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REVIEW

Safety and efficacy of ketamine use in patients with vaso-occlusive crisis: A systematic review and meta-analysis

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Abstract

Introduction: Sickle cell disease (SCD) is characterized by acute episodes called vaso-occlusive crises (VOC). VOC is marked by severe pain due to blocked blood vessels by sickled cells. Ketamine has been reported to be effective and safe in managing VOC in SCD patients.

Objectives/methods: This review aims to determine ketamine's safety and efficacy through analysis of clinical trials and observational studies.

Methods: Adhering to PRISMA guidelines, this systematic review and meta-analysis systematically searched seven databases on May 20, 2024 for randomized control trials (RCT), cohorts, and case–control studies.

Results: Five studies with 689 participants met the inclusion criteria. A meta-analysis of two studies (518 observations) for the Numerical Rating Scale (NRS) pain score showed no significant difference, with a standardized mean difference (MD) of 0.23 (95% CI: −0.13 to 0.59, $p = 0.21$, $I^2 = 0\%$). For morphine milligram equivalent (MME), a meta-analysis of two studies (344 observations) resulted in an MD of −0.03 (95% CI: −0.09 to 0.04, $p = 0.45$, $I^2 = 97\%$). However, the side effects analysis from four studies (608 observations) showed a significantly higher relative risk (RR) of 5.74 (95% CI: 2.80–11.79, $p < 0.0001$, $I^2 = 0\%$) for mild side effects, including nausea, vomiting, and dizziness.

Conclusion: Ketamine qualitative synthesis shows potential for improving pain management in SCD patients during VOC, but without statistically significant differences in pain reduction. It is associated with increased mild side effects, though no severe adverse events were reported. Further research is needed to increase the sample size and power of the analysis to clarify optimal dosing and administration protocols for ketamine in this context.

KEYWORDS
ketamine, opioids, pain management, sickle cell disease (SCD), vaso-occlusive crisis (VOC)

1 | INTRODUCTION

Sickle cell disease (SCD) is the most common genetic blood disorder in the world, and it is prevalent mostly in African Americans. It is estimated that over 100,000 people in the United States are living with SCD [1]. SCD is characterized by the abnormal shape of red blood cells. It most frequently presents with chronic anemia, organ damage, and acute complaints such as stroke, acute chest syndrome, dactylitis, priapism, and right upper quadrant syndrome [2]. Acute VOC is a hallmark of SCD, characterized by intense pain and tissue ischemia due to occlusion of small blood vessels by sickled red blood cells [3]. It usually is an episode of pain in the extremities, back, abdomen, or head that leads to a prompt visit to the emergency department (ER) of SCD patients [4].

To relieve pain in VOC, we can use topical lidocaine patches in adjunct to opioids, NSAIDs, and acetaminophen. Non-pharmacologic interventions such as hydration, heat, reiki, massage, and cognitive behavioral therapy can also be used [5]. The standard treatment for relieving pain is intravenous opioid administration. Nevertheless, this is not always effective in achieving pain control, especially in patients who are frequently administered with opioids. It has been hypothesized that frequent exposure to opioids in these patients could lead to tolerance and opioid-induced hyperalgesia (OIH), which is thought to contribute to opioid refractory pain [6].

OIH results are due to the upregulation of NMDA receptors in chronic pain, which leads to the downregulation of mu-opioid receptors. OIH could be abolished by ketamine, suggesting an *N*-methyl-d-aspartate-receptor mechanism [6]. Ketamine antagonizes NMDA receptors in the central nervous system, which produces a dissociative anesthesia effect. Further, ketamine has been shown to modulate hyperalgesia and opioid-related tolerance in the management of chronic pain. Because of its ability to modify opioid-related tolerance, it is often used along with opioids in relieving pain in VOC. Ketamine can be given through the oral, IV, intramuscular, subcutaneous, epidural, transdermal, or intra-articular route. Recent studies have shown that when compared to opioids, ketamine has a potential efficacy for lowering pain during VOC. The ketamine group did, however, experience a higher rate of adverse effects than the opioid group, while these were mild and transient [7]. The aim of this analysis is to determine if the use of ketamine in this type of patient is safe and effective when compared with opioids alone.

2 | METHODS

The present study employed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to conduct a comprehensive systematic review [8].

2.1 | Searching methods

The present systematic review followed the recommendations and criteria established by the PRISMA [8] reporting guidelines. The protocol was pre-registered at the International Prospective Register of Systematic Review (PROSPERO) with the identifier CRD42024547550.

2.2 | Eligibility criteria

2.2.1 | Types of study

We conducted a systematic review of relevant studies published from inception to 2024, available in English; we meticulously included only randomized controlled trials (RCT), cohort, case-crossover, and case–control studies. We excluded case reports, case series, dissertations, book chapters, protocol articles, among others. Furthermore, we excluded studies that did not clearly describe their operationalizations, were duplicated, and could not obtain the necessary data or receive a response from the original author via email.

2.2.2 | Types of participants

This study has a broad set of participant selection criteria, including pediatric and adult patients with the diagnosis of SCD with VOC. Exclusion criteria are SCD patients with pain and complications not related to vascular occlusive disease. The study aims to include a variety of participants to gain a better understanding of the intervention.

2.2.3 | Types of interventions

The focus will be on SCD patients treated with ketamine with/without opioids compared to patients utilizing opioids or standard treatment as a standalone treatment.

2.2.4 | Outcomes

A thorough evaluation of specific outcomes was vital for assessing the effectiveness of ketamine intervention in this study. The primary outcome was the reduction in pain measured by a pain scale. Secondary outcomes evaluated are reduction in morphine milligram equivalent (MME) units, and side effects.

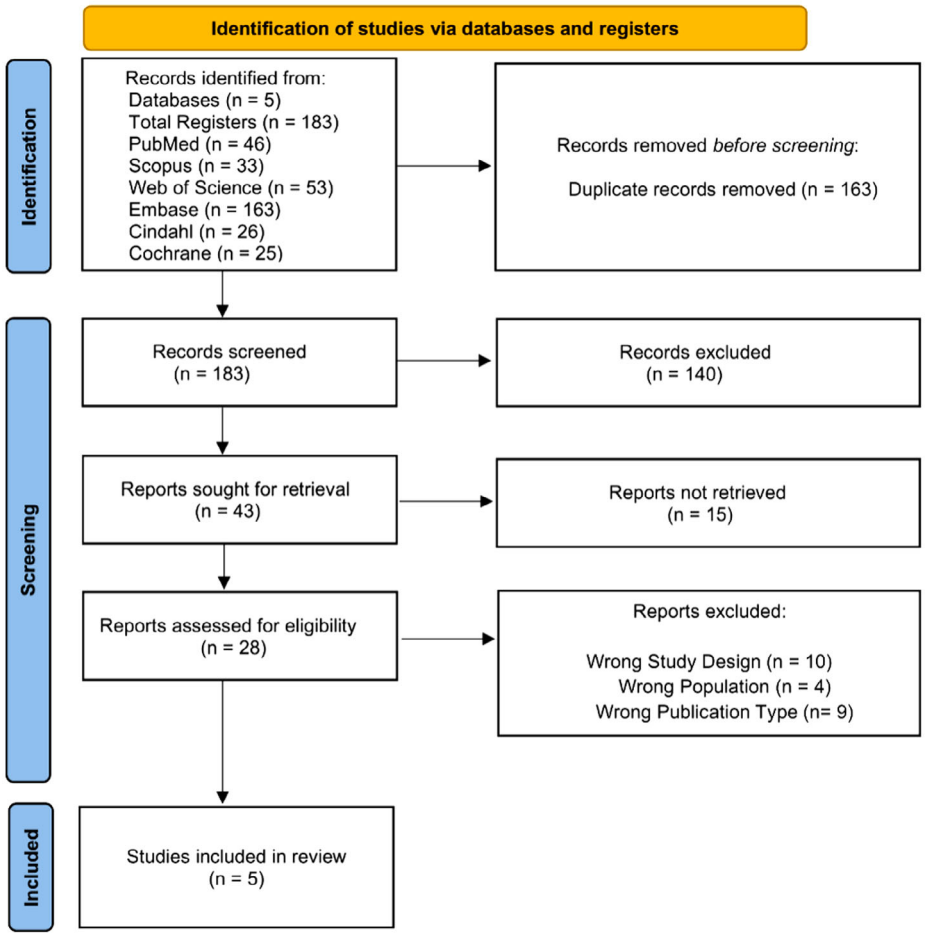

FIGURE 1 PRISMA flow diagram delineates the systematic process of identifying and screening studies across multiple databases, culminating in selecting five pertinent studies.

2.2.5 | Search methods

A systematic search was initially conduced on May 20, 2024 in PubMed, MEDLINE, Cochrane, Scopus, Web of Science, EMBASE, and CINAHL using the following keywords: "Ketamine," "Sickle cell disease," "Vaso-occlusive crisis." All detailed search strategies can be found in the Tables S1–S6.

2.2.6 | Selection of studies

All references were exported to Rayyan [9], and duplicates were removed. Two authors independently completed the eligibility assessment, first by title and abstract analysis, and afterward, by full-text assessment. In disagreements between reviewers, consensus was reached with the help of a third reviewer.

2.2.7 | Data extraction

The data extraction was performed by two independent reviewers and disagreements were solved by consensus, when multiple overlapping reports from the same study were identified, the information from the one containing the most relevant information or the first published report was included.

2.2.8 | Assessment of risk of bias in included studies

Two reviewers independently examined the methodological quality of the included studies using the Cochrane Risk of Bias (ROB2) tool [10] and Newcastle–Ottawa Scale (NOS) [11] for randomized and cohort or case–control studies, respectively. Any disagreements were resolved by discussion with a third author.

2.2.9 | Statistical analysis

Meta-analysis was performed by using the R Software version (3.6.0) to calculate the effect size [12]. Effect sizes were presented as mean differences (MD) and relative risk (RR), with 95% confidence intervals (CI). The random-effects model was used for pooling analysis to compensate for the heterogeneity of studies [13, 14] statistics. In this regard, I^2 ≥50% and ≥75% indicated substantial and considerable

heterogeneity [13], study removal method to the subanalysis to assess whether any individual study exerted influence on the overall effect size [15, 16], *p*-values less than 0.05 were considered statistically significant.

3 | RESULTS

During the initial identification process using the database and registers, 163 duplicate records were screened out, leaving 183 unique records. After further screening, an additional 140 records were excluded, leaving 43 for retrieval. Ultimately, only 28 records were retrieved. These retrieved reports were then assessed for eligibility, with 23 reports being excluded. Among the excluded reports, nine were of the wrong publication type, 10 had the wrong study design, and four focused on the wrong population. After the screening process, we were left with five pertinent studies that met the inclusion criteria. We have summarized this process in our PRISMA flowchart, which is shown in Figure 1. Five studies were included in the final review, encompassing a total of 689 participants. Three studies (60%) were conducted in the United States, one (20%) in Uganda, and one (20%) in Saudi Arabia. The study designs comprised two randomized control trials and three retrospective observational studies. The primary outcomes assessed were pain reduction, side effects, and length of stay. Four of the five studies used the NRS pain scale, with two also using the Wong–Baker FACES scale, and one using the FLACC scale. One study did not assess pain using a pain scale.

Two out of the five studies (40%) reported significant reductions in pain intensity with ketamine. One study (20%) found no significant difference in pain reduction between ketamine and control groups. Another study (20%) noted a significant increase in pain scores in the ketamine group. The last study (20%) does not report the change in pain intensity. Four studies (80%) observed a significant decrease in opioid consumption with ketamine, highlighting its potential opioid-sparing effects. One study (20%) reported an increase in opioid use in the ketamine group. Four studies found that side effects were more common in the ketamine group, with symptoms including nausea, vomiting, dizziness, nystagmus, dysphoria, salivation, hallucinations, altered mental status, and vivid dreams. Two studies analyzed hospital admissions and length of stay. Froomkin et al. [17] found no significant difference in the median length of stay between ketamine and control admissions. Alshahrani et al. [18] reported no significant difference in hospital admission rates between ketamine and morphine groups, indicating that ketamine did not affect the likelihood of hospital admission. A more comprehensive report of this information can be found in Table 1.

The risk-of-bias assessment utilized Cochrane's Risk of Bias 2.0 tool for the two randomized control trials, which showed some concerns in both articles, as represented in Figure 2A and Figure 2B. The three retrospective studies were assessed using the NOS, and were all rated as good quality, as shown in Table 2.

3.1 | Meta-analysis results

3.1.1 | Numerical rating scale pain score

This meta-analysis included two studies with 518 observations (258 in experimental groups and 260 in control groups) using the random effects model. The MD for NRS changes with ketamine intervention compared to standard treatment was 0.23 (95% CI: −0.13 to 0.59, $p = 0.21$, $I^2 = 0\%$) (Figure 3).

3.1.2 | Morphine milligram equivalent

This meta-analysis included two studies with 344 observations (171 in experimental groups and 173 in control groups) using the random effects model. The MD for MME changes with ketamine intervention compared to standard treatment was −0.03 (95% CI: −0.09 to 0.04, $p = 0.49$, $I^2 = 97\%$) (Figure 4).

3.1.3 | Side effects

This meta-analysis assessed the side effects of ketamine and opioids in four studies (608 observations). The RR was 5.74 (95% CI: 2.80–11.79, $p < 0.0001$, $I^2 = 0\%$) (Figure 5).

3.1.4 | Publication bias

The funnel plot and Egger test for all the variables were not conducted due to the limited number of studies.

3.1.5 | Sensibility analysis and subgroup analysis

For NRS and MME variables, we did not perform a subgroup analysis or sensitivity analysis due to the low number of studies. For side effects analysis, we did not perform due to low heterogeneity in the results.

4 | DISCUSSION

Throughout this meta-analysis, the ketamine use efficacy and safety for patients with VOC was evaluated rigorously. Initially, our systematic review analyzed the intensity of pain reduction in patients receiving ketamine, showing effective pain reduction compared to opioids alone. However, there was no statistically significant difference in the numerical pain score reduction analysis, showing high heterogeneity in the results; this variability suggests that ketamine's effectiveness may depend on several other factors such as dosage, duration of administration, and patient characteristics. The limitations on small sample size and the form of reporting data in the studies we analyzed

TABLE 1 General outcomes.

Author	Year	Country	Study design	Intervention	Key findings
Lubega et al. [19]	2018	Uganda	Randomized control trial	Ketamine infusion	The study was effective for pain relief in children with severe VOC. The primary outcome measured was the maximum change in pain scores, which showed no significant difference between the two groups, patients in the morphine group required more doses than the ketamine group. Side effects were more common in the ketamine group, such as nystagmus and dysphoria. No serious or life-threatening events were observed.
Alshahrani et al. [18]	2022	Saudi Arabia	Randomized control trial	Ketamine infusion	The study revealed no significant difference in pain reduction between the ketamine and morphine groups over a 2-h period. However, ketamine administration led to a significantly lower cumulative opioid dose. Hospital admission rates and drug-related side effects were similar in both groups, with no significant difference. Side effects observed were dizziness, nausea, and vomiting. The study concludes that early ketamine use in VOC offers effective pain relief with reduced opioid use and no major safety concerns.
Neri et al. [20]	2014	USA	Retrospective observational study	Ketamine infusion ± opioids	Low-dose ketamine demonstrates a satisfactory short-term safety profile for patients with SCD during VOE hospitalizations. The study found that pain scores and opioid consumption were higher during hospitalizations involving ketamine compared to opioid PCA alone. The lack of an opioid-sparing effect probably reflects its use in cases of more severe VOE pain. Side effects reported were vivid dreams, delusions, and dizziness.
Nobrega et al. [21]	2018	USA	Retrospective observational study	Ketamine infusion ± opioids	Study showed that ketamine, when combined with opioids, significantly reduced both pain scores and opioid consumption. The study highlighted those younger patients specially males experienced greater pain relief compared to older patients and females. Multivariate analysis identified sex, age, pain location, and infusion duration as independent predictors of pain score changes. The study calls for further controlled trials to determine which subsets of SCD patients would benefit most from ketamine therapy.
Froomkin et al. [17]	2022	USA	Retrospective observational study	Ketamine infusion ± opioids	The median length of stay was similar between the ketamine and control admissions, indicating that ketamine did not significantly affect the hospitalization duration. Patients required lower total daily opioid dose during and following the ketamine infusion when compared to 24 h prior to administered ketamine, but it was not statistically significant. Ketamine was generally well-tolerated, and no patients receiving ketamine required naloxone. Side effects reported were somnolence, altered mental status, feeling of dissociation and hallucinations, all of which were reported only on the initial infusion and not on subsequent infusions.

Abbreviations: PCA, patient controlled analgesia; SCD, sickle cell disease; VOC, vaso-occlusive crisis; VOE, vaso-occlusive pain event.

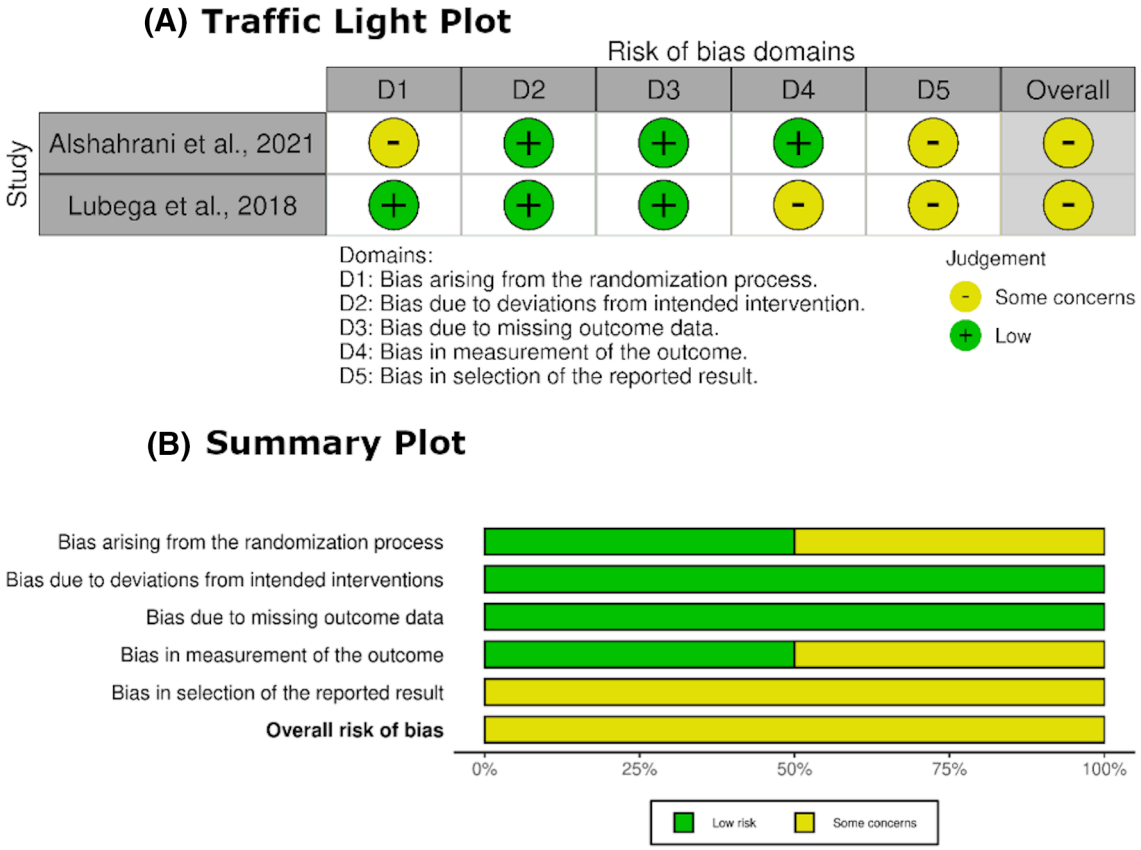

FIGURE 2 (A and B) Risk of bias of RCT included in the study. Traffic Light Plot and Summary Plot. Fifty percent of included studies report low risk of bias in randomization process (D1); 100% of included studies report low risk of bias in deviations from intended interventions (D2); 100% of included studies report low risk of bias in missing outcome data (D3); 50% of included studies report low risk of bias in measuring outcomes (D4); and 100% of included studies report some concern in risk of bias in selection of the reported result (D5). Overall risk of bias 100% of included studies report some concern.

TABLE 2 Risk of bias with Newcastle–Ottawa Scale.

No.	Author year	Study design	Selection	Comparability	Outcome/ Exposure	Total	Subjective evaluation
1	Neri et al., 2014 [20]	Retrospective case-crossover	★★★★	★	★★★	8	Good quality
2	Froomkin et al., 2022 [17]	Retrospective cohort	★★★	★	★★★	7	Good quality
3	Nobrega et al., 2018 [21]	Retrospective cohort	★★★	★	★★★	7	Good quality

Note: The Newcastle–Ottawa Scale (NOS) evaluates studies across three domains: the selection of study groups, comprising 4 items; the comparability of cohorts, consisting of 1 item; and the outcome of interest, encompassing 3 items. Within the selection and outcome domain, one star was allocated per item. The comparability domain permits a maximum allocation of two stars. Consequently, the highest achievable score on the NOS is 9 points.

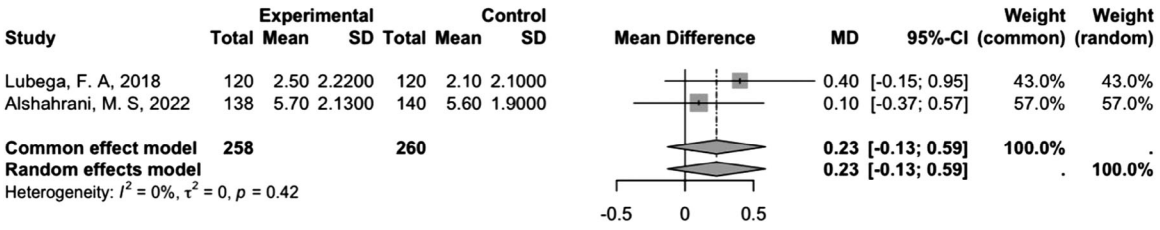

FIGURE 3 Forest plot detailing standard mean difference and 95% confidence interval for the effect on numerical rating scale pain score (NRS) of ketamine intervention against morphine intervention.

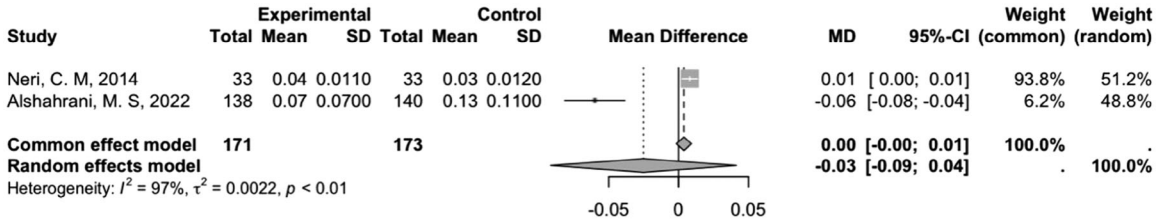

FIGURE 4 Forest plot detailing standard mean difference and 95% confidence interval for the effect on morphine milligram equivalent (MME) of ketamine intervention against morphine intervention.

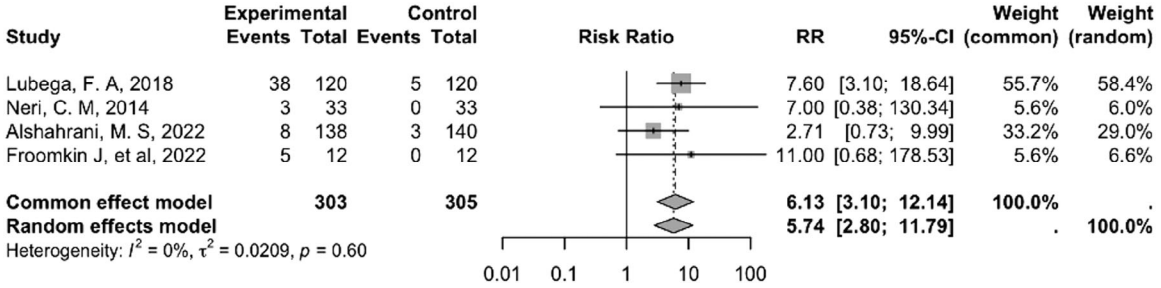

FIGURE 5 Forest plot detailing relative risk and 95% confidence interval for side effects of ketamine intervention against morphine intervention.

affected the meta-analysis results. Currently, no prior meta-analyses have addressed this question. However, a previous systematic review reported the promising efficacy of ketamine for reducing pain during VOC compared to other opioids; they consider that the specific dose is the cause of this effect, based on the dosage differences between studies, like our qualitative analysis [7].

The outcomes of this meta-analysis offer important insights for clinicians regarding the use of ketamine for pain management in patients with VOC. The findings suggest that while our qualitative synthesis shows that ketamine can be effective in reducing pain, its effectiveness can be influenced by various factors such as dosage, duration of administration, and patient characteristics. The lack of statistically significant difference in numerical pain score reduction and low sample size highlights the high heterogeneity in the results, indicating that ketamine may not consistently outperform opioids in every scenario, for this reason the data interpretation of these data must proceed cautiously.

For clinicians, these results underscore the need for a personalized approach when considering ketamine for pain management in VOC. Decisions should consider individual patient factors, careful dosage considerations, and close monitoring of response and side effects. The observed variability suggests that standardizing protocols for ketamine administration might enhance its effectiveness and reliability. Moreover, the noted side effects of ketamine, such as nausea, vomiting, dizziness, and hallucinations, should be carefully weighed against its benefits. Clinicians should be prepared to manage these potential adverse effects and consider them when discussing treatment options with patients. Overall, these findings advocate for cautious optimism regarding ketamine's role in pain management for VOC. While it shows promise, further research with larger sample sizes and standardized reporting is necessary to establish more definitive guidelines. In the meantime, clinicians can use these insights to make more informed, individualized treatment decisions, balancing efficacy with safety.

Opioid consumption was significantly decreased in four studies (80%) with ketamine, highlighting its potential as an opioid-sparing agent. This trend supports ketamine's role in reducing opioid requirements, which is crucial in the context of the opioid crisis and managing OIH. However, our meta-analysis did not show any statistical significance with opioid use, this is probably because the analysis included only two studies with small sample size. Previous studies have reported that there is a potential opioid-sparing effect, especially in those patients with mild to moderate pain [22].

The outcome of the qualitative synthesis highlights that ketamine has significant potential as an opioid-sparing agent, reducing opioid consumption in the studies reviewed. This finding is particularly relevant in the context of the opioid crisis and managing OIH. Although the meta-analysis did not show statistical significance, likely due to small sample sizes, the trend is promising. Clinicians can consider ketamine for patients with mild to moderate pain to reduce opioid use, with careful dosing and monitoring to balance benefits and risks. Further research is needed to confirm the findings and establish definitive guidelines.

It is evident from our review that the four outcomes that were analyzed in the study were pain reduction, length of stay, MME reduction and side effects. Only two out of five studies have shown clinical improvement with no statistical significance in the reduction of pain

intensity with the help of ketamine. The other studies have been inconclusive. As per Froomkin et al. (2022), there was no difference between the length of stay. Alshahrani et al. (2022) study concludes that there is no significant difference in recurrent hospitalizations. One of the critical aspects of the study is the dose-associated side effects with ketamine-nausea, vomiting, dizziness, nystagmus, dysphoria, salivation, hallucinations, altered mental status, and vivid dreams. It is important to understand the appropriate dosage and patient characteristics before considering ketamine for VOC. Though there is a reduction in pain intensity with ketamine, there is no proven statistical significance also, keeping in mind the limitation of small sample size and limited data on specific dosages of ketamine. This limitation led to organizations like the Food and Drug Administration (FDA) to still not approve ketamine to be used for pain control. More research is needed on ketamine as a monotherapy and adjunctive, with the standardization of the pain scale for the reliability of the study.

About the common side effects in the ketamine group, the qualitative analysis showed a high rate of common side effects in the ketamine group, such as nausea, vomiting, and dizziness, no severe or life-threatening events were reported, this difference compared to opioids was statistically significant in our meta-analysis reaching and RR of 5.74 (95% CI: 2.80–11.79, $p < 0.0001$, $I^2 = 0\%$). These findings highlight the importance of careful patient monitoring and management when using ketamine. This finding is particularly important, because one of the primary reasons ketamine is frequently used in VOC patients is its potential to reduce overall side effects, especially those related to opioid usage. Therefore, these finding merits further study and the development of questions such as optimal dosage, patient selection strategies, and risk–benefit analysis in cases such as recurrent hospitalizations and chronic opioid use. Although it is noteworthy that in the ketamine group, there were no severe or life-threatening side effects reported. It is important to recognize in medical practice that there is currently no consensus on the optimal dosage for these patients, and thus, no established safe window for administration exists. Most of the side effects are reported while using a bolus instead of a continuous infusion and at higher doses; thus, avoiding such scenarios could help with the effectiveness and safety of ketamine usage in these patients [22, 23]. With VOC, recurrent hospitalizations, and the use of opioids, patients could develop tolerance to the drug or chronic opioid use [20].

In this systematic review and meta-analysis, ketamine shows potential as an opioid-sparing option despite varying efficacy in pain reduction. Clinicians should consider utilizing ketamine for patients who require decreased opioid usage due to concerns related to tolerance or hyperalgesia. Tailoring treatment approaches is essential, considering variables such as dosage, duration of administration, and individual patient characteristics. Careful management is necessary to address the increased occurrence of side effects associated with ketamine, such as nausea, vomiting, and hallucinations, requiring continuous monitoring and adjustment of treatment strategies. Before starting ketamine therapy, clinicians need to thoroughly assess the risks and benefits to weigh its advantages against potential side effects and variable pain relief outcomes. Continuous education for healthcare providers is essential to ensure the safe and informed use of ketamine, given the mixed findings and associated risks.

4.1 | Limitations

The major limitation of our study is the sample size. Though we assessed similar outcomes like pain reduction and MME reduction with opioids and ketamine among the studies, four out of five studies have used different reporting formats to determine pain reduction, leading to variation bias due to the lack of a standardized pain scale there.

Further research needs to be conducted in the future on the standardization of pain scales using ketamine with a specific dose and monitoring its side effects. The observed trend in the reduction in pain factors within the ketamine group highlights its potential as a significant alternative or adjunct to traditional opioid therapy. This study contributes to the growing body of evidence supporting the role of ketamine in pain management, particularly for conditions characterized by chronic pain and opioid tolerance.

To enhance the comparability and reliability of future research, further studies should focus on the standardization of pain scales when evaluating the efficacy of ketamine. Investigating ketamine's effects using specific dosages and closely monitoring its side effects will provide clearer insights into its potential benefits and risks. Additional research should also explore the combined effects of ketamine in young adults, examining hospitalization rates for VOC and comparing these outcomes to those associated with opioids. Such studies will be crucial for optimizing pain management strategies for SCD patients and improving their overall quality of life.

5 | CONCLUSION

The systematic review and meta-analysis highlight ketamine's potential in managing VOC among patients previously receiving opioids. The qualitative synthesis conducted showed that the intensity of pain was improved in patients receiving ketamine and that there was an opioid-sparing effect, with a considerable increase in side effects. However, a further meta-analysis of the data did not yield significant results in relationship to the reduction in the intensity of pain and the opioid-sparing effect. There was a significant association between the use of ketamine and the incidence of common side effects. However, no severe or life-threatening events were reported. It should be considered when interpreting this study that there was a diversity of study population, different scales, and small sample sizes while conducting the meta-analysis. There is currently no consensus on the optimal dosage and safe administration window for ketamine in this patient population. To establish ketamine as a safe and effective treatment for patients with sickle cell disease experiencing a VOC, additional studies are required to increase the statistical power of the research and to improve patient outcomes.

AUTHOR CONTRIBUTIONS

Ernesto Calderon Martinez: Conceptualization; project administration; supervision; writing—review and editing. **Stephin Zachariah Saji**: Data curation; validation; visualization; writing—original draft. **Thomas Campos Carmona**: Investigation; validation; writing—review and editing. **Druvini Fernando**: Formal analysis; writing—review and editing. **Nithin Karnan**: Investigation; validation; writing—original draft and review and editing. **Suchita Mylavarapu** and **Mishell Estefanía Llerena Vargas**: Methodology; writing—review and editing. **Mohammad Salman; Vaidarshi Abbagoni**; **Nathalia Schettino Samad**; **Arvapalli Lakshmi Sheethal**; and **Camila Sanchez Cruz**: Writing—original draft and review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

FUNDING INFORMATION

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article.

ETHICS STATEMENT

This study did not require ethical approval in accordance with local guidelines.

PATIENT CONSENT STATEMENT

As this study is a meta-analysis of previously published data, no new individual patient data were collected or analyzed. Therefore, patient consent was not required for this research. All data used in this analysis were derived from studies that had obtained necessary ethical approvals and informed consent from participants.

CLINICAL TRIAL REGISTRATION

PROSPERO ID-CRD42024547550.

PERMISSION TO REPRODUCE MATERIAL

This manuscript does not reproduce any material from other sources. All tables, figures, and content were generated through the authors' original analysis of the data included in the meta-analysis.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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