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Opioid-Sparing Versus Opioid-Free Anesthesia Following Cancer Surgery: Effect On Pain Severity And Patient-Reported Outcomes

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ABSTRACT : Opioid use in anesthesia during cancer surgery causes concerns about adverse effect related to opioid use and potential impacts regarding cancer recurrence. Opioid-sparing and opioid-free anesthesia procedures are emerging potential methods to reduce opioid consumption while still providing effective pain management. This paper objective is to analyze the outcome of opioid-sparing anesthesia compared to opioid-free anesthesia on pain severity and patient-reported outcomes following cancer surgery. Randomized controlled studies and observational researches matched predefined inclusion criteria were selected, then extracted and analyzed. The analysis revealed that both opioid-sparing and opioid-free anesthesia techniques reduced postoperative pain severity significantly in comparison to traditional opioid-based anesthesia. Additionally, patients who received opioid-free anesthesia reported better overall outcomes, including reduced nausea, faster recovery times, and improved satisfaction scores. Pain control between opioid-sparing and opioid-free anesthesia techniques was found statistically insignificant, suggesting that both approaches are viable alternatives.

KEYWORDS: cancer surgery; opioid-sparing anesthesia; opioid-free anesthesia; pain severity; patient-reported outcomes.

I. INTRODUCTION

Historically, opioids have been a cornerstone of anesthesiology. In France, opioid prescriptions surged by 104% from 2004 to 2017, with 1.1% of the population receiving strong opioids in 2017. Overconsumption of opioids was accompanied by a 98% rise in overdose incidents during the same period.(1) Postoperatively, approximately 50% of patients are given prescriptions for strong opioids, and over 3% continue using them three months later.(2) Several unfavorable effects related to opioid use namely depression of respiratory system, sedation, chest stiffness, cough depression, bronchoconstriction, and of postoperative nausea and vomiting (PONV), affects 25% and 52% of patients, respectively.(3,4) Furthermore, opioids can lead to hyperalgesia, tolerance, and dependence, complicating pain control and increasing the risk of unfavorable effects.Between 2001 and 2013, global opioid prescriptions exhibited uniform growth except in Africa and South Asia. Notably, cancer incidence rates in Asia were substantially higher than would be expected given moderate substance abuse rates. The considerable disparity in morphine consumption, with North America and Europe accounting for 90% of the global supply in 2009, has prompted concerns that cancer patients in other regions are receiving inadequate pain relief. In response to evolving opioid practice, the World Health Organization is re-evaluating its previous pain management framework, incorporating novel opioid administration for patients undergoing cancer surgery. Studies show that decreased opioid prescriptions due to regulations and stigmatization may have complicated opioid use trends. In a study, morphine doses given to cancer patients significantly reduced from 2010-2015. Surprisingly, cancer patients are less likely to die from opioids than the general population, with a ratio of 10:1. Mortality from opioids in the population is more likely among young, less-educated males. The opioid death rate among cancer patients rose from 0.52 to 0.66 per 100,000, while the general population's rate increased from 5.33 to 8.97 per 100,000.(5)

New anesthetic approaches aim to reduce opioid use through alternative strategies.(5,6) Opioid-Free Anesthesia (OFA) and Opioid-Reduced Anesthesia (ORA) are two such methods. OFA employs a multimodal analgesia approach, using a combination of regional anesthesia, NMDAR antagonists, anti-inflammatory drugs, and α-2 agonists to minimize opioid use. This approach targets multiple mechanisms of nociception, the sensory process of pain. Despite its potential, OFA remains controversial, with mixed findings in recent meta-analyses. Some

Studies report improved postoperative outcomes and reduced PONV with OFA, while others find no significant differences in analgesia or opioid consumption. ORA, on the other hand, seeks to reduce rather than eliminate opioid use during surgery.(7,8) Any oncologic surgery, a major and often lengthy procedure, frequently results in severe postoperative pain, with 50% of patients experiencing uncontrolled pain. These surgeries are complex, involving multiple sites that contribute to intricate pain mechanisms. Moreover, patients often have preexisting conditions like addiction, comorbidities, and malnutrition, exacerbating postoperative complications and increasing opioid use. Considering the elevated morbidity and mortality rates linked to cervicofacial cancer surgeries, it's important to explore effective pain control strategies.(6–10) This systematic review evaluates the impacts of opioid-sparing and opioid-free anesthesia regarding pain severity and patient-reported results after cancer surgeries. The focus will be on comparing opioid requirements during and after surgery, pain scores, and side effects related to opioids between traditional opioid-based anesthesia and OFA/ORA protocols. This review will assess the effectiveness of these new approaches in improving pain management and overall patient outcomes.

II. METHOD

Inclusion and Exclusion : For this review, the inclusion criteria were (1) studies involving patients undergoing cancer surgery, (2) comparative of opioid-sparing anesthesia (OSA) versus opioid-free anesthesia (OFA), (3) inclusion of randomized controlled trials (RCTs) and observational studies, and (4) availability of full-text versions. Reviewers independently evaluated papers, and data extraction was conducted using a standardized form. Key information extracted included study authorship, publication year, method of research, number of sample, and details on anesthesia protocols and outcomes.

Search Strategy and Information Sources : Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, the authors systematically searched English-language studies published from 2014 to 2024 across several databases: PubMed, ScienceDirect, Sage Database, Cochrane. Relevant articles were identified using the keywors ("analgesics opioid"[Pharmacological Action] OR "analgesics, opioid"[MeSH Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields] OR "opioids"[All Fields] OR "opioid s"[All Fields]) AND "free"[All Fields] AND ("anaesthesia"[All Fields] OR "anesthesia"[MeSH Terms] OR "anesthesia"[All Fields] OR "anaesthesias"[All Fields] OR "anesthesias"[All Fields]) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) AND ("surgery"[MeSH Subheading] OR "surgery"[All Fields] OR "surgical procedures, operative"[MeSH Terms] OR ("surgical"[All Fields] AND "procedures"[All Fields] AND "operative"[All Fields]) OR "operative surgical procedures"[All Fields] OR "general surgery"[MeSH Terms] OR ("general"[All Fields] AND "surgery"[All Fields]) OR "general surgery"[All Fields] OR "surgery s"[All Fields] OR "surgerys"[All Fields] OR "surgeries"[All Fields])) AND (y_10[Filter]) AND Additionally, we reviewed reference lists of key papers to identify further relevant studies manually.

Description of Studies Based on Criteria : A total of 1530 entries were found during the identification phase by searching databases. 1230 records were left for screening after 300 duplicates were eliminated. 330 full-text articles remained to be evaluated for eligibility after 900 records were eliminated during the screening phase due to title and abstract screening. 275 of these papers were disqualified for a variety of reasons, including failure to meet inclusion requirements, insufficient data, or results that were not pertinent. Ultimately, the systematic review contained 55 studies. This graphic clearly illustrates the exacting procedure of screening and choosing research to guarantee that only those that satisfy particular standards are incorporated into the final analysis.

Quality Assessment and Risk of Bias Assessment : The authors applied the Risk of Bias in Non-randomized Studies of Exposure (ROBINS-E) to assess potential bias in observational studies. Figure 2 provides a visual representation of the results. Any disagreements were settled by consensus. Based on an evaluation of the thirteen examined studies, the majority show a minimal risk of bias with regard to blinding of outcome assessment and random sequence generation.
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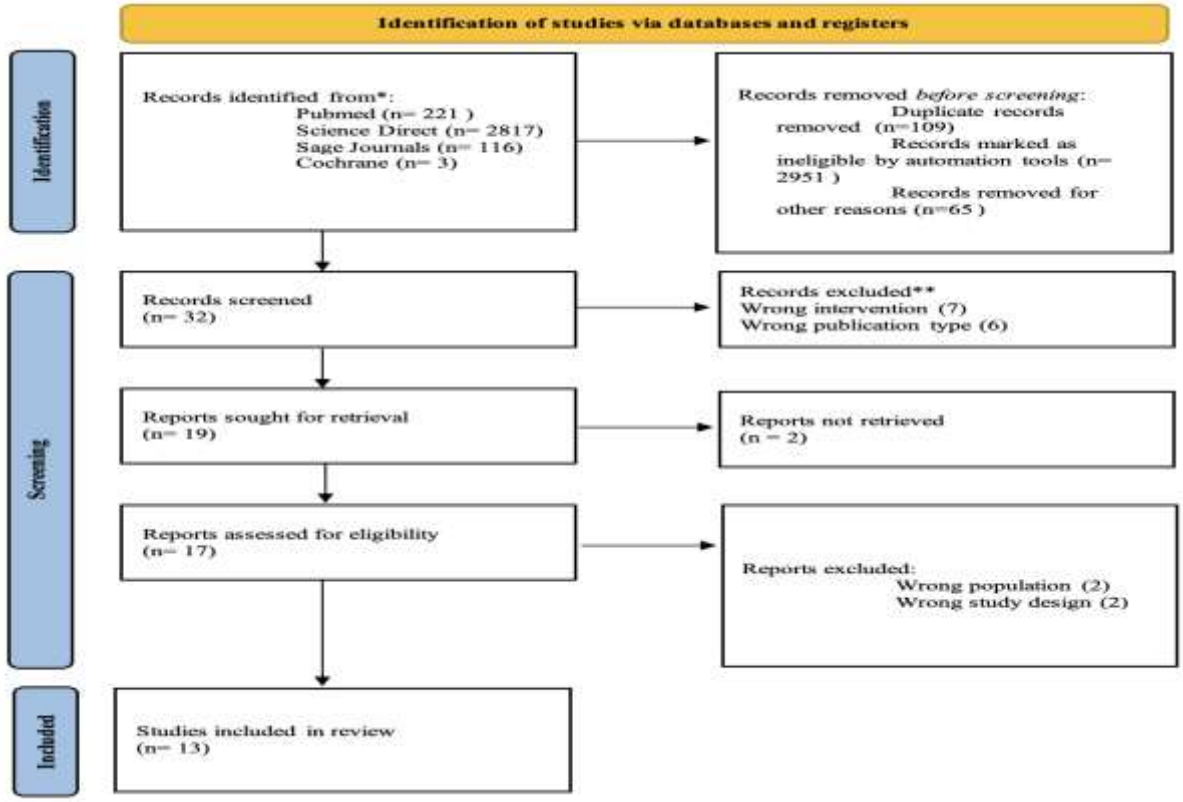

Figure 1. Flowchart of the study

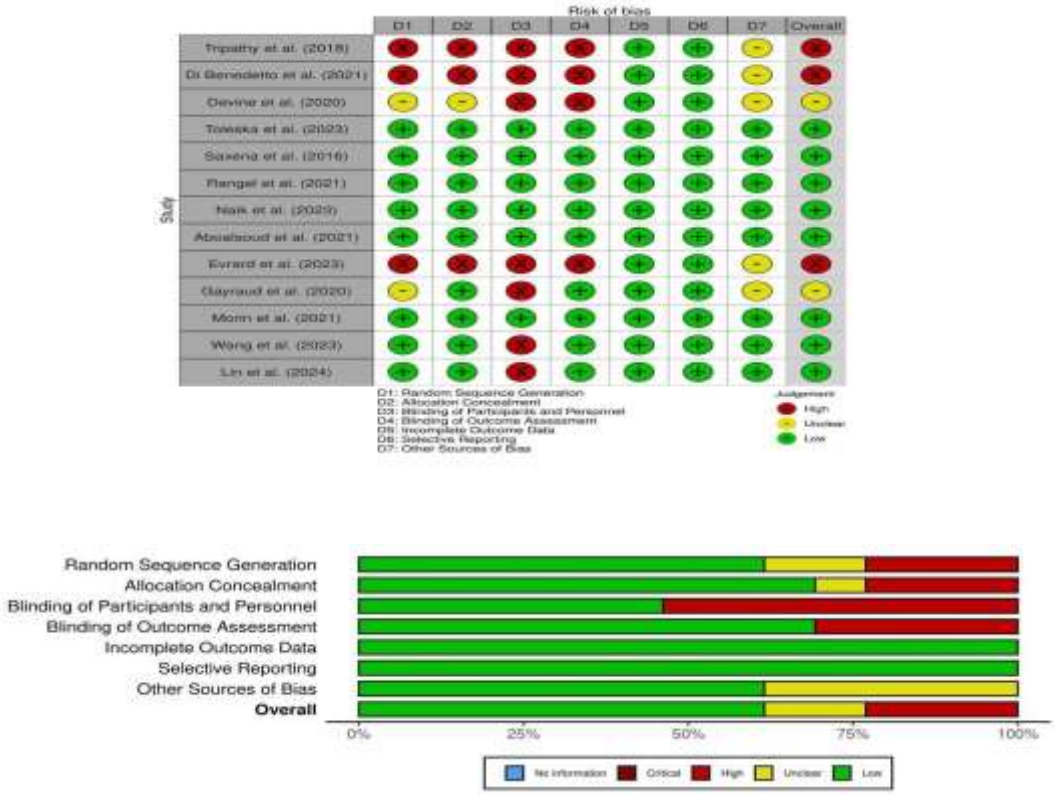

Figure 2. Risk of bias assessment

III. RESULTS

Study Characteristics : The studies explored various aspects of opioid-free and opioid-sparing anesthesia across a variety of surgical procedures and settings. In India, Tripathy S et al. (2018) conducted an observational study analyze participants received opioid-free compared to opioid-based anesthesia in breast malignancy surgeries. They found that opioid-free anesthesia reduced recovery time, less nausea, decreased analgesic requirements, and improved overall patient satisfaction (11). Similarly, Di Benedetto P et al. (2021) performed a cross-sectional study on quadrantectomy patients. Previous study observed the effect of opioid-free anesthesia in the reduction of pain severity, nausea, dan vomiting after surgeries (12).In Australia, Devine G et al. (2020) on case-control study on lung cancer resections reported that opioid-free anesthesia provided similar pain management at the 24-hour mark. However, it was associated with lower pain severity one hour after surgery, with morphine usage remaining comparable between the groups (13). Toleska M et al. (2023) from Israel compared opioid-based, opioid-sparing, and opioid-free anesthesia during colorectal malignancy surgical procedure, finding that opioid-free anesthesia resulted in the lowest pain scores, no nausea/vomiting, and reduced need for additional analgesics (14).In Belgium, a study conducted a randomized controlled trial to observe the impact of opioid-free anesthesia and opioid-based anesthesia. They found that opioid-free anesthesia improved postoperative recovery quality scores and reduced piritramide usage, indicating reduced opioid consumption (15). In Brazil, a previous study explored the impact of opioid-free compared to opioid-based anesthesia in relation to recurrence in prostate cancer. The study found no significant difference in recurrence rates, with other factors having a more pronounced effect on outcomes (16).

In India, Naik S et al. (2023) evaluated opioid-free and opioid-based anesthesia in breast malignancy surgical procedures. The study showed that opioid-free anesthesia led to fewer episodes of postoperative nausea and vomiting and more stable hemodynamics (17). Aboalsoud RA et al. (2021) in Egypt conducted a randomized controlled trial on breast cancer surgery, observing that opioid-free anesthesia significantly lowered pain severity, nausea/vomiting and improved patient satisfaction (18).In France, Evrard E et al. (2023) conducted a retrospective research in opioid-reduced anesthesia versus standard anesthesia in major head and neck oncological surgery. They found that the opioid reduction group used less morphine but had more bradycardia and hypoxemia (19). Gaylot G et al. (2020) conducted a retrospective analysis in France on opioid-sparing anesthesia and reported decreased opioid consumption, the intensity of pain, and nausea/vomiting after surgery. (20). In the United States, Morin S. et al. (2021) in a cohort study of tumor resection patients found that opioid-free anesthesia led to lower pain severity, less opioid administration, and a reduced occurrence of severe postoperative pain. (21).In China, Wang D et al. (2023) conducted a randomized controlled study in conventional versus opioid-free anesthesia for major hepatectomy. The result showed pain control between groups is comparable but there were fewer cases of nausea/vomiting in the opioid-free group (22). Lin Z et al. (2024) also assessed opioid-free anesthesia with conventional anesthesia in laparoscopic radical gastrectomy in China. The result showed pain severity is comparable between groups, but noted faster recovery time and less nausea/vomiting in the opioid-free group (23). In conlusion, these studies highlight the possible advantages of both opioid-free and opioid-assisted anesthesia method, including reduced postoperative pain, lower rates of nausea/vomiting, and greater patient satisfaction. However, the specific benefits may differ depending on the type of surgery and anesthesia used.

Outcomes of Opioid-Free and Opioid-Sparing Post-Surgery Anesthesia : Tripathy et al. (2018) conducted an observational study in India comparing opioid-free anaesthesia (OFA) with opioid-based anaesthesia (OBA) in 24 radical mastectomies with axillary dissection. The study concluded that opioid-free anesthesia was effective, significantly shortened recovery room time, reduced postoperative nausea, decreased analgesic use, and improved the score of visual analog scale (VAS) compared to opioid-based anesthesia. Surgeons and patients reported high satisfaction and good quality of life on the seventh postoperative day (11). Di Benedetto et al. (2020) performed a retrospective analysis of 89 patients who underwent quadrantectomy and compared patients who obtained opioid-free anesthesia (OFA) compared to those given opioid-inclusive anesthesia (OIA). Results showed that postoperative pain scores at various time points in OFA group were lower and the need for additional analgesics was reduced. Postoperative nausea and vomiting (PONV) was also lower in the OFA group, while patient satisfaction remained similar in both groups. (12)

Devine et al. (2020) A study conducted in Australia involving 83 patients undergoing lung cancer resection in both the OFA and standard anesthesia (STD) groups reported that the difference in pain severity at 0 or 24 hours after surgical procedure was not significant. However, the OFA group reported significantly lower pain levels one hour after surgery. Although mean patient-controlled analgesia morphine consumption and recovery time were comparable in both groups, the OFA group spent less time in hospital (13).

Toleska et al. (2023) report on a randomized clinical study in Israel comparing opioid-based anesthesia (OBA), low-opioid anesthesia (LOA), and opioid-free anesthesia (OFA) in 60 patients undergoing colorectal tumor surgery. The OFA group showed significan lower VAS at 2, 12, 24, and 48 hours postoperatively compared with the OBA and LOA groups. Furthermore, the OFA group experienced a decreades incidence of postoperative nausea and vomiting (PONV) and less reliance on additional analgesics (14). Saxena et al (2016) carried out a RCT study in Belgium in 66 patients to analyze opioid-free anesthesia versus opioid-based anesthesia. The OFA Group had a doubtful clinical meaning of this difference, but in comparison to the OBA group, postoperative recovery rating 40 (Qor-40) was higher. The OFA Group has little use of piritramide after surgery, indicating a decrease in opioid consumption (15). Rangel et al. (2021) conducted a prospective randomized clinical study in 146 subjects undergoing prostate cancer surgery in Brazil, analyzing non-opioid anesthesia versus opioid-based anesthesia. No significant differences were found in biochemical recurrence-free survival in comparison of different categories. There was a correlation between obesity, high risk of dummy colon, laparoscopic surgery, stage 3 tumor pathology, and positive surgical margins with shorter biochemical recurrence-free survival, while the choice of anesthesia had no impact on these outcomes. (16).Naik et al. (2023) In randomized controlled study in India, included 130 patient in breast malignancy surgical procedure, opioid-free anesthesia was more superior in minimizing side effects namely postoperative nausea, vomiting, stabilizing bleeding, compated to opioid-based anesthesia. (17). Aboalsud et al (2021) noted that in a randomized controlled trial in Egypt of 40 patients in unilateral radical mastectomy, the OFA group had significantly diminished pain severity at rest and on mobilization, lower nausea and vomiting after surgery, and higher patient satisfaction scores relative to the opioid-based anesthesia group. Furthermore, the OFA group showed a reduced incidence of neuropathic pain and significant changes in inflammatory markers (18).

Ebrard et al. (2023) compared opioid-reduced anesthesia with standard anesthesia in a retrospective study conducted in France in 172 patients undergoing major head and neck tumor surgery and found that opioid-reduced anesthesia consumed less morphine in the end of the surgical operation. However, a study observed no differences in the postoperative pain management and also pain scores between the two categories, although this group had a higher incidence of bradycardia and hypoxemia (19). Gayraud et al (2020) on a retrospective study in France to analyze the impact of a single preoperative paravertebral block on opioid use and postoperative pain in radical mastectomy with immediate reconstruction. Their results have shown that the use of the paravertebral block reduced the administration of opioids during the operation, reduced the severity of pain and reduces the occurance of nausea and vomiting after surgery(20). Morin et al. (2021) compared participants that were given an opioid-sparing multimodality analgesia protocol with those who did not in a United States prospective cohort study of 1,153 tumor resection patients. The study found that the opioid-sparing protocol significantly reduced mean pain scores and decreased the occurence of severe pain. Participants in the previous study with opioid-free group were also given with reduced doses of opioid medications after discharge (21). A previous study conducted a randomized controlled non-inferiority trial to compare opioid-free pain management for postoperative recovery with a conventional opioid-based approach following major hepatectomy in China. There were no significant differences in the need for additional analgesics or in pain scores among groups. However, the opioid-free group experienced a decrease rate of nausea and vomiting after surgery, as well as fewer serious complications (22). Lin et al (2024) on a randomized controlled trial in China that was compared opioid-free postoperative pain control with conventional opioid-based treatment after laparoscopic radical gastrectomy. Although the difference in pain scores was not significant, groups that did not include opioids experienced faster recovery time, such as previous defecation, post -operative nausea and vomiting (23).

IV. DISCUSSION

Efficacy opioid-free anesthesia (OFA) versus opioid-based anesthesia (OBA) has been investigated in several studies, reflecting a growing interest in minimizing opioid consumption due to their associated side effects. Each study contributes to understanding the efficacy and safety of opioid-free techniques in various surgical contexts. An observational study comparing opioid-free and opioid-anesthesia for modified radical mastectomy was carried out in India by Tripathy et al. (2018). According to their findings, anesthesia without opioids decreased postoperative nausea, decreased the need for analgesics, and increased patient satisfaction. (11) This aligns with the study by Naik et al. (2023), which supports opioid-free anesthesia's effectiveness in reducing postoperative nausea and vomiting while maintaining stable hemodynamics. Both studies emphasize improved recovery metrics and patient satisfaction with opioid-free approaches in breast malignancy surgical procedure.(17) Devine et al. (2020) and Wang et al. (2023) explored opioid-free anesthesia in different contexts. Devine's case-control study revealed that opioid-free techniques did not show significant differences in pain scores compared to standard techniques, although opioid-free groups reported lower pain scores at specific intervals.(13) Wang's study on major hepatectomy found similar postoperative

Pain management efficacy between opioid-free and conventional methods, with opioid-free strategies leading to fewer complications such as nausea and vomiting. These studies underscore the promising advantages of opioid-free anesthesia in lowering certain side effects and maintaining similar pain control.(22) Toleska et al. (2023) and Lin et al. (2024) provided insights into opioid-sparing and opioid-free approaches for colorectal and gastrectomy surgeries, respectively.(14,23) Toleska's randomized clinical trial highlighted that opioid-free anesthesia resulted in lower Visual Analogue Scale (VAS) scores for pain compared to opioid-based and low-opioid strategies. Similarly, Lin's study found opioid-free postoperative pain management to be non-inferior to conventional methods but superior in terms of faster recovery and reduced nausea. These results suggest that opioid-free techniques may offer both analgesic efficacy and improved recovery profiles.(14) Two previous studies investigated the broader implications of opioid-free anesthesia. Rangel's study biochemical recurrence rates were comparable between groups for prostate cancer patients between opioid-free and opioid-based groups, indicating that the choice of anesthesia might not influence cancer recurrence.(16) On the other hand, Aboalsoud's research on breast cancer surgery found opioid-free anesthesia associated with decreased pain scores, reduced incidence of neuropathic pain, and improved immune response markers. These findings suggest potential benefits of opioid-free anesthesia beyond mere pain management.(18)

When comparing opioid-reduces anesthesia to control groups in major cervicofacial surgery, Evrart et al. (2023) saw lower opioid use and fewer postoperative problems. (19) Guillaume et al. (2020) explored paravertebral blocks, highlighting their role in reducing opioid use and postoperative pain.(20) Similarly, Morin et al. (2021) reported superior pain control with opioid-sparing multimodal analgesia in lumpectomy patients, supporting the practice of various opioid-sparing techniques to improved pain control.(21) In conclusion, these studies collectively suggest that opioid-free and opioid-sparing anesthetic strategies can be efficient in managing postoperative pain, reducing opioid-related side effects, and improving patient outcomes across various types of surgeries. The opioid method is expected to improve patient recovery and satisfaction, but opioid and standard approaches need to adapt to individual patients and surgical contexts.Low and middle-income countries (LMICs) are encountering 24.1 million cases of new cancer annually by 2030, and 70% of cancer mortality are estimated to occur in LMICs. Since cancer has a significant social and economic impact in many LMICs, resolving social and economic inequality and promoting economically sustainable development all depend on lowering the global burden of cancer and NCDs. Sustainable Development Goal [SDG] with 13 focus is part of the United Nations Sustainable Development Goals 2025-2030. One of these goals, SDG 3.4, is for the control and management of noncommunicable diseases (NCDs). The possibility that SDG 3.4 won't be accomplished is a major worry. Prevention is important, but it won't be enough to reduce NCDs by 30% by 2023, according to the WHO Best Buys for NCDs. Similarly, since hospital facilities and community services are likely to be necessary for the best management of all NCDs, a more robust health system is needed. This showed a significant issue for low-resource countries (LRCs) since the majority of them now have underdeveloped health systems that require improvement, including cancer services. A nation's ability to respond to a variety of health issues across demographic groups can be improved, and the health system can be strengthened by implementing cost-effective cancer therapies across the care continuum. Therefore, it is essential to reach the SDGs in general as well as the health targets. Sustainable development depends on a healthy population, as we all know, but a healthy population also depends on sustainable development. (24,25)

V. STRENGTH AND LIMITATION

The systematic review presents several strengths that support its overall credibility. A key advantage is incorporating a broad variety of study designs and populations, including randomized controlled trials, cohort studies, and observational studies. This variety enhances the applicability of the findings across variety of surgeries and patient demographics. The comparative evaluation of opioid-free anesthesia (OFA) against opioid-based anesthesia (OBA) in various contexts allows for a thorough examination of OFA's effectiveness and safety. Furthermore, the review considers an extensive array of outcomes, namely pain severity, postoperative nausea and vomiting, opioid usage, recovery duration, and patient satisfaction, thus providing a comprehensive understanding of OFA's impact. By including recent studies, the review ensures that its findings are aligned with contemporary practices and advancements in anesthesia techniques, keeping the results relevant.Nevertheless, there are several limitations to be mindful of. The diversity among the included studies regarding surgical procedures, anesthesia methods, and outcome metrics introduces variability in the results, making it challenging to draw firm conclusions. Some studies may exhibit methodological flaws, such as small sample sizes, retrospective approaches, or inadequate blinding, which could undermine the reliability of the findings. Additionally, discrepancies in how outcomes are reported and measured across studies further complicate the synthesis of results and hinder the possibility of conducting a thorough meta-analysis. Moreover, the review predominantly emphasizes short-term outcomes like immediate postoperative pain and recovery, with

insufficient data addressing long-term effects and quality of life. There is also the potential for bias, as research with promising results are tend to be presented, which could skew the perceived advantages of OFA over OBA.

VI. CONCLUSION

The findings from this systematic review demonstrate the potential advantages of opioid-free anesthesia (OFA) and opioid-sparing anesthesia (OSA) over conventional opioid-based anesthesia (OBA) in the perioperative management of cancer surgeries. Across various studies and surgical contexts, OFA and OSA were consistently associated with improved postoperative results, such as lower pain severity, reduced postoperative nausea and vomiting (PONV), and better patient satisfaction. Notably, several studies highlighted that OFA led to reduced recovery times, fewer analgesic requirements, and more stable hemodynamics, emphasizing its utility in minimizing opioid-related side effects. Studies on the impact of OFA and OSA on patient-reported outcomes revealed improvements in postoperative quality of recovery and reduced reliance on opioids post-discharge. This aligns with evidence supporting the role of OFA in addressing the broader challenges of opioid-related dependence and hyperalgesia, which complicate long-term pain management. Despite the promising results, some studies noted potential drawbacks, such as increased incidences of bradycardia and hypoxemia in opioid-reduced protocols. Additionally, the variability in outcomes across different surgical types and patient populations indicates the need for further research to tailor anesthesia strategies to individual patient and procedural needs.

CONFLICT OF INTEREST : There is no conflicts of interests in this study

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LIST OF ABBREVIATIONS : LOA : *Low opioid anesthesia ;* PONV : *Postoperative nausea and vomiting* ; OBA : *Opioid-based anesthesia* ; OFA : *Opioid-Free Anesthesia ;* OLA : *Opioid-inclusive anesthesia ;* ORA : *Opioid-Reduced Anesthesia ;* OSA : *Opioid-sparing anesthesia ;* PRISMA : *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* ; QoR-40 : *Quality of Recovery-40 ;* RCT : *Randomized controlled trial ;* ROBINS- E : *Risk of Bias in Non-randomized Studies of Exposure ;* STD : *Standard anesthesia ;* VAS : *Visual analog scale*

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Table 1. Various aspects of opioid-free and opioid-sparing anesthesia across different surgical procedures

No.	Author	Study (Year)	Country	Study design	Sample	Post Surgery Anesthesia	Description
1.	Tripathy et al.,(11)	2018	India	Observational study	24 patients	Opioid free vs Opioid anesthesia	Opioid-free anesthesia resulted in less recovery time, nausea, and analgesic use. Better overall satisfaction.
2.	Di Benedetto et al.,(12)	2020	India	Cross-sectional Study	89 patients	Opioid free vs Opioid anesthesia	Opioid-free group experienced lower pain scores and nausea/vomiting, with similar patient satisfaction.
3.	Devineet et al.,(13)	2020	Australia	Retrospective, propensity-matched, case-control study.	83 patients	Opioid free vs control (standard technique)	Opioid-free group had less pain at 1 hour post-surgery; pain scores and morphine use were similar at 24 hours.
4.	Toleska et al.,(14)	2019	Israel	Prospective and randomized clinical	27 patients	Opioid based vs Opioid Sparing vs Opioid Free Anesthesia	Opioid-free anesthesia resulted in lower pain scores and no nausea/vomiting, with reduced need for additional analgesics.
5.	Saxena, et al.,(15)	2016	Belgium	A prospective, randomized, controlled trial	66 patients	Opioid free vs control	Opioid-free group had better quality of recovery scores and used less piritramide.
6.	Rangel et al.,(16)	2021	Brazil	A randomized prospectiv	146 patients	opioid-free anesthesia vs opioid-based	Biochemical recurrence rates were

				e clinical trial		anesthesia groups.	similar; other factors influenced recurrence more than anesthesia type.
7.	Naik et al.,(17)	2023	India	Randomized control trial	130 patients	Opioid-Based vs Opioid-Free Anesthesia	Opioid-free anesthesia reduced nausea/vomiting and maintained stable hemodynamics.
8.	Rana et al.,(18)	2021	Egypt	Randomized control trial	40 patients	Opioid free versus opioid based anesthesia	Opioid-free group had lower pain scores, less nausea/vomiting, and higher patient satisfaction.
9.	Evrardet al.,(19)	2023	France	A retrospective study	172 patients	Opioid Reduced vs control	Opioid-reduced anesthesia used less morphine, had fewer complications, but more bradycardia and hypoxemia.
10.	Guillaume et al.,(20)	2020	France	Retrospective study with propensity-adjusted analysis.	175 patients	Opioid sparing	Opioid-sparing anesthesia reduced opioid use, pain scores, and incidence of nausea/vomiting.
11.	Morin et al.,(21)	2021	US	Prospective cohort	1153 patients	Opioid sparing anesthesia vs control	Opioid-sparing group had lower pain scores and opioid use, with fewer severe pain episodes.
12.	Wang et al.,(22)	2023	China	An open-label, randomized, controlled, non-inferiority trial	106 patients	opioid-free postoperative pain management strategy versus a conventional opioid-based	Both groups had similar pain control; opioid-free group had lower nausea/vomiting rates.
13.	Lin et al.,(23)	2024	China	An open-label, randomized, controlled, non-inferiority trial.	96 patients	opioid-free postoperative pain management strategy versus a conventional opioid-based	No significant difference in pain levels; opioid-free group had quicker recovery and less nausea/vomiting.