ultra-rapid offset of remifentanil.

Regarding hypotensive complications, Dolsan et al. (2020) identified in a randomized clinical trial with 70 patients undergoing ambulatory dental surgery that the remifentanil bolus at anesthesia induction was associated with drops in mean arterial pressure greater than 20% from baseline in 62.2% of cases, against 27.8% in the sufentanil group (p = 0.006), although the absolute blood pressure values remained clinically acceptable (no episode of MAP below 67 mmHg) and without differential need for vasopressors between groups.

Pan et al. (2019), evaluating 84 patients undergoing hepatic radiofrequency ablation, reported significantly lower heart rate in the dexmedetomidine group compared to the remifentanil group at multiple intraoperative and PACU time points ($p < 0.05$), without significant differences in mean arterial pressure or in the incidence of hypotension requiring dopamine (23.4% versus 34%; p = 0.362).

Lai et al. (2021), in a randomized clinical trial comparing two target concentrations of remifentanil (1.0 versus 2.0 ng/mL) associated with intermittent midazolam boluses during percutaneous transluminal angioplasty under MAC, demonstrated that the higher target concentration provided better patient comfort, however at the cost of greater incidence of adverse respiratory events, a dose-dependent pattern that reinforces the narrow therapeutic window of the drug in patients under conscious sedation.

These findings, taken together, suggest that although fentanyl and remifentanil are equivalent in hemodynamic stability when administered as titrated

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ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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continuous infusions during the intraoperative period, remifentanil presents greater propensity to cardiovascular instability during pharmacological transitions — specifically at induction (post-bolus hypotension) and at anesthetic emergence (hypertensive rebound after cessation of infusion) — a profile that demands careful anesthetic planning and intensified hemodynamic vigilance during critical periods.

3.3 Respiratory Safety

Respiratory depression constitutes a potentially serious complication associated with opioid use in the perioperative period, particularly relevant in ambulatory contexts, geriatric populations, and patients without protected airways. The interpretation of findings on adverse respiratory events requires stratification by anesthetic context, given that the risk and management of respiratory depression differ substantially between general anesthesia with protected airway — in which ventilation is controlled and the event is managed in an assisted environment — and conscious sedation or MAC without advanced airway — in which clinical risk is amplified by the absence of immediate ventilatory support. Studies that evaluated remifentanil in comparison with other non-opioid sedatives revealed a concerning respiratory safety profile in certain populations.

In contexts of conscious sedation without advanced airway, Kaya et al. (2022), in a double-blind randomized clinical trial with 80 geriatric patients (65 to 80 years) undergoing ambulatory cataract surgery, documented an incidence of respiratory depression of 25% in the remifentanil group versus 0% in the dexmedetomidine group ($p = 0.02$), characterizing substantial risk in a vulnerable population without protected airway. Furthermore, peripheral oxygen saturation and respiratory rate values were significantly lower in the remifentanil group at multiple intraoperative time points ($p < 0.05$ for both parameters), evidencing persistent respiratory compromise during sedation. This finding signals dose-dependent risk even in the context of conscious sedation, broadening clinical concern beyond traditional general anesthesia scenarios.

Corroborating such findings and pointing to mitigation strategies, Won et al. (2023) demonstrated that remifentanil administration guided by SPI significantly

REMUNOM
ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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reduced both the perioperative dose of the opioid and the incidence of adverse respiratory events postoperatively. This finding suggests that individualization of the dose based on objective nociception monitoring may attenuate the respiratory risk profile of remifentanil, representing a promising alternative to empirical regimens based on hemodynamic response, especially in populations vulnerable to opioid-induced respiratory depression.

In patients under general anesthesia with protected airway, remifentanil also demonstrated clinically relevant residual respiratory effects in the post-anesthesia recovery period. Kim et al. (2016) observed in 64 patients undergoing craniotomy for cerebral aneurysm clipping that respiratory rate was significantly lower in the remifentanil group at two and five minutes after tracheal extubation compared to the dexmedetomidine group ($p < 0.01$), characterizing transient respiratory depression that, although self-limited, represents an additional concern in neurosurgical patients in whom hypercapnia may elevate intracranial pressure and compromise neurological outcomes.

Regarding gastrointestinal adverse events, Kaya et al. (2022) reported significantly higher incidence of nausea in the immediate postoperative period among patients who received remifentanil ($p < 0.05$ at 40 and 45 minutes), a finding consistent with the well-known emetogenic profile of mu-opioid agonists. The Choi et al. (2016) study did not identify significant differences in the incidence of postoperative nausea or vomiting between fentanyl and remifentanil at sedative doses during laparoscopic hysterectomy (10% in both groups; $p > 0.05$). Paradoxically, Ding et al. (2019), in a randomized clinical trial with 154 patients undergoing laparoscopic surgery for colon cancer, documented lower incidence of nausea, vomiting, shivering, agitation, cough, and tachycardia during anesthetic recovery in the remifentanil group compared to the fentanyl group ($p = 0.029$, 0.016, 0.009, 0.025, and 0.003, respectively), in addition to reporting significant reduction in serum levels of pro-inflammatory cytokines (IL-6, IL-8, TNF-α, CRP) and oxidative stress markers in the remifentanil group (all $p < 0.001$). These findings suggest that, in specific contexts with intense inflammatory stimulus, remifentanil may offer a favorable profile of modulation of the surgical stress response, although the

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ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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heterogeneity of outcomes among studies prevents definitive conclusions.

The integrated analysis reveals clear dissociation between two distinct anesthetic contexts. In general anesthesia with protected airway, fentanyl and remifentanil present comparable incidences of nausea, vomiting, and moderate respiratory depression, with management facilitated by controlled ventilatory support. By contrast, in conscious sedation or MAC without advanced airway, remifentanil was associated with substantially elevated rates of respiratory compromise, particularly in vulnerable populations such as the elderly, configuring a scenario of amplified risk due to the absence of immediate ventilatory support. Neurosurgical patients at anesthetic emergence represent an additional category of vulnerability, even under protected airway, given the risk of transient hypercapnia upon intracranial pressure. Such findings reinforce the need for contextual stratification of respiratory risk, with amplified caution and rigorous ventilatory monitoring in scenarios without advanced airway, recognizing that the pharmacokinetic advantage of remifentanil's ultra-rapid offset does not eliminate the risk of transient respiratory depression in the critical window following infusion cessation.

3.4 Specific Clinical Applications

The contrasting pharmacokinetic characteristics between fentanyl and remifentanil determine clinical application niches in which each drug demonstrates relative advantages, transcending the comparative analysis of efficacy and safety under controlled conditions to contemplate specific surgical and population scenarios. Remifentanil, characterized by a constant context-sensitive half-life of three to four minutes regardless of infusion duration due to metabolism by nonspecific plasma esterases, presents a kinetic profile theoretically ideal for short-duration procedures in which rapid recovery is a priority. Dolsan et al. (2020) documented in 70 patients undergoing ambulatory dental surgery that the time to reach an Aldrete score of 10 — a criterion for discharge from PACU — was significantly shorter in the remifentanil group compared to the sufentanil group (4,650 seconds versus 5,310 seconds; p = 0.029), corroborating the advantage of

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ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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ultra-rapid offset in ambulatory contexts that demand high turnover.

Palumbo et al. (2017), in a randomized series with 960 patients undergoing inguinal hernia repair in day surgery, reinforced the role of remifentanil under MAC as a safe and effective anesthetic strategy in this context, highlighting the profile of few adverse effects and optimal hemodynamic stability that facilitate early discharge. However, this same pharmacokinetic characteristic imposes a substantial challenge: the abrupt cessation of intraoperative analgesia in the absence of an adequate transition strategy.

In contrast, fentanyl, with a context-sensitive half-life of approximately 260 minutes after eight hours of continuous infusion, provides prolonged residual analgesia that may be advantageous in major surgeries in which intense postoperative pain is anticipated. Jain et al. (2019) demonstrated in 133 patients undergoing laparoscopic cholecystectomy that objective titration of fentanyl guided by SPI — resulting in greater intraoperative consumption (169 ± 47.2 µg versus 151 ± 39.3 µg in the conventional group; p = 0.017) — was paradoxically associated with lower VAS scores in recovery (2.8 ± 2.1 versus 3.4 ± 2.0; p = 0.04) and reduced need for rescue fentanyl (36.0 ± 16.7 µg versus 43.0 ± 15.3 µg; p = 0.01), evidencing that intraoperative analgesic adequacy with titrated doses of fentanyl positively impacts the quality of analgesia in the immediate recovery period.

Such a finding contrasts with the frequently raised hypothesis that higher intraoperative opioid doses would necessarily elevate postoperative demand, instead suggesting a favorable dose-response relationship when titration is objectively guided. Moghadam et al. (2024) expanded this perspective by demonstrating, in patients undergoing total knee arthroplasty, that patient-controlled analgesia with remifentanil provided sustained pain control over 24 hours, challenging the traditional notion that the drug's ultra-rapid offset would render it unsuitable for prolonged postoperative analgesia when administered as controlled continuous infusion.

Specific populations demand additional considerations in the selection between fentanyl and remifentanil. In neurosurgical patients, the hemodynamic instability at anesthetic emergence observed with remifentanil (hypertensive

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ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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rebound documented by Kim et al., 2016) suggests the need for caution in its use, particularly in contexts requiring rigorous pressure control for the prevention of intracranial rebleeding and cerebral edema, without such a finding alone configuring absolute contraindication. It should be noted that this evidence derives from comparison with dexmedetomidine, not directly with fentanyl, recommending contextual interpretation.

In geriatric patients undergoing procedures under conscious sedation, the 25% respiratory depression rate documented by Kaya et al. (2022) with remifentanil signals relevant clinical concern, recommending caution in its routine use in this population — preferably accompanied by advanced ventilatory monitoring — or consideration of non-opioid alternatives or reduced doses of fentanyl. It is important to highlight that this finding derives from comparison with dexmedetomidine, not allowing, by itself, definitive conclusions about comparative superiority of fentanyl in this context.

In morbidly obese patients, Gaszyński et al. (2016) demonstrated that strategies of low-dose opioid associated with dexmedetomidine may effectively replace fentanyl-based regimens in the attenuation of the response to intubation, considering the increased risk of postoperative respiratory insufficiency induced by opioids in this population. In patients undergoing interventional procedures under conscious sedation, Lai et al. (2021) evidenced the need for careful titration of remifentanil in TCI regimen to balance comfort and respiratory safety. On the other hand, in monitored anesthesia care procedures requiring titratable sedation with rapid awakening for intraoperative neurological evaluation, such as craniotomies for resection of lesions in eloquent areas, remifentanil maintains an advantage due to superior controllability, provided it is coupled with multimodal analgesic planning that prevents painful gap after cessation. In the obstetric context, Weigl et al. (2016) demonstrated that the addition of intrathecal fentanyl to spinal anesthesia for cesarean section represents an effective strategy for perioperative analgesia, exemplifying clinical application distinct from intravenous findings and reinforcing the versatility of fentanyl as a neuraxial adjuvant in specific populations.

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ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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3.5 Methodological Limitations

The interpretation of the findings of this review requires recognition of methodological limitations inherent to the included studies. The first lies in the scarcity of RCTs with direct comparison between the two opioids under equivalent conditions: only three studies (Choi et al., 2016; Farzi et al., 2019; Palumbo et al., 2017) evaluated fentanyl and remifentanil as parallel arms under identical anesthetic technique, and one (Ding et al., 2019) performed direct comparison in combined anesthesia for oncologic surgery. Most of the remaining studies compared one of the opioids with agents from distinct pharmacological classes, notably dexmedetomidine, hindering direct inferences about relative advantages, since observed differences may reflect intrinsic properties of the non-opioid comparators.

The heterogeneity of surgical and population contexts constitutes a second relevant limitation. The studies covered procedures of markedly distinct durations and complexities — from ambulatory ophthalmologic surgery (Kaya et al., 2022) to craniotomy (Kim et al., 2016), oncologic laparoscopic surgery (Ding et al., 2019), bariatric surgery (Gaszyński et al., 2016), and hepatic ablation (Pan et al., 2019) — with populations ranging from young parturients to ASA III elderly patients and morbidly obese patients, compromising the homogeneity necessary for quantitative meta-analysis. Dosing regimens also varied substantially: fentanyl between 1.0 µg/kg in single bolus (Choi et al., 2016) and SPI-guided titration schemes (Jain et al., 2019), and remifentanil between target concentrations of 1.0 to 2.0 ng/mL in TCI (Lai et al., 2021) and continuous infusion of 0.05 µg/kg/min (Kaya et al., 2022), hindering direct dose-dependent comparisons.

Limited temporal follow-up represents a third limitation. Most studies evaluated analgesic outcomes exclusively in the immediate post-anesthesia recovery period (30 to 60 minutes), without systematic evaluation in the first 24 or 48 hours — a critical window for identification of late phenomena such as OIH. Choi et al. (2016), the study of greatest comparative representativeness, evaluated pain scores only up to 30 minutes. Notable exceptions were Moghadam et al. (2024) and Weigl et al. (2016), with follow-up extended to 24 hours.

Additionally, only a portion of the studies reported adequate blinding of the

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ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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executing anesthesiologist, with most maintaining blinding only of the assessor and patient, introducing potential performance bias. Finally, the absence of standardization of multimodal analgesia among studies constitutes a confounding factor that limits the causal attribution of observed differences exclusively to the investigated opioids.

3.6 Clinical Implications

The integrated analysis of the included randomized clinical trials allows the delineation of practical guidelines for rational selection between fentanyl and remifentanil in different anesthetic contexts, based on evidence about analgesic efficacy, hemodynamic profile, respiratory safety, and pharmacokinetic characteristics. The consolidated findings reinforce that the choice between the two opioids must transcend purely pharmacokinetic considerations, incorporating careful analysis of the individual risk profile of the patient and the specific characteristics of the surgical procedure.

In intermediate-complexity surgical procedures under balanced general anesthesia in healthy adult patients, fentanyl and remifentanil demonstrated equivalence in perioperative pain control and hemodynamic stability when administered at adequately titrated sedative doses, with comparable incidences of nausea, vomiting, and cardiovascular events, supporting selection based on secondary considerations such as cost, institutional familiarity, and preparation logistics. However, this equivalence does not extend uniformly to all populations and clinical scenarios, with specific contexts emerging in which differences in pharmacological profile translate into clinically significant relative advantages.

First, in short-duration ambulatory procedures in which early discharge from PACU constitutes an operational priority, such as inguinal hernia repair (Palumbo et al., 2017) and dental surgery (Dolsan et al., 2020), remifentanil offers an advantage due to faster recovery and awakening with less residual sedation, provided that a rigorous transition analgesic strategy is implemented — ideally involving multimodal analgesia with regional blocks, NSAIDs, and acetaminophen administered prophylactically — to prevent a painful window following the abrupt cessation of

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ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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infusion.

Second, in neurosurgical patients, the hemodynamic instability at anesthetic emergence associated with remifentanil, manifested as hypertensive rebound and tachycardia upon PACU admission (Kim et al., 2016), recommends caution in its use in this context, suggesting that titrated fentanyl or non-opioid agents such as dexmedetomidine may constitute advantageous alternatives, particularly when rigorous pressure control is a clinical priority. The definitive choice, however, must consider additional variables such as the need for rapid awakening for neurological evaluation, individual patient profile, and institutional protocols.

Third, in geriatric patients undergoing conscious sedation without advanced airway, the 25% respiratory depression rate documented with remifentanil (Kaya et al., 2022) signals clinical concern that recommends caution in its routine use in this scenario — requiring, when selected, continuous ventilatory monitoring and a team trained for management of respiratory events — or preferential consideration of alternatives with less respiratory impact, such as dexmedetomidine.

Fourth, in morbidly obese patients, strategies of low-dose opioid associated with dexmedetomidine prove equally effective to fentanyl in attenuation of the response to intubation (Gaszyński et al., 2016), offering a clinically relevant alternative given the greater vulnerability of this population to postoperative respiratory depression.

Fifth, in obstetric contexts, intrathecal fentanyl as an adjuvant to spinal bupivacaine for cesarean section emerges as an effective strategy for perioperative analgesia (Weigl et al., 2016), with an acceptable maternal and neonatal safety profile.

Beyond pharmacological considerations, the choice between fentanyl and remifentanil must incorporate logistical, economic, and institutional variables rarely addressed in clinical trials. Remifentanil requires mandatory administration by calibrated infusion pump — preferably in target-controlled infusion (TCI) regimen — , a team trained in dynamic titration, continuous hemodynamic and respiratory monitoring, and a structured multimodal transition analgesia protocol, requirements that may be limiting in lower-complexity services or in emergency scenarios.

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Additionally, the direct cost per procedure is substantially higher, particularly in prolonged surgeries. Fentanyl, in contrast, presents greater institutional availability, reduced cost, consolidated clinical familiarity, and flexibility of administration (intermittent bolus, continuous infusion, intrathecal and epidural routes), although it demands caution regarding tissue accumulation in prolonged infusions and the risk of residual respiratory depression postoperatively. Such institutional and economic variables, although not captured in the primary clinical outcomes of the analyzed studies, integrate the real decision-making of the anesthesiologist and should be explicitly considered in opioid selection protocols, especially in healthcare systems with resource restrictions or heterogeneous assistance complexity.

Evidence gaps identified in this review point to directions for future investigations. The scarcity of randomized clinical trials with direct comparison fentanyl versus remifentanil in samples adequately sized for subgroup analyses, particularly in high-risk populations such as the elderly, the morbidly obese, patients with obstructive sleep apnea syndrome, and carriers of chronic obstructive pulmonary disease, limits the capacity to formulate specific recommendations based on robust evidence. Additionally, studies with follow-up extended to the first 24 to 48 postoperative hours are necessary for definitive evaluation of dose-dependent phenomena such as opioid-induced hyperalgesia and impact on global recovery quality, outcomes that follow-ups limited to immediate PACU do not adequately capture. The investigation of titration regimens guided by objective nociception monitoring, such as Surgical Pleth Index or nociceptive evoked potentials, applied to both fentanyl and remifentanil in direct comparative studies, may elucidate whether differences observed in analgesic efficacy reflect intrinsic pharmacological properties or adequacy of titration to individual nociceptive stimuli. Finally, findings such as the favorable modulation of pro-inflammatory cytokines documented by Ding et al. (2019) in oncologic surgery open a new field of investigation about immunomodulatory effects of perioperative opioids and their potential impact on long-term oncologic outcomes.

4. Conclusion

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ISSN 2178-6925

Received: 13/03/2026 - **Accepted:** 13/05/2026
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The present integrative review evidenced that the rational choice between fentanyl and remifentanil depends less on a hierarchy of absolute superiority than on the contextual adequacy of each pharmacokinetic profile to the specific clinical scenario, considering that only four of the fifteen included studies performed direct comparison between the two opioids. At titrated sedative doses during balanced general anesthesia in healthy adult patients, both opioids presented equivalence regarding immediate postoperative analgesic efficacy and intraoperative hemodynamic stability — an equivalence that, nevertheless, does not extend to all clinical scenarios.

In short-duration outpatient procedures, remifentanil presented contextual advantage, conditioned upon the implementation of multimodal transition analgesia. The indirect evidence suggests that fentanyl may offer advantages in major surgeries, neurosurgical patients, and as a neuraxial adjuvant in obstetric anesthesia. The scarcity of direct comparisons in high-risk populations, the heterogeneity of comparators, and the temporally restricted follow-up constitute the main limitations of the available evidence.

It is concluded that fentanyl and remifentanil constitute complementary pharmacological tools, whose selection requires careful and contextual individualization, the current evidence not authorizing unrestricted interchangeability between the drugs.

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