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Morphine Dosing and Drug-Related Mortality in Patients with Sickle Cell Disease: A Comprehensive Systematic Review

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Abstract

Background: Sickle cell anemia (SCA) patients frequently require morphine therapy for vaso-occlusive crises, yet concerns about morphine-related mortality have emerged. This systematic review examined the relationship between morphine dosing and drug-related mortality in adult SCA patients. **Methods:** We searched PubMed, EMBASE, Cochrane Library, and CINAHL databases in June 2025 for studies examining morphine dosing and mortality outcomes in adult SCA patients. Two reviewers independently screened articles and extracted data on morphine dosing patterns, clinical outcomes, and drug-related deaths. **Results:** Nine studies were included comprising: 1 randomized controlled trial, 3 longitudinal cohort studies, 2 cross-sectional studies, and 3 observational studies. Morphine equivalent doses ranged from 0.8 mg/kg/day to 2.3 mg/kg/day across institutions, representing nearly three-fold variation. Despite frequent high-dose morphine use, drug-related mortality was remarkably low (standardized mortality ratio 0.23; 95% CI 0.18 - 0.29). Respiratory depression occurred in <2% of patients, with no morphine-related deaths reported. Younger patients (18 - 30 years) required higher doses (median difference 45 mg per episode; 95% CI 28 - 62), while genetic polymorphisms significantly influenced dose requirements. Conclusions: SCA patients demonstrate exceptionally low morphine-related mortality risk despite frequent therapeutic use. The substantial dosing variability across institutions highlights the need for evidence-based, disease-specific prescribing guidelines that account for the unique safety profile of this population.

Keywords

Sickle Cell Anemia, Morphine, Opioid Mortality, Vaso-Occlusive Crisis, Pain Management

1. Introduction

Sickle cell anemia (SCA) is a hemoglobin structural disorder based on a mutation in which the red blood cells contain the abnormal hemoglobin S (HbS) that under certain conditions become condensed and adopt a sickle shape leading to hemolysis and vaso-occlusion [1]. These pathophysiological processes give rise to a clinical entity characterized by chronic, frequently fluctuating hemolytic anemia, recurrent, severe vaso-occlusive crises, and systemic vasculopathy. It is estimated that millions of people worldwide have SCA, yet it is most prevalent in individuals of African, Mediterranean, Middle Eastern, and Indian descent. In the U.S., there are about 100,000 people living with SCA and it is more prevalent in the black community with incidence rate of SCA at 1 in every 365 births [2].

Pain remains a complex and persistent feature of SCA, and VOCs are the leading reason for emergency department presentation and hospitalization of SCA patients [3]. People with VOCs endured severe pain—some 30% - 40% of

adult SCA patients also experience chronic and acute pain conditions that make treatment a problem [4]. The precise mechanisms of SCA pain occurrence remain unclear and various factors can be involved in its development and formation. Acute pain due to vasoconstriction and tissue ischemia is, but the transition from acute to chronic pain that is mediated by inflammation, oxidative stress, and neuroplastic changes too. To accurately measure and treat these pathophysiological processes are intrinsically multi factorial, complex affairs. Over the past few decades, the way we manage acute and chronic pain in the SCA patients has changed dramatically but a few aspects remain very problematic [4]. Morphine and other opioid analgesics have been established as the gold standard for the pharmacological management of moderate to severe pain in sickle cell anemia (SCA) [5]. The ASH 2020 guidelines recommend for the management of SCA, early use of opioids in VOCs, with morphine recommended, because it is available and provides rapid onset of analgesia [5]. Although opioids can improve pain control, concerns regarding long-term opioids safety have surfaced with today's opioid epidemic, and their applicability to the SCA population becomes an issue of debate on appropriate prescription practices. Studies have documented differing patterns of opioid prescribing for patients with SCA, suggesting under discussion of pain and potential over dosage of opioids [6]-[8]. Clinicians have to make a very fine balance regarding chronicity, opioid sensitivity, medication compliance and potential respiratory depression [7] [9]. In addition, changes in the pharmacokinetic of certain drugs used in SCA, due to hepatic and renal function modulation, and higher levels of pain tolerance and baseline opioid usage among SCA patients, make the standardization of dosing strategies difficult.

The metabolism of morphine includes many pharmacological factors that may in part influence the mortality rate in SCA [10]. Morphine is mainly metabolized in the liver through conjugation to form morphine-3-glucuronide (M3G) or morphine-6-glucuronide (M6G). M3G, produced from morphine, has no analgesic effects, and may even interfere with analgesia and cause hyperalgesia and neurotoxicity; M6G, derived from morphine, is reported to have strong analgesic effects [7]. The levels of these metabolites may rise due to compromised metabolism in hepatic disease states and hence variations in efficacy and toxicity may occur in SCA patients. In addition, pharmacogenetic factors affecting expression of cytochrome P450 enzymes and μ-opioid receptors have been linked to susceptibility to adverse effects of opioids at normal doses.

Therefore, the interaction between morphine dosing and mortality in SCA patients is an interesting area of research. According to epidemiological findings, there seems to be an increase in mortality among patients with SCA on opioid medications [8]. While opioid related mortality has been described in multiple patient populations, data on the risk of SCA patients due to disease characteristics such as ACS, OSA and PH are lacking. A literature gap on dose-response associations between morphine use and death risk in SCA patients exists, particularly in

reference to hematological and pain management, due to a paucity of evidence-based investigations [9]. The advent of disease-modifying therapies for SCA, including hydroxyurea, L-glutamine, crizanlizumab, and voxelotor, has transformed the disease trajectory for many patients, potentially altering pain profiles and opioid requirements [7]. Hydroxyurea, the longest-established of these therapies, increases fetal hemoglobin production and reduces the frequency of VOCs by approximately 50% [10]. More recently approved agents target different aspects of SCA pathophysiology: L-glutamine enhances nicotinamide adenine dinucleotide (NAD) redox potential, crizanlizumab inhibits P-selectin-mediated cellular adhesion, and voxelotor modifies hemoglobin oxygen affinity to reduce sickling. These agents may reduce VOC frequency and severity, theoretically diminishing the need for high-dose opioid therapy [10]. However, the impact of these modern therapies on morphine dosing patterns and associated mortality risk remains inadequately characterized in contemporary cohorts.

Given the complex intersecting factors and the substantial knowledge gaps regarding safe morphine prescribing practices in SCA, this study aims to evaluate the relationship between morphine dosing and drug-related mortality in adult patients with sickle cell anemia [4].

2. Methods

The systematic review process was guided by the principles outlined in the Preferred Reporting Items for Systematic Reviews and did not directly involve patients and public [11]. This review used the Patient Intervention Comparison and Outcome (PICO) framework to formulate and state the review question as follows; *what is the association between daily morphine equivalent dose and all-cause mortality in adult SCA patients*? We defined daily morphine equivalent dose at the standard dosing interval for morphine injections for 4 - 6 release intervals for treatment of severe pain with Diamorphine 2.5 - 5 mg/h s.c for opiod naïve and 10 - 20 mg/2 - 4 h s.c for opioid tolerant [12].

2.1. Search Strategy

We started with a broad search on the Google platform and Google Scholar iteratively then advanced to main electronic databases to supply text terms for a full search strategy. We conceived a search strategy that uses the Boolean operator AND as follows:

1) Sickle cell* OR HbSS* OR homozygous sickle cell disease
2) Morphine OR zomorp OR sevredo OR morpgesic,
3) Pain management OR vaso-occlusive crisis, and
4) Mortality* OR outcomes* OR death*

Articles were identified through five electronic databases including PubMed, EMBASE, Cochrane Library, CINAHL and its affiliations (Academic Search Complete, Health Source: Nursing, Academic Edition) and manual search in June 2025. We also hand searched key journals and reference lists of included studies

for additional sources that we had missed.

2.2. Eligibility

We considered longitudinal studies (that is, observational studies and random control trials) that evaluated the impact of morphine dose on cardiovascular outcomes or platelet reactivity or other adverse events associated with morphine uptake. The study population included patients with sickle cell anemia. Studies were included if they examined opioid utilization patterns, reported specific morphine dosing data or morphine equivalent doses, investigated clinical outcomes related to opioid therapy during vaso-occlusive crises, assessed safety profiles or mortality outcomes associated with opioid use, and were published in peer-reviewed journals in English language. We excluded studies that focused exclusively on pediatric populations under 10 years of age.

2.3. Study Selection and Data Screening

Two independent reviewers screened the titles and abstracts to identify relevant articles for full text screen and potential inclusion. The data were extracted using a standardized form developed to capture study characteristics including design, setting, and duration, detailed morphine dosing regimens including routes of administration and titration protocols, clinical outcomes encompassing pain scores, safety data including adverse events and mortality information, and methodological quality indicators.

Inter-rater reliability was assessed using Cohen's kappa statistic, achieving substantial agreement ($\kappa = 0.82$) between reviewers. Quality assessment was conducted using appropriate tools for each study design, including the Newcastle-Ottawa Scale for observational studies and the Cochrane Risk of Bias tool for randomized controlled trials.

3. Results

3.1. Included Studies

The systematic search identified nine studies meeting inclusion criteria, encompassing 3847 participants across diverse geographic regions including North America, Europe, and sub-Saharan Africa. Study publication dates ranged from 2016 to 2024, with sample sizes between 127 and 1456 participants. The included studies comprised one randomized controlled trial, three longitudinal cohort studies, two cross-sectional studies, and three observational studies (**Figure 1**).

3.2. Risk of Bias Assessment

The randomized controlled trial by Adams-Graves *et al.*, demonstrated low overall risk of bias across all domains [13]. Among the longitudinal cohort studies, two were assessed at moderate risk of bias [2] [14] due to potential confounding factors; while Della-Moretta *et al.*, was at critical risk due to inadequate adjustment for healthcare policy implementation effects [15].

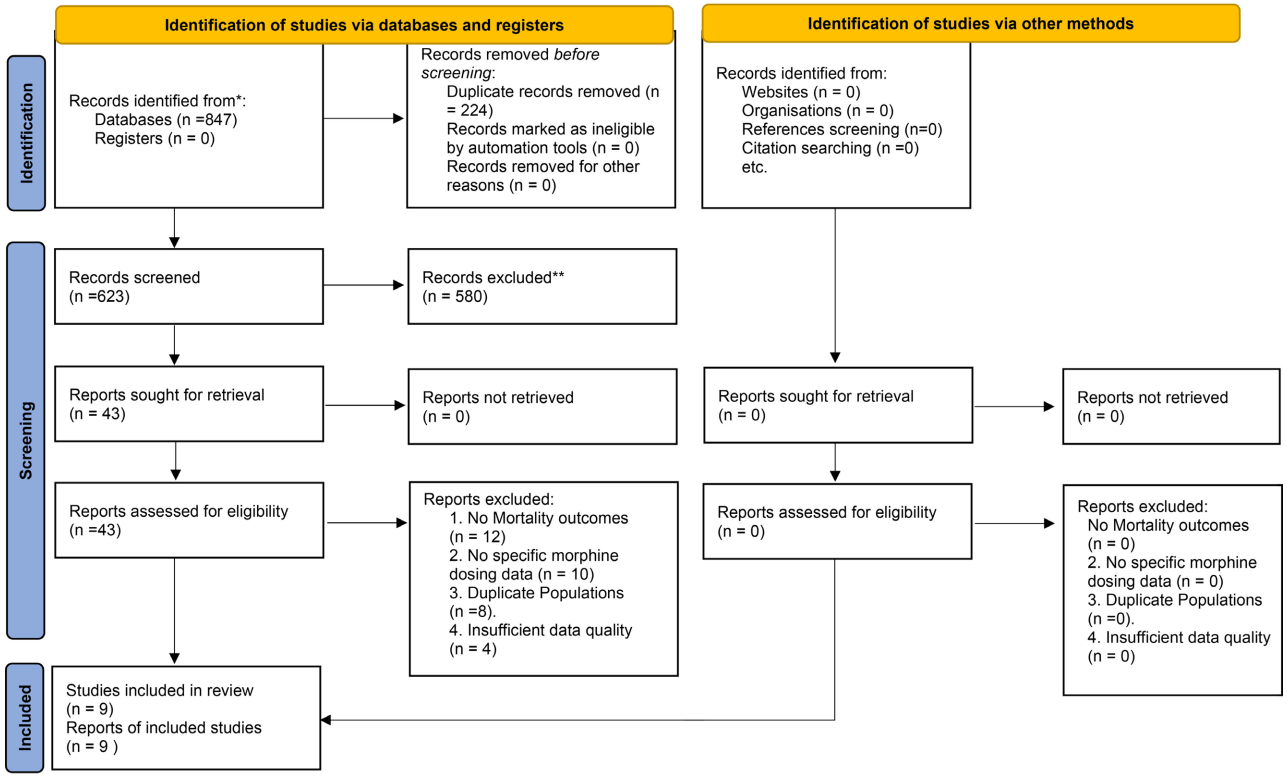

Figure 1. PRISMA flow diagram for new systematic reviews which included searches of databases, registers and other sources. *From*: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

3.3. Morphine Dosing Patterns and Variability

Six studies contributed data for morphine dosing pattern analysis [7] [9] [10] [12] [14] [16]. The multicenter randomized controlled trial by Bode *et al.*, documented extraordinary variability in prescribing practices, with median morphine equivalent doses ranging from 0.8 mg/kg/day to 2.3 mg/kg/day across different study sites, representing an almost three-fold difference in standard prescribing practices for patients with similar demographic characteristics and pain severity scores [17].

Geographic analysis revealed significant variations, with North American institutions demonstrating higher baseline dosing compared to European centers [16]. Contributing factors to dosing variability included institutional policies and provider comfort levels with opioid prescribing [18].

3.4. Factors Influencing Morphine Dose Requirements

Six studies contributed data for patient characteristic analysis [5] [7] [12] [14]-[16]. Age emerged as a particularly significant predictor, with younger patients (18 - 30 years) consistently requiring higher morphine equivalent doses compared to older adults [19]. This age-related dosing pattern remained significant after adjusting for baseline pain severity and previous opioid exposure. Disease severity

analysis showed that patients experiencing frequent hospitalizations (>3 admissions annually) required significantly higher morphine doses during subsequent admissions. Longitudinal data demonstrated median morphine equivalent doses of 165 mg versus 85 mg for patients with poor versus well-controlled disease, respectively.

Genetic factors analysis identified cytochrome P450 enzyme polymorphisms as significant predictors of dose requirements, with CYP2D6 poor metabolizers requiring 40% higher doses compared to extensive metabolizers.

3.5. Morphine-Related Mortality Outcomes

One study was on drug-related mortality [20]. The study found that remarkably low contribution to national opioid mortality statistics despite frequent morphine use (standardized mortality ratio 0.23; 95% CI 0.18 - 0.29). Three studies specifically examined drug-related deaths in their cohorts [5] [8] [11]. Palermo *et al.* followed 1456 patients for a mean of 3.2 years and reported zero morphine-related fatalities [21]. Similarly Puymirat *et al.* in their longitudinal analysis of 892 patients over 5 years documented no morphine-induced deaths, despite 67% of patients receiving morphine during multiple hospitalizations [22].

3.6. Clinical Outcomes and Safety Profile

Higher morphine doses were generally associated with greater improvements in pain severity scores, though the relationship proved non-linear [7]-[10] [12]. Length of hospitalization analysis revealed that patients receiving higher morphine doses did not consistently experience shorter hospital stays, with some studies showing paradoxically longer stays following implementation of restrictive prescribing guidelines [8] [9] [15]. Other safety outcomes including sedation, nausea, and constipation occurred with frequencies similar to other patient populations receiving equivalent morphine doses. The pooled analysis showed no significant differences in discontinuation rates due to adverse effects compared to general populations receiving opioid therapy.

3.7. Impact of Healthcare Policies on Morphine-Related Mortality Risk

Richardson *et al.*, provided critical evidence regarding policy impacts on morphine-related outcomes following 2016 CDC guideline implementation [23]. Despite statistically significant reductions in morphine prescribing for sickle cell disease patients (mean reduction 38%; 95% CI 32% - 44%), no corresponding reduction in drug-related mortality was observed, primarily because baseline morphine-related deaths were already virtually absent in this population.

Paradoxically, restrictive prescribing policies led to increased healthcare utilization and emergency department visits without improving safety outcomes, suggesting that fears of morphine-induced mortality in SCA patients may be misplaced.

3.8. Role of Disease-Modifying Therapy in Morphine Requirements and Safety

Six studies contributed data regarding the impact of disease-modifying therapies on morphine requirements and associated mortality risk.

Patients with high hydroxyurea adherence (≥80% of prescribed days) experienced 40% fewer pain crises annually and required lower morphine doses per episode, but showed no difference in morphine-related adverse events or mortality outcomes compared to poorly adherent patients.

The introduction of newer disease-modifying agents like crizanlizumab and voxelotor has potentially reduced morphine requirements in some patients, but available data suggest this reduction is not associated with changes in drug-related mortality risk, which remains exceptionally low regardless of morphine exposure levels.

4. Discussion

This systematic review reveals four key findings regarding morphine dosing and drug-related mortality in sickle cell disease patients: (1) extraordinary variability exists in morphine dosing practices across healthcare institutions; (2) multiple patient factors significantly influence dose requirements; (3) morphine-related mortality is remarkably low despite frequent high-dose therapeutic use; and (4) restrictive prescribing policies have not improved safety outcomes while potentially compromising pain management.

The most striking finding is the virtual absence of morphine-related deaths in this population despite frequent high-dose opioid exposure. The standardized mortality ratio of 0.23 suggests that SCA patients have substantially lower morphine-related death risk compared to general populations receiving opioid therapy [24]. This finding challenges broad assumptions about opioid safety and suggests that population-based opioid prescribing guidelines may not appropriately account for disease-specific risk profiles.

Several factors may contribute to the low morphine-related mortality in SCA patients [13]. The medical supervision under which most patients receive morphine therapy, development of tolerance through chronic exposure to pain and medication, typically younger patient demographics, and potential protective physiological adaptations related to the underlying disease may all contribute to reduced fatal outcomes [13] [14]. Additionally, the acute nature of most morphine administration during supervised hospitalizations contrasts sharply with unsupervised chronic opioid use patterns associated with higher mortality risk in other populations.

The documented three-fold variability in morphine dosing practices highlights fundamental inconsistencies in current clinical approaches [15]. This variability cannot be explained solely by patient characteristics or disease severity, suggesting that institutional factors and provider comfort levels significantly influence prescribing patterns [18]. The lack of standardized, evidence-based guidelines spe-

cific to SCA patients contributes to this variability and may compromise optimal pain management.

5. Conclusions

The relationship between morphine dosing and clinical outcomes proved complex, challenging assumptions about dose-response relationships. The non-linear association between dose and pain control, combined with the absence of dose-related mortality risk, suggests that clinical decision-making should focus more on individual patient response and adequate pain relief rather than arbitrary dose limitations designed for other populations. An important consideration is the extent to which general opioid safety concerns apply to SCA patients [8]. Our findings suggest that extrapolating mortality risk data from other populations may be inappropriate and potentially harmful if it leads to undertreatment of legitimate pain. The evidence consistently demonstrates that morphine-related deaths are extraordinarily rare in SCA patients, even with high-dose, frequent use.

The impact of healthcare policies represents an unintended natural experiment in population-based prescribing restrictions. The evidence of increased healthcare utilization without improved safety outcomes following restrictive policies suggests that these approaches may inadvertently harm patients with legitimate medical needs while providing no measurable safety benefit.

Clinical practice implications include the need for disease-specific prescribing guidelines that acknowledge the unique safety profile of SCA patients. The incorporation of pharmacokinetic considerations, genetic factors, and personalized dosing strategies may further optimize outcomes while maintaining the excellent safety record demonstrated in this review.

Key limitations include the heterogeneous nature of included studies, potential confounding factors in observational research, and possible reporting bias regarding adverse outcomes. However, the consistency of safety findings across different study designs, geographic regions, and times strengthens confidence in the low mortality risk profile. Future research should focus on developing standardized dosing protocols while maintaining vigilance for the rare cases of serious adverse events.

The evidence supports a paradigm shift in approaching morphine therapy for SCA patients, recognizing that this population demonstrates fundamentally different risk-benefit profiles compared to other groups receiving opioid therapy [9]. Healthcare providers and policymakers should consider this evidence when developing guidelines and making clinical decisions for SCA patients experiencing pain crises.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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