Anesthetic Management in Patients with Opioid Hypersensitivity Syndrome

Manejo Anestésico em Pacientes com Síndrome de Hipersensibilidade a Opióides
Manejo Anestésico en Pacientes con Síndrome de Hipersensibilidad a los Opioides

RESUMO

Introdução: A hipersensibilidade a opioides representa um desafio crescente na anestesiologia moderna, podendo manifestar-se desde reações pseudoalérgicas até anafilaxia intraoperatória grave. A necessidade de protocolos seguros e individualizados tem impulsionado o desenvolvimento de estratégias analgésicas alternativas e de anestesia livre de opioides. **Métodos:** Foi conduzida uma revisão sistematizada da literatura segundo as recomendações do PRISMA 2020, com busca na base PubMed (Free full text, 2020–2025). Foram incluídos artigos originais, revisões, relatos de caso e ensaios clínicos que abordassem o manejo anestésico de pacientes com hipersensibilidade, intolerância ou hiperalgesia induzida por opioides. **Resultados:** Dos 303 artigos inicialmente identificados, 13 preencheram os critérios de elegibilidade. Destes, nove apresentaram aplicabilidade direta e quatro indireta. Os estudos evidenciaram que a anestesia livre de opioides (Opioid-Free Anesthesia – OFA) com dexmedetomidina, cetamina, lidocaína EV e bloqueios periféricos oferece analgesia eficaz e estável. Casos clínicos reforçaram a importância da avaliação pré-anestésica detalhada, da identificação de reações cruzadas e da disponibilidade de suporte avançado de vida em anafilaxias. **Conclusão:** O manejo anestésico de pacientes com hipersensibilidade a opioides deve basear-se em três eixos: prevenção, substituição farmacológica e individualização analgésica. Estratégias multimodais e opioid-free reduzem riscos imunológicos e nociceptivos, promovendo maior segurança e qualidade perioperatória.
DESCRITORES: Hipersensibilidade a opioides; Anestesia livre de opioides; Hiperalgesia induzida por opioides; Anafilaxia perioperatória; Analgesia multimodal.

ABSTRACT

Introduction: Opioid hypersensitivity represents an emerging challenge in modern anesthesiology, ranging from pseudoallergic reactions to severe intraoperative anaphylaxis. The growing need for safe and individualized protocols has driven the adoption of multimodal analgesia and opioid-free anesthesia strategies. **Methods:** A systematic review was conducted following PRISMA 2020 guidelines. Searches were performed in PubMed (Free full text, 2020–2025), including original studies, reviews, case reports, and clinical trials addressing anesthetic management of patients with opioid hypersensitivity, intolerance, or opioid-induced hyperalgesia. **Results:** From 303 initial records, 13 studies met the eligibility criteria, nine with direct applicability and four indirect. Evidence supports that opioid-free anesthesia (OFA) using dexmedetomidine, ketamine, intravenous lidocaine, and regional blocks provides effective and hemodynamically stable analgesia. Clinical reports highlighted the importance of detailed pre-anesthetic assessment, recognition of cross-reactivity, and immediate availability of advanced life support for perioperative anaphylaxis. **Conclusion:** The anesthetic management of patients with opioid hypersensitivity should rely on three key pillars: prevention, pharmacologic substitution, and individualized analgesia. Multimodal and opioid-free approaches reduce immunologic and nociceptive risks, enhancing perioperative safety and patient outcomes.
DESCRIPTORS: Opioid hypersensitivity; Opioid-free anesthesia; Opioid-induced hyperalgesia; Perioperative anaphylaxis; Multimodal analgesia.

RESUMEN

Introducción: La hipersensibilidad a los opioides representa un desafío creciente en la anestesiología moderna, pudiendo manifestarse desde reacciones pseudoalérgicas hasta anafilaxia intraoperatoria grave. La necesidad de protocolos seguros e individualizados ha impulsado el desarrollo de estrategias analgésicas alternativas y de anestesia libre de opioides. Métodos: Se realizó una revisión sistemática de la literatura según las recomendaciones de PRISMA 2020, con una búsqueda en la base de datos PubMed (texto completo gratuito, 2020-2025). Se incluyeron artículos originales, revisiones, informes de casos y ensayos clínicos que abordaban el manejo anestésico de pacientes con hipersensibilidad, intolerancia o hiperalgesia inducida por opioides. Resultados: De los 303 artículos identificados inicialmente, 13 cumplían los criterios de elegibilidad. De ellos, nueve presentaban aplicabilidad directa y cuatro indirecta. Los estudios demostraron que la anestesia sin opioides (Opioid-Free Anesthesia, OFA) con dexmedetomidina, cetamina, lidocaína EV y bloqueos periféricos ofrece una analgesia eficaz y estable. Los casos clínicos reforzaron la importancia de la evaluación preanestésica detallada, la identificación de reacciones cruzadas y la disponibilidad de soporte vital avanzado en casos de anafilaxia. Conclusión: El manejo anestésico de pacientes con hipersensibilidad a los opioides debe basarse en tres ejes: prevención, sustitución farmacológica e individualización analgésica. Las estrategias multimodales y sin opioides reducen los riesgos inmunológicos y nociceptivos, lo que promueve una mayor seguridad y calidad perioperatoria.
DESCRIPTORES: Hipersensibilidad a los opioides; Anestesia sin opioides; Hiperalgesia inducida por opioides; Anafilaxia perioperatoria; Analgesia multimodal.

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INTRODUCTION

Opioids have been the basis of perioperative analgesic management for decades due to their efficacy in controlling acute and chronic pain. However, the increasing incidence of adverse reactions, hypersensitivity, and paradoxical phenomena such as opioid-induced hyperalgesia (OIH) has attracted growing attention in modern anesthesiology [1,7–9]. These manifestations range from mild anaphylactoid and pseudoallergic reactions to severe anaphylaxis and intraoperative cardiovascular collapse, which can endanger the patient's life [3,6].

The distinction between true allergic reactions and predictable pharmacological effects represents a significant diagnostic challenge. Multicenter studies indicate that up to 10% of surgical patients have a history of "opioid allergy," although most have no immunological confirmation [5]. This mislabeling negatively impacts anesthetic management, leading to the unjustified avoidance of potent analgesics and limiting the available therapeutic options.

In recent years, robust evidence has emerged in favor of opioid-free anesthesia (OFA) and opioid-sparing protocols, which combine adjuvant agents such as ketamine, dexmedetomidine, intravenous lidocaine, and peripheral blocks [4,6–8]. These approaches seek to reduce immunological and nociceptive risk while maintaining hemodynamic stability and adequate postoperative analgesia, representing a paradigm shift in the management of perioperative pain.

Advances in the understanding of neuroimmune and glial mechanisms demonstrate that OHI and opioid hypersensitivity share pathophysiological pathways related to the activation of NMDA receptors, microglia, and the release of proinflammatory cytokines [1,7,9]. These findings reinforce the importance of prevention strategies, accurate diagnosis, and rational opioid substitution, especially in patients with a history of severe adverse reactions.

MATERIALS AND METHODS

Study Design

This is a systematic review of the literature, descriptive and exploratory in nature, developed in accordance with the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

The objective was to identify, gather, and critically analyze the most recent scientific evidence on anesthetic management in patients with hypersensitivity or intolerance to opioids, covering manifestations such as anaphylactoid and pseudoallergic reactions and opioid-induced hyperalgesia.

Data Sources and Search Strategy

The bibliographic search was conducted in the PubMed database (National Library of Medicine), using the "Free full text" filter and the time frame from 2020 to 2025, in order to ensure the inclusion of contemporary and fully accessible studies.

The following combinations of free descriptors (in English) were applied, identified after semantic refinement and exploratory reading of titles and abstracts:

opioid hypersensitivity AND anesthesia management AND perioperative

opioid allergy AND anesthesia AND perioperative management

opioid-induced hyperalgesia AND anesthesia management

opioid allergy AND multimodal analgesia AND perioperative

These combinations covered the main terms related to hypersensitivity and paradoxical response to opioids, with an emphasis on their implication in perioperative anesthetic practice.

Inclusion Criteria

Studies that met the following criteria were included:

Original articles, systematic or narrative reviews, clinical trials, case reports, and study protocols;

Publications written in English;

Research involving patients undergoing general, regional, or combined anesthesia who presented with opioid-induced hypersensitivity, allergy, or hyperalgesia;

Availability in free full text.

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Exclusion Criteria

The following were excluded:

Preclinical or experimental studies without direct correlation with anesthetic practice;

Duplicate, incomplete, or non-peer-reviewed studies;

Letters to the editor, editorials, and conference abstracts without detailed clinical data.

Data Selection and Extraction Process

The screening of articles took place in two sequential stages:

Reading of titles and abstracts, excluding studies that did not address anesthesia, drug hypersensitivity, or perioperative management.

Full reading of eligible texts, with manual extraction of the following data:

Authors and year of publication;

Type and design of the study;

Population and clinical context;

Type of opioid involved and nature of the adverse reaction;

Anesthetic strategies used (multimodal analgesia, opioid-free anesthesia, adjuvants, and blocks);

Clinical outcomes and reported complications.

Synthesis and Classification of Studies

Of the 303 articles initially identified, 13 met the inclusion criteria after complete screening. Of these, 9 were directly applicable to the topic, specifically addressing anesthetic management in situations of allergy, hypersensitivity, or hyperalgesia due to opioids. Another 4 articles were classified as indirectly applicable, as they dealt with related topics, such as non-opioid pain control strategies and the impact of anesthetic doses on the nociceptive response.

The data were synthesized qualitatively and descriptively, with categorization according to:

Type of adverse response to opioids (immunological, pseudoallergic, or hyperalgesic);

Anesthetic approach adopted (opioid-free anesthesia, multimodal analgesia, use of adjuvants);

Clinical outcomes and perioperative safety.

References Used in the Final Sample

The following 13 studies were included: With direct applicability:

Gregus et al. (2021); Chen et al. (2024); Sirohiya et al. (2025); Atlapure et al. (2025); Thomas et al. (2021); Bansal et al. (2024); Wilson et al. (2021); Koponen et al. (2024); Martinez et al. (2022). With indirect applicability: Yu et al. (2025); Martin-Orr & Yun (2025); Ren et al. (2022); Aroke et al. (2020).

TABLE 1 – CHARACTERISTICS OF THE INCLUDED STUDIES

AUTOR/ANO	TIPO DE ESTUDO	POPULAÇÃO E CONTEXTO CLÍNICO	ESTRATÉGIA ANESTÉSICA	PRINCIPAIS OBSERVAÇÕES	CONCLUSÃO
Gregus et al., 2021	Revisão experimental e translacional	Modelos pré-clínicos e análise de dor em humanos, com enfoque em diferenças sexuais na resposta neuroimune	Uso comparativo de agonistas opioides e observação de sensibilização glial	Diferenças de sexo influenciam mecanismos gliais e neuroimunes na hipersensibilidade a opioides	O reconhecimento de variáveis neuroimunes pode otimizar o manejo anestésico e reduzir reações paradoxais
Chen et al., 2024	Ensaio clínico randomizado	120 pacientes pediátricos submetidos à laparoscopia	Comparação entre morfina e nalbufina	Nalbufina promoveu analgesia eficaz com menor incidência de efeitos adversos	Alternativas não morfínicas reduzem risco de hipersensibilidade e náusea pós-operatória
Sirohiya et al., 2025	Relato de caso	Paciente submetido à anestesia geral que apresentou anafilaxia à morfina	Suspensão imediata do agente e suporte avançado de vida	Reação anafilática grave associada à morfina intravenosa	Destaca a importância do preparo para anafilaxia em anestesias com opioides
Atlapure et al., 2025	Relato de caso	Criança com eosinofilia e múltiplas comorbidades em toracoscopia	Anestesia livre de opioides com adjuvantes multimodais	Controle adequado da dor e estabilidade hemodinâmica	Abordagem opioid-free mostrou-se segura em pacientes com risco imunológico elevado
Thomas et al., 2021	Estudo multicêntrico observacional	3.500 pacientes cirúrgicos eletivos em 5 centros do Reino Unido	Avaliação de manejo anestésico frente a rótulos de alergia medicamentosa	10% dos pacientes apresentavam "alergia a opioide" no prontuário, frequentemente sem confirmação clínica	A educação sobre rotulagem incorreta é essencial para manejo anestésico racional
Bansal et al., 2024	Relato de caso	Paciente com múltiplas hipersensibilidades medicamentosas, incluindo opioides	Analgesia multimodal e bloqueios regionais	Controle adequado da dor sem reações adversas	Estratégias combinadas permitem evitar opioides com segurança
Wilson et al., 2021	Revisão narrativa	Literatura clínica e experimental sobre OIH (opioid-induced hyperalgesia)	Comparação entre opioides e uso de adjuvantes (cetamina, dexmedetomidina, lidocaína EV)	Identificação de mecanismos NMDA e sensibilização central	Sugere protocolos preventivos e anestesia livre de opioides em pacientes predispostos

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Koponen et al., 2024	Revisão sistemática e metanálise	Estudos pré-clínicos sobre hiperalgesia induzida por remifentanil	Intervenções farmacológicas alternativas (ketamina, gabapentina)	Ketamina e antagonistas NMDA reduziram a hiperalgesia em modelos experimentais	Fundamenta o uso clínico de adjuvantes não opioides para controle da dor
Martinez et al., 2022	Relato de caso	Paciente com anemia falciforme e hiperalgesia induzida por opioides	Adição de cetamina ao regime analgésico	Redução significativa da dor e da necessidade de opioides	Cetamina é eficaz como adjuvante em casos de hiperalgesia induzida por opioides

Source: Prepared by the authors based on data extracted from articles selected in the systematic review: Gregus et al. [1]; Chen et al. [2]; Sirohiya et al. [3]; Atlapure et al. [4]; Thomas et al. [5]; Bansal et al. [6]; Wilson et al. [7]; Koponen et al. [8]; Martinez et al. [9].

TABLE 1.2 – CHARACTERISTICS OF THE INCLUDED STUDIES (INDIRECT APPLICABILITY)

AUTOR/ANO	TIPO DE ESTUDO	POPULAÇÃO E CONTEXTO CLÍNICO	ESTRATÉGIA ANESTÉSICA	PRINCIPAIS OBSERVAÇÕES	CONCLUSÃO
Yu et al., 2025	Protocolo de ensaio clínico randomizado	Pacientes politraumatizados em emergência	Irradiação ganglionar perioperatória como adjuvante	Intervenção não farmacológica visa reduzir estresse pós-operatório	Estratégias adjuvantes podem modular resposta autonômica sem opioides
Martin-Orr & Yun, 2025	Revisão narrativa	Pacientes com transtorno por uso de opioides (OUD)	Manejo perioperatório individualizado com substitutivos	Ênfase em equilíbrio analgésico e abstinência controlada	Relevante para condutas anestésicas em pacientes dependentes, não alérgicos
Ren et al., 2022	Estudo observacional	180 pacientes submetidos à anestesia com remifentanil	Análise da relação entre dose e dor pós-operatória	Doses elevadas correlacionadas com aumento da dor e hiperalgesia	Suporta ajustes de dose para evitar OIH, embora sem enfoque imunológico
Aroke et al., 2020	Revisão de abordagem prática	Pacientes com dor crônica no pós-operatório	Protocolos multimodais com redução de opioides	Abordagem centrada na analgesia individualizada	Reforça uso racional de opioides em cirurgias de alta complexidade

Source: Prepared by the authors based on data extracted from articles selected in the systematic review: Yu et al. [10]; Martin-Orr & Yun [11]; Ren et al. [12]; Aroke et al. [13].

RESULTS

After applying the inclusion and exclusion criteria, the screening resulted in 13 studies eligible for qualitative and quantitative analysis. The selected articles encompassed different methodological designs—including clinical trials, systematic reviews, case reports, and observational studies—that addressed anesthetic management in patients with hypersensitivity, allergy, or opioid-induced hyperalgesia.

The synthesis of the results was organized descriptively, covering the main thematic axes identified during the analysis: study profile, hypersensitivity and anaphylaxis reactions, alternative anesthetic strategies, mechanisms and control of opioid-induced hyperalgesia, associated clinical factors, adjuvant interventions of indirect applicability, and emerging patterns in perioperative management.

This structure allowed us to integrate recent clinical and experimental evidence, providing a comprehensive view of the role of opioid-free anesthesia, the rational use of adjuvants, and preventive measures in patients at increased risk of adverse reactions to opioids.

3.1. Profile of Included Studies

Of the 13 selected studies, nine were directly applicable to anesthetic management in patients with hypersensitivity or paradoxical response to opioids, while four were indirectly applicable, addressing complementary strategies for analgesia and opioid consumption reduction.

The sample included different methodological designs, including four clinical trials and systematic reviews, three case reports, two multicenter observational studies, and four narrative reviews, providing a broad view of pharmacological and non-pharmacological approaches in the perioperative context.

There was a predominance of recent publications (2021–2025), evidencing growing concern with the rational and safe use of opioids and the advancement of opioid-free anesthesia (OFA) protocols as a safe alternative in patients at risk of hypersensitivity [1–13].

3.2. Hypersensitivity and Anaphylaxis to Opioids

The reports by Sirohiya et al. [3] and Bansal et al. [6] described episodes of severe intraoperative anaphylaxis associated with morphine, characterized by cardiovascular collapse, bronchospasm, and sudden hemodynamic instability, requiring immediate intervention with epinephrine, ventilatory support, and suspension of the suspected agent.

These cases illustrate the rarity, but potentially lethal severity, of hypersensitivity reactions to opioids, especially when diagnosis is delayed or confused with other causes of intraoperative instability.

Evidence also suggests the possibility of cross-reactivity between opioids

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of different structural classes, which reinforces the importance of careful preoperative investigation. This assessment should include a detailed history of previous exposures, identification of the type of reaction (immune-mediated, pseudoallergic, or pharmacological), and, when possible, specific allergy testing before any re-exposure.

This emphasizes the need for individualized anesthetic planning, including multimodal analgesia strategies and preparation of the team for the management of anaphylactic emergencies.

The immediate availability of epinephrine, advanced life support, and standardized rapid response protocols is essential to reduce the morbidity and mortality associated with these reactions.

Therefore, prevention and early recognition of opioid hypersensitivity are critical steps to ensure anesthetic safety and therapeutic efficacy in the perioperative setting [3,6].

3.3. Alternative Anesthetic Strategies

Opioid-free anesthesia (OFA) has established itself as a safe and effective strategy for patients with proven allergy, severe intolerance, or increased risk of hypersensitivity to opioids.

Clinical studies and case reports demonstrate the success of multimodal protocols based on the combination of dexmedetomidine, ketamine, intravenous lidocaine, and peripheral blocks, which provide adequate analgesia, hemodynamic stability, and a significant reduction in adverse effects [4,6].

Such approaches demonstrate that opioid-free analgesia is not only feasible but also offers additional benefits, such as reduced incidence of postoperative nausea and vomiting, less respiratory depression, and more predictable anesthetic recovery.

In addition, the integration of adjuvant agents acts on multiple pain mechanisms, allowing multimodal blockade of nociception and decreased central sensitization, which are fundamental aspects for safe pain control in opioid-sensitive patients.

The review by Wilson et al. [7] and the meta-analysis by Koponen et al. [8] corroborate the role of ketamine as a prominent adjuvant due to its NMDA receptor antagonist action, which prevents remifentanil-induced hyperalgesia and modulates the neuroglial response.

These strategies have been associated with consistent reduction in postoperative pain, reduced need for rescue analgesics, and improved functional recovery, supporting OFA as an efficient, physiologically balanced, and clinically safe alternative for patients with contraindications to opioid use [4,6–8].

4. Opioid-Induced Hyperalgesia (OIH)

Opioid-induced hyperalgesia (OIH) has been addressed in six publications [1,7–9,12], which converge in describing the phenomenon as a paradoxical response of increased pain sensitivity after acute or chronic exposure to opioids.

Studies indicate that OIH is associated with the activation of N-methyl-D-aspartate (NMDA) receptors, proinflammatory glial modulation, and amplification of central nociceptive pathways, culminating in neuronal hypersensitization and reduction of the pain threshold.

The analyses by Gregus et al. [1] and Wilson et al. [7] highlight the participation of neuroimmune and glial mechanisms in the genesis of OHI, evidencing differences related to sex, hormonal profile, and systemic inflammatory status, which can modulate the intensity of the hyperalgesic response.

This neuroimmune component reinforces the hypothesis that OHI is not only pharmacological but also the result of complex interactions between opioids, the immune system, and neuronal plasticity.

In the clinical context, the most effective management strategies included gradual reduction of the opioid dose, replacement with atypical opioids such as nalbuphine and tramadol, and implementation of opioid-free multimodal analgesia.

The use of non-opioid adjuvants, such as ketamine, dexmedetomidine, and intravenous lidocaine, has been particularly beneficial in inhibiting neuronal excitability, modulating NMDA receptors, and restoring the balance between excitatory and inhibitory neurotransmitters [7–9,12].

These interventions have contributed to reversing central sensitization, reducing the need for opioids in the postoperative period, and improving overall analgesic quality, establishing themselves as fundamental pillars in the prevention and management of POCID.

5. Associated Factors and Clinical Contexts

Individual variability in response to opioids represents one of the main challenges in safe and personalized anesthetic management.

The experimental study by Gregus et al. [1] demonstrated that hormonal, neuroimmune, and glial differences between the sexes influence susceptibility to opioid-induced hypersensitivity and hyperalgesia (OIH). These mechanisms involve differential modulation of the inflammatory response, variations in cytokine expression, and microglia activity, which may explain the higher prevalence of adverse effects and exacerbated pain responses in certain population groups.

Complementarily, the multicenter DALES study, conducted by Thomas et al. [5], revealed that approximately 10% of surgical patients had a record of "opioid allergy." However, most of these cases corresponded to incorrect labels resulting from predictable adverse effects, such as nausea, pruritus, or hypotension, without confirmation by specific immunological tests.

This reinforces the importance of distinguishing pharmacological reactions from true immune-mediated reac-

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tions, avoiding unnecessary therapeutic restrictions and optimizing the selection of analgesic agents in the perioperative period.

Such evidence emphasizes the need for critical review and standardization of allergy records in electronic medical records, as well as continuous training of anesthetic and surgical teams. These measures reduce classification errors, improve risk stratification, and increase the safety and predictability of anesthetic management in patients with a history of opioid hypersensitivity [1,5].

7. Emerging Standards

The integrated analysis of the studies identified three fundamental axes that guide contemporary anesthetic management in patients with opioid hypersensitivity. These axes reflect both the evolution of pathophysiological knowledge and the advancement of clinical strategies aimed at perioperative safety.

Prevention: This involves thorough preoperative assessment, with an emphasis on identifying a detailed history of adverse reactions, previous opioid use, and documented anaphylactic events. Replacing drugs with greater allergenic potential, such as morphine and meperidine, with alternatives with lower immunological reactivity is an essential measure [3,5,6].

Targeted medical history and standardized recording in electronic medical records are crucial tools for reducing risks and guiding individualized anesthetic approaches.

Pharmacological substitution: The literature highlights the role of opioid-free multimodal analgesia, using ketamine, dexmedetomidine, and intravenous lidocaine as prominent adjuvants [4,6–8].

These agents, combined with peripheral blocks and regional techniques, promote effective analgesia, hemodynamic stability, and a lower incidence of adverse effects, while reducing central sensitization and opioid-induced hyperalgesia.

Individualization of analgesia: The personalization of analgesic protocols represents the most advanced approach in contemporary practice.

Opioid-sparing and opioid-free strategies have been successfully applied in various surgical contexts, prioritizing continuous intraoperative and postoperative monitoring, multimodal pain assessment, and prevention of inadvertent re-exposure to sensitizing opioids [1,4,7–9].

This approach promotes safer, patient-centered anesthetic practice aligned with the principles of modern pharmacovigilance.

Comprehensively, these standards reflect a paradigm shift in current anesthesiology, in which the focus shifts from the routine and empirical use of opioids to a personalized, rational, and immunologically safe approach, supported by growing evidence of efficacy and risk reduction.

TABLE 2: QUANTITATIVE SYNTHESIS

VARIÁVEL AVALIADA	Nº DE ESTUDOS	PROPORÇÃO (%)	OBSERVAÇÕES PRINCIPAIS
Total de estudos analisados	13	100%	Período 2020–2025; 9 diretos e 4 indiretos
Aplicabilidade direta ao tema	9	69,2%	Envolvem hipersensibilidade, anafilaxia ou hiperalgesia induzida
Aplicabilidade indireta ao tema	4	30,8%	Estratégias adjuvantes e prevenção não farmacológica
Relatos de caso	3	23%	Casos de anafilaxia e manejo multimodal sem opioides
Ensaios clínicos / revisões sistemáticas	4	31%	Comparações entre opioides e adjuvantes analgésicos
Revisões narrativas e observacionais	6	46%	Síntese de mecanismos e recomendações clínicas
Anestesia livre de opioides (OFA) descrita	5	38%	Uso de cetamina, dexmedetomidina, lidocaína EV e bloqueios
Uso de adjuvantes não opioides	8	61%	Principalmente cetamina e dexmedetomidina
Reações anafiláticas relatadas	2	15%	Casos graves relacionados à morfina intravenosa
Hiperalgesia induzida por opioides (OIH)	6	46%	Envolvendo remifentanil e mecanismos NMDA/gliais
Rotulagem incorreta de alergia	1	8%	Frequente em cirurgias eletivas, segundo Thomas et al.
Período de publicação 2021–2025	11	85%	Evidencia atualização e relevância crescente do tema

Source: Prepared by the authors based on the consolidation of qualitative and quantitative data extracted from the 13 included studies, considering frequency of applicability, methodological design, and predominant anesthetic interventions [1–13].

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DISCUSSION

There has been significant progress in the understanding and anesthetic management of patients with opioid hypersensitivity syndrome, highlighting the need for individualized, safe, and physiologically balanced care. It is indicated that detailed preoperative assessment, the use of multimodal analgesia strategies, and the replacement of conventional opioids with non-opioid adjuvants are the main pillars for reducing immunological and nociceptive complications in the perioperative period.

Clinical cases reported by Sirohiya et al. [3] and Bansal et al. [6] illustrate the severity of anaphylactic reactions associated with morphine, characterized by bronchospasm, cardiovascular collapse, and the need for immediate intervention. These episodes reinforce the importance of detailed anesthetic history, rigorous recording of previous exposures, and distinction between truly immune-mediated reactions and pseudoallergic responses. The absence of standardized protocols for diagnostic confirmation still represents a gap in clinical practice, which reinforces the need to develop specific guidelines for the management of these cases.

Opioid-free anesthesia (OFA) has established itself as an effective alternative for patients with hypersensitivity or severe intolerance, as demonstrated by Atlapure et al. [4] and Bansal et al. [6]. Multimodal protocols involving dexmedetomidine, ketamine, intravenous lidocaine, and peripheral blocks have shown adequate analgesia, hemodynamic stability, and more predictable recovery without the need for opioids. The review by Wilson et al. [7] and the meta-analysis by Koponen et al. [8] confirm the efficacy of NMDA antagonists, such as ketamine, in preventing remifentanil-induced hyperalgesia (RIH) and attenuating central sensitization. These strategies represent a paradigm shift, in which the focus shifts from purely pharmacological pain control to neurophysiological and inflammatory modulation of the nociceptive response.

OIH has been described in six publications [1,7–9,12], which elucidate neuroimmune and glial mechanisms in the genesis of paradoxical pain sensitization. Studies by Gregus et al. [1] and Wilson et al. [7] demonstrate that the activation of NMDA receptors and microglia leads to the release of proinflammatory cytokines, amplifying central nociceptive pathways. From a clinical standpoint, gradually reducing the dose of opioids, replacing them with atypical analgesics such as nalbuphine or tramadol, and using non-opioid adjuvants—especially ketamine, dexmedetomidine, and IV lidocaine—have proven to be effective measures for preventing and reversing OHI. In addition, Ren et al. [12] associated high doses of remifentanil with increased postoperative pain, reinforcing the need to limit intraoperative exposure to potent opioids.

Individual variability in response to opioids, discussed by Gregus et al. [1], shows that hormonal and neuroimmune differences between the sexes can modulate susceptibility to hypersensitivity and OHI. The multicenter DALES study, conducted by Thomas et al. [5], revealed that approximately 10% of surgical patients had a history of "opioid allergy," although most of these cases represented incorrect labeling without immunological confirmation. This finding highlights the importance of critically reviewing medical records and training medical and nursing teams to distinguish predictable adverse reactions from true allergies, avoiding analgesic undertreatment and promoting greater perioperative safety.

Studies of indirect applicability also offer relevant contributions. Yu et al. [10] explored stellate ganglion stimulation with polarized light as a non-pharmacological method to modulate perioperative stress and autonomic response. Ren et al. [12] reinforced the relationship between remifentanil dose and poorer postoperative pain control, while Martin-Orr and Yun [11] addressed the management of patients with opioid use disorder (OUD), highlighting the balance between analgesic control and relapse prevention. Aroke et al. [13], in turn, emphasized the rational use of multimodal analgesia to reduce dependence and adverse events in patients with chronic pain. Although they do not directly address hypersensitivity, these studies complement the literature by reinforcing the importance of adjuvant strategies and non-opioid interventions to minimize exacerbated nociception and systemic exposure to opioids.

The integration of the results allows us to identify three central pillars for the anesthetic management of these patients: prevention, pharmacological substitution, and individualization of analgesia. Prevention is based on detailed preoperative assessment and replacement of opioids with greater allergenic potential [3,5,6]; pharmacological substitution involves the use of non-opioid adjuvants, such as ketamine, dexmedetomidine, and IV lidocaine, associated with regional blocks and multimodal analgesia [4,6–8]; and the individualization of analgesia requires continuous intra- and postoperative monitoring, with opioid-sparing and opioid-free protocols adapted to each patient's risk profile [1,4,7–9]. These axes reflect a transformation in modern anesthesiology, which is shifting from the empirical and routine use of opioids to a practice based on physiological precision and immunological safety.

Among the limitations of this approach are the small number of controlled clinical trials, methodological heterogeneity, and the scarcity of studies with specific populations, such as pediatric patients and patients with multiple drug sensitivities. Despite these restrictions, the evidence gathered provides consistent support for the formulation of preliminary protocols and clinical guidelines aimed at safe anesthesia in individuals with opioid hypersensitivi-

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ty. Prospective multicenter studies and translational research in neuroimmunology are needed to deepen the understanding of pathophysiological mechanisms and consolidate evidence-based approaches.

CONCLUSION

Anesthetic management in patients with opioid hypersensitivity syndrome requires an approach focused on safety, prevention, and therapeutic individualization. Early identification of adverse reactions and thorough preoperative evaluation are fundamental steps in reducing the risk of anaphylaxis and complications related to opioid exposure.

Opioid-free anesthesia (OFA) and opioid-sparing protocols are effective alternatives, providing adequate analgesic control, hemodynamic stability, and reduced induced hyperalgesia. The use of adjuvants such as ketamine, dexmedetomidine, intravenous lidocaine, and regional blocks has proven to be safe and feasible, offering concrete clinical solutions for patients with proven intolerance or allergy.

Finally, consolidating opioid-free anesthesia as a safe and evidence-based practice depends on conducting multicenter studies of higher methodological quality. The integraation of anesthesiology, immunology, and neuroscience represents the path to the development of increasingly personalized and effective protocols aligned with the overarching principle of perioperative medicine: ensuring patient comfort, safety, and quality.

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