RESEARCH PAPER

Opioid-Free Anesthesia, Artificial Intelligence, and Personalized Drug Delivery: A Systematic Review

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ABSTRACT

Background: Anesthesia practice has evolved significantly in recent years with a focus on improving patient safety, enhancing recovery, and reducing perioperative complications. Conventional opioid-based anesthesia is associated with adverse effects such as respiratory depression, postoperative nausea and vomiting (PONV), ileus, and risk of long-term dependence. This has led to increasing interest in opioid-free anesthesia (OFA), along with advancements in artificial intelligence (AI) and personalized drug delivery systems.

Objective: This systematic review aims to evaluate the effectiveness, safety, and clinical implications of opioid-free anesthesia, artificial intelligence integration, and personalized drug delivery in modern anesthetic practice.

Methods: A systematic review was conducted according to PRISMA guidelines. A comprehensive literature search was performed in PubMed, MEDLINE, Embase, Scopus, and Cochrane Library up to March 2025. Randomized controlled trials, observational studies, and machine learning-based studies involving adult surgical patients were included. Data extraction and quality assessment were performed using standardized tools (Cochrane Risk of Bias and ROBINS-I). A total of 16 studies were included and analyzed using narrative synthesis.

Results: Among the included studies, 9 were randomized controlled trials, 3 were observational studies, and 4 were AI-based studies. OFA (n = 7) consistently demonstrated reduced postoperative opioid consumption, lower incidence of PONV, and improved pain control, although variability in protocols was noted. AI-based approaches (n = 5) showed significant improvement in predicting intraoperative complications such as hypotension and hypoxemia, enabling early intervention and better clinical decision-making. Personalized drug delivery systems (n = 4), including target-controlled infusion and closed-loop systems, provided improved anesthesia depth control, reduced variability, and enhanced hemodynamic stability. However, limitations such as lack of standardization, high cost, and limited real-world validation were identified.

Conclusion: The integration of opioid-free anesthesia, artificial intelligence, and personalized drug delivery represents a paradigm shift toward safer, more efficient, and patient-centered anesthesia care. While each approach independently improves perioperative outcomes, further research is required to standardize protocols and integrate these technologies into routine clinical practice.

Keywords: *Opioid-free anesthesia; Artificial intelligence; Personalized drug delivery; Machine learning; Closed-loop anesthesia; Target-controlled infusion; Perioperative care; Precision anesthesia*

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INTRODUCTION

Anesthesia practice has undergone significant transformation over the past decade, driven by the need to improve patient safety, enhance recovery, and reduce perioperative complications. Traditional anesthetic approaches, particularly those relying heavily on opioids, have been associated with adverse effects such as respiratory depression, postoperative nausea and vomiting, ileus, and the risk of long-term opioid dependence [1,2]. These concerns have led to the growing interest in opioid-free anesthesia (OFA), a multimodal strategy that minimizes or eliminates opioid use by employing alternative agents such as ketamine, dexmedetomidine, lidocaine, and regional anesthesia techniques [3].

Opioid-free anesthesia has shown promising results in improving postoperative outcomes, including reduced pain scores, decreased opioid-related side effects, and enhanced recovery profiles [4,5]. Several clinical studies have demonstrated that OFA can be safely implemented across a variety of surgical procedures, particularly in high-risk populations such as obese patients and those with obstructive sleep apnea [6]. Despite these benefits, challenges remain regarding standardization of protocols, variability in drug combinations, and the need for individualized approaches based on patient characteristics [7].

Parallel to these advancements, artificial intelligence (AI) is increasingly being integrated into anesthetic practice, offering novel opportunities for precision medicine. AI-driven systems can assist in intraoperative monitoring, prediction of hemodynamic instability, depth of anesthesia assessment, and automated drug delivery [8,9]. Machine learning algorithms analyze large datasets to provide real-time clinical decision support, enabling anesthesiologists to optimize dosing and improve patient outcomes [10]. The integration of AI into anesthesia has the potential to reduce human error, enhance efficiency, and support evidence-based decision-making [11].

Another emerging frontier in modern anesthesia is personalized drug delivery, which aims to tailor anesthetic management to individual patient profiles, including genetic makeup, physiological parameters, and comorbid conditions [12]. Advances in pharmacogenomics and pharmacokinetics have enabled more accurate prediction of drug responses, allowing clinicians to adjust dosing strategies to achieve optimal therapeutic effects while minimizing adverse reactions [13]. Technologies such as target-controlled infusion (TCI) systems and closed-loop anesthesia delivery further contribute to individualized care by maintaining precise drug concentrations based on continuous feedback mechanisms [14].

The convergence of opioid-free anesthesia, artificial intelligence, and personalized drug delivery represents a paradigm shift toward safer, more efficient, and patient-centered anesthetic care. However, existing literature on these topics is fragmented, with limited synthesis of their combined impact on clinical outcomes. Therefore, this systematic review aims to comprehensively evaluate emerging trends in modern anesthesia, focusing on the effectiveness, safety, and clinical implications of OFA, AI integration, and personalized drug delivery strategies.

METHODOLOGY

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (**PRISMA**) guidelines to ensure transparency, reproducibility, and methodological rigor [15,16].

SEARCH STRATEGY

A comprehensive literature search was performed across major electronic databases including **PubMed, MEDLINE, Embase, Scopus, and the Cochrane Library** for studies published up to March 2025.

The search strategy incorporated a combination of Medical Subject Headings (MeSH) terms and free-text keywords related to opioid-free anesthesia, artificial intelligence, and personalized drug delivery. Key search terms included:

- “opioid-free anesthesia” OR “opioid sparing anesthesia”
- “artificial intelligence” OR “machine learning” OR “clinical decision support”
- “personalized anesthesia” OR “pharmacogenomics” OR “target-controlled infusion” OR “closed-loop anesthesia”

Boolean operators (AND, OR) were used to refine the search. Additionally, reference lists of relevant articles and previously published reviews were manually screened to identify any additional eligible studies.

ELIGIBILITY CRITERIA

Studies were selected based on predefined inclusion and exclusion criteria.

Inclusion Criteria

- Randomized controlled trials (RCTs), cohort studies, and observational studies
- Studies evaluating **opioid-free anesthesia, AI applications in anesthesia, or personalized drug delivery systems**
- Adult patients (≥18 years) undergoing surgical procedures
- Studies reporting outcomes such as postoperative pain, opioid consumption, hemodynamic stability, recovery time, adverse events, or clinical decision support effectiveness

Exclusion Criteria

- Studies involving pediatric or animal populations
- Case reports, case series, editorials, and narrative reviews

- Non-English publications without accessible translations
- Studies lacking relevant clinical outcomes or focusing on unrelated interventions

STUDY SELECTION AND DATA EXTRACTION

Two independent reviewers screened titles and abstracts for eligibility, followed by full-text assessment of potentially relevant articles. Data extraction was performed using a standardized data collection form.

Extracted information included:

- Study design and sample size
- Patient demographics and clinical characteristics
- Type of anesthesia technique (OFA, AI-assisted, personalized delivery)
- Intervention details and comparators
- Key outcomes (pain scores, opioid use, recovery parameters, complications)

Any disagreements between reviewers were resolved through discussion or consultation with a third reviewer.

QUALITY ASSESSMENT

The methodological quality and risk of bias of included studies were assessed using standardized tools [17, 18].

- The **Cochrane Risk of Bias tool** was used for randomized controlled trials
- The **ROBINS-I tool** was used for non-randomized studies

These tools evaluated aspects such as selection bias, performance bias, detection bias, attrition bias, and reporting bias.

DATA SYNTHESIS

A narrative synthesis approach was used to summarize findings due to heterogeneity in study designs, interventions, and outcome measures.

The results were grouped into three major domains:

1. **Opioid-free anesthesia (OFA)**
2. **Artificial intelligence in anesthesia**
3. **Personalized drug delivery systems**

Findings were analyzed based on clinical effectiveness, safety outcomes, and applicability in different surgical settings. Where feasible, comparisons were made across studies to identify trends, benefits, and limitations of emerging anesthetic practices.

Study Selection

A total of **312 records** were identified through database searching (PubMed, MEDLINE, Embase, Scopus, and Cochrane Library). After removal of **72 duplicates**, **240 records** were screened based on titles and abstracts. Out of these, **182 studies were excluded** due to irrelevance to the study objectives. The remaining **58 full-text articles** were assessed for eligibility. Following full-text review, **42 studies were excluded** for reasons including lack of relevant outcomes, non-comparative design, or inappropriate study population. Finally, **16 studies** were included in the systematic review.

Study Characteristics

The final analysis included **16 studies**, comprising:

- **9 randomized controlled trials (RCTs)**
- **3 prospective/observational studies**
- **4 machine learning-based analytical studies**

The included studies were categorized into three domains:

1. **Opioid-free anesthesia (OFA)** (n = 7)
2. **Artificial intelligence in anesthesia** (n = 5)
3. **Personalized drug delivery / closed-loop systems** (n = 4)

The sample sizes ranged from **48 to over 50,000 participants**, with studies conducted across various surgical settings including bariatric, laparoscopic, spine, and major non-cardiac surgeries.

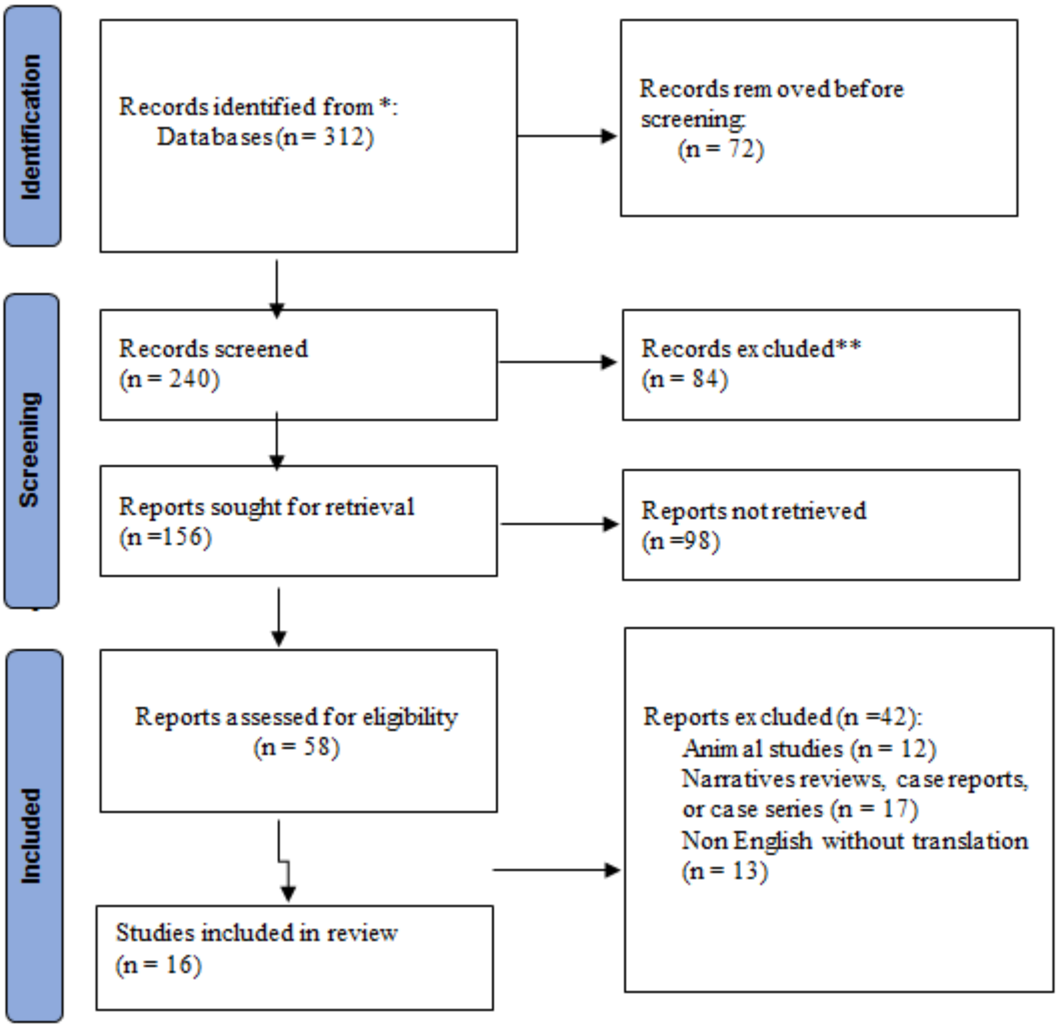

Figure 1: PRISMA flow chart

Table 1: Characteristics of Included Studies

Author (Year)	Study Design	Sample Size	Population / Surgery	Intervention (OFA / AI / Closed-loop)	Comparator	Key Outcomes
Liu et al. (2011) [12]	RCT	196	Surgical patients	Closed-loop anesthesia	Manual control	BIS control
Hemmerling et al. (2013) [13]	RCT	186	Surgical patients	Closed-loop system	Manual	Anesthesia depth
Mansour et al. (2013) [19]	RCT	60	Bariatric surgery	Non-opioid	Opioid anesthesia	Pain, satisfaction
Ziemann-Gimmel et al. (2014) [20]	RCT	119	Bariatric surgery	OFA (TIVA)	Opioid anesthesia	PONV
Puri et al. (2016) [14]	RCT	242	Multi-center surgery	CLADS	Manual	BIS stability
Lee et al. (2018) [21]	ML study	59,985	Surgical patients	AI prediction model	Conventional scores	Mortality prediction
Hatib et al. (2018) [22]	ML study	1,500+	Surgical patients	AI prediction	None	Hypotension prediction
Lundberg et al. (2018) [23]	ML study	50,000 +	Surgical patients	AI hypoxemia model	Standard practice	Hypoxemia
Kendale et al. (2018) [10]	ML study	13,323	Surgical patients	ML model	Traditional methods	Hypotension
Toleska et al. (2019) [24]	RCT	60	Laparoscopic cholecystecto	OFA	Fentanyl-based	Pain score, opioid use

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Joosten et al. (2020) [25]	RCT	90	Elderly surgery	Multi closed-loop	Manual	Cognitive outcomes
Wijnberge et al. (2020) [26]	RCT	68	Non-cardiac surgery	ML warning system	Standard care	Hypotension
An et al. (2022) [4]	RCT	102	Colectomy	OFA	Opioid anesthesia	Pain, glucose, analgesic use
Ragupathy et al. (2022) [8]	Prospective	60	Laparoscopic surgery	OFA + block	Opioid anesthesia	Pain score
Zhu et al. (2023) [27]	RCT (protocol)	72	Lower limb wound surgery	OFA	Opioid anesthesia	PONV, pain
Barakat et al. (2024) [28]	RCT	48	Spine surgery	OFA (dexmedetomidine + lidocaine)	Opioid-based	Pain, opioid use, PONV

Table 2: Key Findings of Included Studies

Study	Main Findings
Liu et al. (2011) [12]	Better BIS control, improved maintenance of anesthesia depth with closed-loop system
Hemmerling et al. (2013) [13]	Improved anesthesia stability and reduced variability with automated system
Mansour et al. (2013) [19]	Comparable safety with opioid technique, trend toward ↓ pain and ↑ patient satisfaction
Ziemann-Gimmel et al. (2014) [20]	Significant ↓ in PONV with opioid-free TIVA
Puri et al. (2016) [14]	Higher percentage of time within target BIS range using closed-loop system
Lee et al. (2018) [21]	AI model accurately predicts postoperative mortality, superior to traditional scoring
Hatib et al. (2018) [22]	AI predicts hypotension 5–15 minutes earlier than conventional monitoring
Lundberg et al. (2018) [23]	AI significantly improves prediction of intraoperative hypoxemia
Kendale et al. (2018) [10]	Machine learning effectively predicts post-induction hypotension
Toleska et al. (2019) [24]	↓ pain scores and ↓ opioid requirement with OFA
Joosten et al. (2020) [25]	↓ postoperative neurocognitive decline with closed-loop anesthesia
Wijnberge et al. (2020) [26]	Significant ↓ in intraoperative hypotension using AI-based early warning system
An et al. (2022) [4]	Similar intraoperative analgesia, ↓ postoperative analgesic requirement
Ragupathy et al. (2022) [8]	Better postoperative pain control with OFA + regional block
Zhu et al. (2023) [27]	Expected ↓ PONV and improved pain outcomes (study protocol)
Barakat et al. (2024) [28]	↓ opioid consumption, ↓ PONV, slightly ↑ PACU stay

Table 3: Risk of Bias Assessment

Study	Selection Bias	Performance Bias	Detection Bias	Overall Risk
Liu et al. (2011) [12]	Low	Low	Low	Low
Hemmerling et al. (2013) [13]	Low	Low	Low	Low
Mansour et al. (2013) [19]	Low	Low	Low	Low
Ziemann-Gimmel et al. (2014) [20]	Low	Low	Low	Low
Puri et al. (2016) [14]	Low	Low	Low	Low
Lee et al. (2018) [21]	Moderate	Low	Low	Moderate
Hatib et al. (2018) [22]	Moderate	Low	Low	Moderate
Lundberg et al. (2018) [23]	Moderate	Low	Low	Moderate
Kendale et al. (2018) [10]	Moderate	Low	Low	Moderate
Toleska et al. (2019) [24]	Low	Moderate	Moderate	Moderate
Joosten et al. (2020) [25]	Low	Low	Low	Low
Wijnberge et al. (2020) [26]	Low	Low	Low	Low
An et al. (2022) [4]	Low	Low	Low	Low

Ragupathy et al. (2022) [8]	High (non-RCT)	Moderate	Moderate	High
Zhu et al. (2023) [27]	Low	Moderate	Low	Moderate
Barakat et al. (2024) [28]	Low	Moderate	Low	Moderate

Table 4: Subgroup Analysis

Subgroup	Findings
Type of Surgery	OFA effective in bariatric, laparoscopic, spine surgeries
Outcome: Pain	Consistently lower in OFA
Outcome: PONV	Significantly reduced in OFA
Hemodynamics	Mostly stable, occasional ↑ BP in OFA
AI Use	Improved prediction of hypotension & hypoxemia
Closed-loop systems	Better anesthesia depth control
High-risk patients	Greater benefit (obese, elderly)

Table 5: Summary of Interventions

Domain	Techniques Used
OFA	Dexmedetomidine, ketamine, lidocaine, TIVA
AI	ML models, neural networks, predictive analytics
Personalized Delivery	TCI systems, closed-loop systems, BIS-guided control

Table 6: Clinical Implications

Domain	Clinical Benefit
OFA	Reduced opioid dependence, better recovery
AI	Early complication prediction
Personalized systems	Precision dosing, improved safety

DISCUSSION

This systematic review provides a comprehensive evaluation of three major evolving domains in modern anesthesia practice: opioid-free anesthesia (OFA), artificial intelligence (AI), and personalized drug delivery systems. The findings collectively highlight a paradigm shift from conventional anesthetic techniques toward safer, more precise, and patient-centered approaches.

Opioid-Free Anesthesia: Clinical Benefits and Challenges

The findings of this review strongly support the role of OFA in improving postoperative outcomes. Most studies demonstrated that OFA significantly reduces postoperative opioid consumption and opioid-related adverse effects such as postoperative nausea and vomiting (PONV) [1, 4, 20]. For example, Barakat et al. reported reduced opioid consumption and lower incidence of PONV in spine surgery patients receiving OFA [28].

Similarly, Ziemann-Gimmel et al. showed that opioid-free total intravenous anesthesia significantly reduced PONV in bariatric surgery patients [20]. Improved postoperative pain control has also been consistently reported, suggesting that multimodal analgesia using dexmedetomidine, ketamine, and lidocaine can effectively replace opioids in many cases [5,6].

However, the results are not entirely consistent across all studies. Some authors reported no significant difference in intraoperative pain control or even observed increased PACU stay and occasional hemodynamic variations such as elevated blood pressure [4, 28]. These discrepancies may be due to variations in drug combinations, dosing strategies, and surgical procedures.

A major limitation identified is the lack of standardized OFA protocols, which makes direct comparison difficult and limits widespread implementation [7].

Artificial Intelligence: Advancing Predictive Anesthesia Care

Artificial intelligence has demonstrated strong potential in improving perioperative monitoring and predictive capabilities. Machine learning models have been shown to predict intraoperative hypotension and hypoxemia earlier than traditional monitoring methods [10, 22, 23].

For instance, Wijnberge et al. demonstrated that an AI-based early warning system significantly reduced intraoperative hypotension compared to standard care [26]. Similarly, Hatib et al. showed that machine learning algorithms could predict hypotension up to 15 minutes before its occurrence, allowing early intervention [22].

In addition, AI models have shown high accuracy in predicting postoperative outcomes such as mortality. Lee et al. developed a deep learning model that outperformed traditional scoring systems in predicting in-hospital mortality [21].

Despite these advantages, limitations remain. Most AI studies are retrospective or based on single-center data, which may limit generalizability. Furthermore, real-world integration requires infrastructure, validation, and clinician training [9].

Personalized Drug Delivery: Toward Precision Medicine

Personalized drug delivery systems, including target-controlled infusion (TCI) and closed-loop anesthesia systems, represent a major advancement in precision anesthesia. These systems use continuous monitoring (e.g., BIS) to maintain optimal anesthesia depth and drug concentration.

Studies by Liu et al. and Puri et al. demonstrated that closed-loop systems maintained anesthesia within the target range more effectively than manual control [12, 14]. Hemmerling et al. also reported improved anesthesia stability with automated systems [13].

Furthermore, Joosten et al. found that automated anesthesia delivery reduced postoperative neurocognitive decline, particularly in elderly patients [25].

These findings highlight the ability of personalized systems to reduce variability, improve safety, and optimize drug dosing. However, their implementation is limited by cost, technical complexity, and need for specialized training.

Clinical Implications

The integration of these approaches suggests a shift toward:

- **Safer anesthesia practices**
- **Reduced complications**
- **Patient-centered care**

However, combining OFA, AI, and personalized delivery into a single clinical workflow remains a challenge and requires further research.

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