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Regional anesthesia and analgesia in sickle cell pain episodes: A scoping review

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ABSTRACT

Review purpose: Sickle cell disease (SCD) vaso-occlusive crises are the most common reason patients with SCD present for medical care in the US. The goal of this scoping review is to outline existing literature on regional anesthesia for sickle cell vaso-occlusive crises (VOC) and identify areas for future research.

Methods: We searched the Cochrane Central Register, Ovid-Medline and EMBASE, PubMed, and additional review sources to identify studies evaluating the benefit of regional anesthetic blocks for medication refractory vaso-occlusive crises in pediatric and adult patients.

Summary of findings: One-hundred and three articles were identified through the above search methodology. Following application of the exclusion criteria, the four pediatric case reports, one pediatric case series, and one adult case report that were found during the scoping review process were analyzed given the scarcity of available published research on nerve blocks for the treatment of SCD pain crises. Five of the 6 articles involved blocks for pain refractory to patient-controlled analgesia (PCA) despite dose escalation. One case report utilized a continuous femoral block in a patient with known morphine and new hydromorphone allergy presenting with right thigh pain. One case report recounts an epidural used for labor pain that eliminated concomitant vaso-occlusive leg pain during labor. All 6 authors achieved analgesia and a marked decrease or a total discontinuation in opioids following the block. In one case, the patient was noted to have a shorter length of stay. No studies other than those reports included were found

Conclusion: There is a severe dearth of evidence evaluating the benefit of regional anesthesia in SCD pain crises. Available case reports and the included case series demonstrate that regional nerve blocks are a potential tool to consider when treating refractory vaso-occlusive pain in patients with SCD. There is urgent need for future research on evaluating regional anesthesia for patients with SCD-related vaso-occlusive crisis pain.

1. Introduction

Sickle cell disease (SCD) occurs when the 6th position on the 11th chromosome, which normally codes for glutamic acid, is substituted by valine [1]. When only a single mutated allele is present, the affected individual is capable of producing greater than 50% normal beta globin chain and is effectively a clinically silent "carrier." However, children that are homozygous for hemoglobin S are incapable of producing normal beta globin chains and instead produce abnormal sickle cell hemoglobin tetramers that are prone to polymerization during periods of physiological stress such as hypoxia, acidosis, infection, and dehydration [2,3]. These changes are responsible for the propagation of the hemolytic anemia and vaso-occlusive events that occur during sickle cell crises [4].

Prior research has demonstrated that the above changes results in 4 characteristic processes that underlie the pathologic sequalae of SCD: 1) Hemoglobin S polymerization results in sickling of blood cells; 2) Sickling results in vaso-occlusion that promotes adhesion between sickled red blood cells, platelets, neutrophils, and vascular endothelium; 3) Microvascular vaso-occlusion promotes ischemic reperfusion injury that promotes sterile inflammation that acts in a positive feedback loop to further promote increased vaso-occlusion; and 4) Sickling induces hemolysis, promotes endothelial dysfunction, decreases nitric oxide formation, and upregulates formation of hydroxyl free radical (OH*) damage via the Fenton reaction [5]. Overall, it is this inflammatory vaso-occlusive cascade that accounts for the characteristic features of SCD including anemia, acute pain in ischemic extremities/digits, acute chest syndrome, renal impairment, auto-splenectomy, stroke, and priapism.

In the United States, this mutation disproportionately affects African

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Americans (1/13 carriers and 1/365 homozygous SCD) and Hispanic-Americans (1/16,300 homozygous SCD) [6]. In total, the estimated number of Americans with SCD is 100,000 [7]. Among affected individuals, population statistics indicate that people born with SCD are living longer (Median life expectancy: 28 years in 1979; 40–53 years in 2017) [8,9] presumably due to early medical interventions in childhood which reduce long term morbidity and mortality.

Evidence based treatment guidelines have been instrumental in reducing morbidity and mortality in SCD [10]. Epidemiological data for American pediatric and adult patients indicate that the average life expectancy for these patients has nearly doubled in the last 5 decades. Despite increased life expectancy over this period of time, the average adjusted (sex, age group, time period) annual death rate has remained stable between 1981 and 2017 (1.54 deaths/100,000 in 1981 to 1.91/100,000 in 2017) [9]. Despite reduced morbidity and mortality, SCD-related pain has remained challenging. Multiple vaso-occlusive crises (VOC) result in high hospitalization rates, patient costs, and strain on the healthcare system. For example, between 2000 and 2016 the Agency for Healthcare Research and Quality (AHRQ) compiled and analyzed data on SCD-related inpatient hospitalizations. In 2016, a total of 134,000 inpatient hospitalizations were related to SCD. Of these hospitalizations, over 75% involved a pain episode. During this time, the aggregate cost of inpatient SCD-related stays was over $811 M during an average 5-day hospitalization. Among those hospitalized for a sickle cell pain episode, 30-day readmission rates were markedly higher when compared to SCD patients not admitted for a pain episode (32.9% versus 21.0%) [11]. Furthermore, studies by Ho et al. on national hospital admission rates demonstrated a steady increase in admissions between 2004 and 2014 (106/100,000 to 137/100,000) [12].

2. Treatment and prevention strategies

The most common reason for hospitalization of patients with SCD is a pain episode secondary to vaso-occlusion mediated inflammation and local cellular damage. In general, patients who have had pain episodes before will have an at home oral pain regimen. As such, patients who present to the hospital are likely a smaller subset of patients with pain refractory to their normal home analgesic regimen. To address this refractory pain, rapid triage ideally within 15 min of hospital arrival, treatment of pain within 30 min with opioids (ideally intravenous (iv) morphine or hydromorphone), and fluid resuscitation if indicated have been advocated [13]. If after 3 or more doses of opioids (spaced apart by the opioid-specific time of peak effect) pain control is inadequate, patients are generally admitted and started on patient controlled/continuous (PCA) opioid analgesia therapy [13]. Despite being the mainstay of treatment for severe SCD pain, continuous and demand opioid medication side effects can preclude treatment success in some patients. Common side effects include sedation, respiratory depression with higher doses, constipation, nausea, and pruritis. In addition, after multiple hospital admissions for VOC, opioid tolerance develops, and the patient's pain becomes more difficult to control with conventional analgesics.

Other treatment approaches for pain control in SCD include hydration to correct underlying hypovolemia often present during pain episodes, ketamine in the case of refractory pain with hyperalgesia, nonsteroidal anti-inflammatory drugs (NSAIDS), ketorolac, and heat packs. Of note, caution should be used when Ketorolac is added to multimodal treatment regimens during VOC, as it can increase the risk of acute kidney injury (AKI) in a dose-dependent manner in an already at-risk patient population [14].

3. Nerve block and neuraxial analgesia in SCD pain episode

Neuraxial and peripheral nerve blocks (either single shot or continuous infusion via catheter) have infrequently been used in conjunction with the traditional treatment strategies to treat SCD pain episodes [15]. Given their favorable prospect for improved pain control, reduction of opioid consumption, decreased length of stay, and prevention of chronic pain sensitization, utilizing these techniques, particularly in patients with localized and medical refractory pain, could potentially lead to improved patient outcomes. Furthermore, while the most recent 2020 American Society of Hematology guidelines for acute and chronic pain management suggest regional anesthesia techniques for "localized pain that is refractory or not effectively treated with opioids alone," peer reviewed quality research evaluating the benefits of these techniques are lacking [15]. As such, we planned the scoping review that follows to obtain existing literature on this topic with the following aim:

4. Study aim

To determine if peripheral nerve blocks reduce pain scores, opioid requirements, hospital length of stay, and readmission rates in SCD VOC we carried out a scoping review using the PRISMA protocol [16]. The review questions and objectives are appropriately studied using a scoping review with an inherently broader scope with more expansive inclusion criteria. This methodology was necessary given the relative dearth of published studies on peripheral nerve blocks for the treatment of SCD VOC.

5. Methods

5.1. Search strategy

A query of the Cochrane Central Register, Ovid-Medline and EMBASE, PubMed, and additional review sources was conducted. Search terms used during query were as follows: ("sickle cell" OR "sickle cell anemia" OR "SCD" OR "hemoglobin SS" OR "pain crisis" OR "pain episode" OR "vaso-occlusive crisis") AND ("nerve block" OR "block" OR "Regional" OR "brachial plexus anesthesia" OR "cervical plexus block" OR "ganglion block" OR "intercostal nerve block" OR "lumbar plexus block" OR "paracervical block" OR "stellate ganglion block").

5.2. Inclusion and exclusion criteria

Prior to conducting the scoping review, search investigators delineated the following inclusion criteria: 1) Articles will include results on peripheral nerve blocks or neuraxial blocks used for pain treatment during an active SCD pain episode; 2) Articles included should utilize either a single shot or continuous catheter-based technique for delivery of local anesthetics/pain adjuncts. 3) Articles included should be published in English, published in any year, and must be peer-reviewed and published. Important exclusion criteria included the following: 1) Articles solely using a block or continuous catheter technique for perioperative pain control (i.e. no active acute pain episode) were excluded; 2) Conference presentations and expert opinion were also excluded due to inferiority of evidence quality, heterogeneity of methodology, and uncertain generalizability.

6. Results

Of the 103 original screened articles, 5 case reports and 1 case series met inclusion criteria for initial scoping review. (Fig. 1). Despite the lack of sufficiently strong scientific level of evidence (Level 1/large randomized control trials (RCT), 2/small RCT or 3/cohort or case control study) [17], the 4 pediatric case reports, 1 pediatric case series, and 1 adult case report included for analysis in this scoping review were analyzed and presented as below.

6.1. Peri-pain episode opioid requirement modulation and hospital length of stay

Five out of 6 of the assessed articles discussed pre- and post-block opioid requirements (Table 1). Hardy et al. describe the use of a lumbar

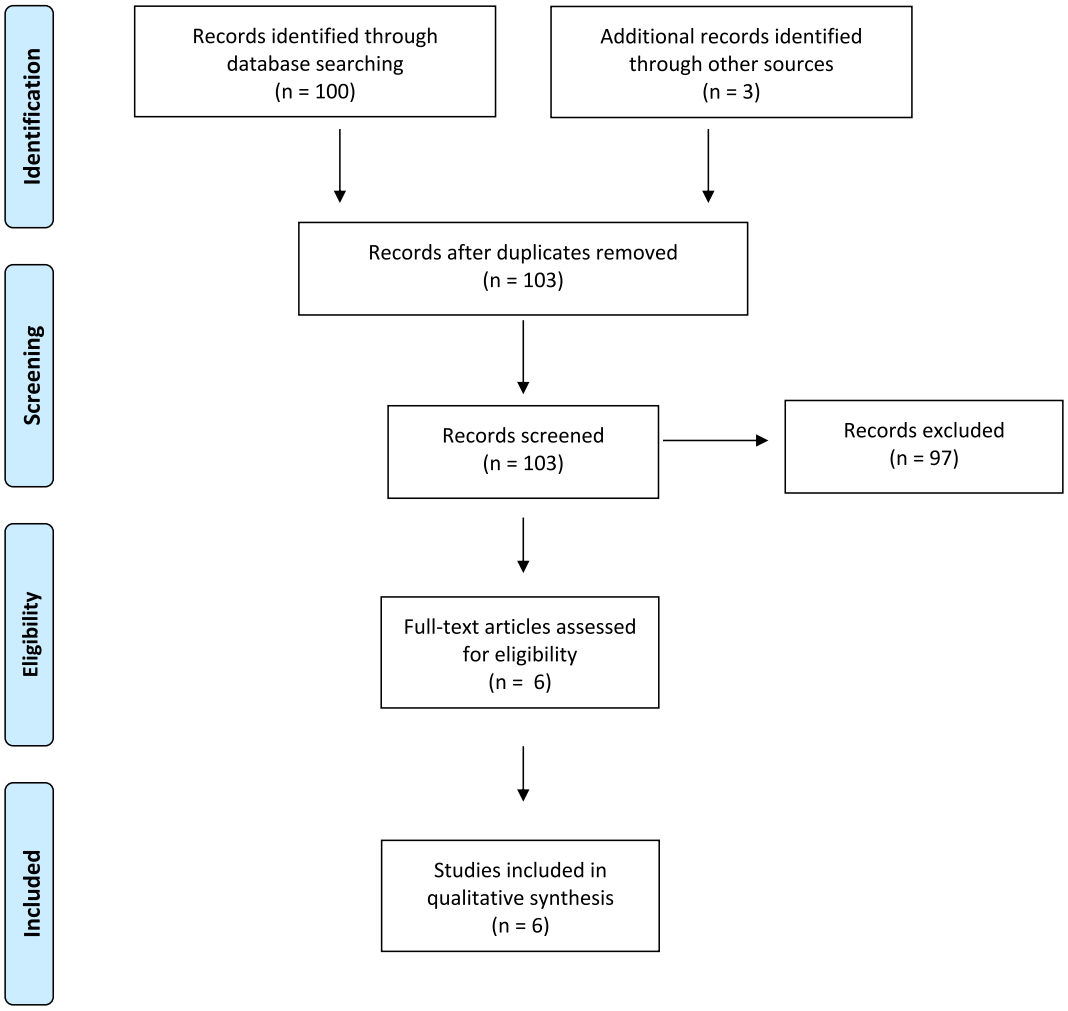

Fig. 1. PRISMA scoping review search yield, exclusion, and inclusion flow diagram.

epidural pain catheter for pre-operative pain control in a case of refractory priapism requiring surgical shunt creation. In their case report, a 7-year-old African American boy was admitted to the hospital with priapism, a low-flow veno-occlusive outflow obstruction of the penis that can result from sickled blood cells when caused during VOC, pleuritic chest pain, and dyspnea at rest. Prior to the procedure the boy required a 40mcg/kg/h morphine infusion for severe (10/10) refractory pain. Following the epidural catheter placement at the L3/4 interspace, and after confirmation with a test dose of 2 ml 0.25% bupivacaine (with additive 1:200,000 epinephrine), the patient had complete resolution of priapism-related penile pain and had partial resolution of priapism without the intended surgical shunt intervention. The epidural catheter anesthetic was 0.125% bupivacaine without opioid infused at a rate of 0.25 ml/kg/h until total resolution of priapism 16 h later [18]. Overall, no additional pain medications were needed for priapism-related pain from the time of epidural block until discharge 48 h after the block placement.

The next case report assessed involved a 12-year-old African American female admitted with refractory right thigh pain (10/10) that her family had attempted to treat at home for the past 24 h with home oral ibuprofen and oxycodone [19]. In the context of initiating a 0.2 mg basal rate/0.2 mg demand with 15 min lockout hydromorphone PCA (given prior history of morphine intolerance with shortness of breath and rash) a pruritic rash erupted and she was switched to oral long acting oxycontin 10 mg every 12 h and oxycodone 5 mg every 4 h with minimal improvement of her right thigh pain.

MRI confirmed a right proximal femur diaphysis infarction, the pain team placed a femoral nerve block catheter with a continuous infusion of 0.2% ropivacaine (7 ml/h titrated down to 3 ml/h given concern for numbness in that thigh) following a single shot 8 ml 2% lidocaine bolus. No IV opioids were needed following block initiation and the catheter was turned off and removed on post-procedure day 4. Prior to discharge the patient was transitioned to oral oxycodone and transdermal fentanyl patch without issue.

The third case report by Wyatt and colleagues involved a 15-year-old male who presented for a vaso-occlusive pain episode involving both of his hips and thighs. Despite 101.5 mg of iv morphine over the first 24-h hospital period, his right hip pain persisted. In conjunction with the pain service, and after MRI confirmation of right femoral epiphyseal osteosclerosis without necrosis, the patient underwent a right sided pericapsular nerve group block (16 ml bupivacaine 0.25% with unspecified dose of dexmedetomidine) and femoral nerve block (8 ml bupivacaine 0.25% with dexmedetomidine). Post-block he reported no (0/10) pain, had full hip range of motion and was able to ambulate. The patient's pain level was maintained between 0 and 2/10 for 24 h post-block. Of note, he required no opioids between the time the block was performed to the time of block sensory extinction. Furthermore, he only required 11 mg iv morphine equivalents after that point and was discharged without adverse events 48 h after the block placement.

The fourth case report by Weber and colleagues described a 14-year-old male who had previously been treated for vaso-occlusive pain crises at that facility multiple times in the past [20]. On presentation he reported right ankle pain for the past day following skin exposure to snow. Despite 4 doses of 3 mg iv morphine at a community hospital his pain was refractory, and he was transferred to his regular tertiary center where he

Table 1
Sickle cell disease (SCD) pain episode case reports that utilized regional anesthesia for refractory pain with salient features and findings. *VAS: Visual Analog Pain Scale; *Dex: Dexmedetomidine. *MME: Morphine Milligram Equivalents. *AVN: Avascular Necrosis.

Author (Year published)	Patient age, sex (M/F)	Pain features	Pre-block pain regimen	Pre-block pain VAS*	Peri-block pain regimen	Post-block pain scores	Notes
Finer et al. (1988)	22yo, F	Diffuse left lower extremity pain.	None; Labor epidural for spontaneous vaginal delivery.	Not listed	L4/5 epidural with test dose of 3 ml of 0.5% bupivacaine with 1:200,000 epinephrine and 10 ml 0.25% bupivacaine, followed by 5mcg/ml fentanyl epidural infusion at 8 ml/h.	0/10	Complete resolution of pain crisis pain following epidural and no recurrence of pain after infusion stopped 12 h post-delivery.
McHardy et al. (2007)	7yo, M	Penile pain secondary to priapism	40mcg/kg/hr morphine infusion	10/10	L3/4 epidural 0.125% bupivacaine at 0.25 ml/kg/h	0/10	Patient epidural was placed to provide pre- and intraoperative pain control for arterio-venous shunt to treat refractory priapism. After the epidural placement his priapism partially resolved without surgery.
Vuong et al. (2012)	12yo, F	Right thigh pain refractory to oxycodone and ibuprofen treatment at home initially	Oxycontin 10 mg q12 h, oxycodone 5 mg q4h, and iv hydromorphone as needed for breakthrough; 17.5 mg iv ketorolac q6h	10/10	Femoral nerve block 2% lidocaine 8 ml bolus 0.2% ropivicaine titrated from 7 ml/h to 3 ml/h; Post block day 3 catheter turned off and bridged to 50mcg/hr fentanyl patch and home oxycodone regimen	No score provided; Noted as "controlled"	The patient was initially on a hydromorphone PCA 0.2 mg basal with 0.2 mg bolus and 15 min lockout, but discontinued after she developed a diffuse rash and pruritis. Prior history of morphine "intolerance" which presented as shortness of breath and pruritic rash. Ropivicaine infusion turned down from 7 ml/h to 3 ml/h for infusion numbness concerns.
Weber et al. (2017)	14yo, M	Right ankle pain, numbness, and cold sensation	4 doses of 3 mg morphine iv prior to transfer to tertiary center; hydromorphone PCA 0.1 mg demand dose with 10-min lockout; 4.7 mg over 24 h prior to block.	9/10	Popliteal sciatic nerve block 0.1% ropivacaine 20 ml bolus and infusion run at 6 ml/h; PCA hydromorphone use decreased to 3.3 mg over 24 h post block. PCA discontinued by the end of the 2nd post block day and transitioned to home oxycodone 5 mg q4h prn, ibuprofen 400 mg and acetaminophen 650 mg q6h	0-2/10	Catheter stopped on hospital day 4 and removed on day 5. Discharge on day 8, which was 1 day earlier than his normal 9-day hospital stay for recurrent pain crisis in the past.
Wyatt et al. (2020)	15yo, M	Bilateral hip and thigh pain	101.5 mg iv morphine over the 1st 24 h hospital stay. 85 mg morphine iv on day 2.	9/10	Pericapsular nerve group (PENG) (16 ml 0.25% bupivacaine with DEX*) and femoral nerve blocks (8 ml 0.25% bupivacaine with DEX*); No opioids required during the 1st 24 h after block; Following block dissipation he required 11 mg morphine equivalents prior to discharge 48 h post block	0-2/10	The patient was unable to bear weight prior to the block despite high dose PCA morphine. Following the block, he was able to walk and had full range of motion of both lower extremities.
Karsenty et al. (2022)	16yo, F 13yo, M 11yo, M	Left upper extremity pain; Back and left shoulder pain; Neck, back, and bilateral upper extremity pain	1.1–1.3 mg/kg MME* daily during hospitalization prior to block; 0.7–0.9 mg/kg MME* daily during hospitalization prior to block; 0.8–0.9 mg/kg MME* daily during hospitalization prior to block	10/10 7/10 6/10	Left supraclavicular nerve block catheter for AVN* left humeral head (40 mg ropivacaine+4mcg DEX* loading; maintenance 0.1 mg/kg/h ropivacaine catheter infusion), ketorolac, ketamine, acetaminophen, lidocaine patch; No opioids required within 24 h of block placement. Left interscalene nerve block catheter (16 mg ropivacaine+4mcg DEX* loading; maintenance 0.1 mg/kg/h ropivacaine catheter infusion), ketorolac, ibuprofen, acetaminophen, lidocaine patch, methocarbamol; No opioids required within 24 h of block placement. Right interscalene nerve block catheter for AVN* right humeral head (50 mg ropivacaine loading; maintenance 0.1 mg/kg/h ropivacaine catheter infusion), ketorolac, ketamine, ibuprofen, acetaminophen, lidocaine patch, methocarbamol, gabapentin, diclofenac gel; No opioids required within 16 h of block placement.	0/10 0/10 0/10	Nerve block for sharp pain from left shoulder to elbow refractory to opioid up-titration and addition of subanesthetic ketamine. Discharged within 48 h of block initiation. Nerve block for left shoulder pain refractory to opioid up-titration with ensuing opioid-induced constipation and sedation which required the use of supplemental oxygen. Discharged within 48 h of block initiation. Nerve block for severe back, neck, and bilateral upper extremity pain initially responsive to subanesthetic doses of ketamine, but hallucinations prompted discontinuation of ketamine infusion and a block was completed when pain became refractory to iv opioid escalation. Discharged within 48 h of block initiation.

was admitted for pain control, advanced management, and observation. Pain medications included 620 mg iv acetaminophen every 6 h, ketorolac 15 mg iv every 6 h, and a hydromorphone PCA with no basal rate and 0.1 mg demand and a 10-min lockout (consumption of 4.7 mg hydromorphone in the first 24 h). Despite this multimodal approach, the pain in his right ankle continued to be 9/10. Following consultation and informed consent, the pain service placed a continuous popliteal sciatic nerve block via a lateral approach at the level of the right popliteal fossa (20 ml bolus 0.1% ropivacaine and continuous rate of 6 ml/h). Following the block, the patient's pain decreased from 9/10 to 3/10 and eventually 0/10 later that day. PCA use decreased significantly (down to 3.3 mg of hydromorphone over the next 24 h). Notably, by hospital day 4 he was transitioned to his home opioid medications, and by day 5 his perineural pain catheter was removed. Although it is unclear why he remained admitted for the next 3 days, he was discharged on hospital day 8, a full 24 h earlier than his multiple previous admissions for similar vaso-occlusive pain crises. Overall, pain control utilizing a continuous popliteal sciatic nerve block was superior to an oral/IV medications-only regimen in this patient.

The fifth case report by Finer and colleagues [21] recounted the presentation of a 22-year-old female who presented in labor with a concomitant sickle cell vaso-occlusive pain crisis in her left lower extremity. Per authors, she had had several left lower extremity pain crises involving her lower extremity joints that required hospitalizations with systemic narcotic treatment of unspecified dosages. The decision was made to proceed with epidural placement for labor analgesia and treatment of lower extremity pain. Following L4/5 interspace epidural placement with test dose of 3 ml of 0.5% bupivacaine with 1:200,000 epinephrine and 10 ml 0.25% bupivacaine the patient had complete resolution of labor pain and lower extremity pain. The patient delivered soon after block placement and given her lower extremity pain a 5mcg/ml fentanyl epidural infusion was started at 8 ml/h for 12 h following delivery and then removed. No recurrence of lower extremity pain was reported, and she was discharged thereafter, and authors confirmed through chart review that no additional analgesics were required prior to discharge. The patient “expressed satisfaction with the epidural technique over iv narcotics, primarily due to the lack of mental obtundation.”

The final included study, a case series by Karsenty and colleagues reported on 3 pediatric patients treated with regional continuous nerve block catheters for vaso-occlusive pain crises [22]. The first patient, a 16yo female, presented with left upper extremity pain resulting from vaco-occlusive-related avascular necrosis (AVN) of the humeral head. Despite up-titration of opioids and after the addition of subanesthetic ketamine infusion her pain was refractory and under minimal sedation (60 mg ketamine and 2 mg midazolam) she underwent a left supraclavicular nerve block (loading dose 40 mg ropivacaine with continuous perineural catheter infusion of ropivacaine at 0.1 mg/kg/h) with resolution of pain and total elimination of required narcotics within 24 h. The remaining 2 patients, a 13yo male and 11yo male, both underwent interscalene nerve blocks with continuous nerve block catheter therapy following development of upper-extremity vaso-occlusive crisis pain. Both interscalene blocks were placed following development of medication side-effects with up-titration and resultant need to discontinue or decrease medications (hallucinations with ketamine initiation in one patient and respiratory depression requiring oxygen in the other patient). Overall, all three patients had reduction in pain scores to 0/10 following block placement (post-block day 0), did not require opioids by 24 h post-block, and were discharged within 48 h of initiating continuous peripheral nerve block catheters.

6.2. Re-admission rates

None of the six included studies discussed readmission rates/events following nerve block for a vaso-occlusive pain episode.

7. Discussion

From as early as the first year of life patients with SCD experience pain directly arising from their disease pathophysiology [23]. As patients progress through childhood and adolescence painful crises often reflect an acute on chronic pain state [24,25]. Notably, SCD pain episodes are the most common reason people with SCD present for medical care in the US [26].

To aid providers in delivering best-practice pain management care for patients in SCD pain episodes, the American Society of Hematology published guidelines for the acute and chronic management of pain in patient with SCD [27]. Among the included recommendations, expeditious assessment and treatment of pain within 60 min of arrival to the emergency department, tailored escalation of opioid therapy when indicated based on patient's home regimen, a short course of nonsteroidal anti-inflammatory drugs pending no contraindications, use of subanesthetic (analgesic) ketamine infusion as an adjunct when pain in refractory to opioids alone, and use of regional anesthetic treatment modalities when pain is localized and refractory to treatment with opioids alone.

As suggested by the above studies, regional techniques for localized pain relief in patients during SCD pain episodes serve as a potential treatment modality in the case of refractory pain. The mechanism of analgesia is two-fold. First, regional nerve blocks directly block afferent nerve conduction through binding of voltage gated sodium channels in the inner pore of plasma membranes, thus inhibiting membrane depolarization and conduction [28]. Second, local anesthetic-mediated regional vasodilation, or sympathectomy-related vasodilation in the case of epidurals, reduces regional blood flow impedance and we hypothesize that the interplay of these two mechanisms are chiefly responsible for block-related analgesia.

Despite progressively larger doses of opioids, investigators from 4 of the 6 studies were unable to adequately treat their pediatric patient's pain with IV medications alone (Table 1). Furthermore, the progressive escalation of opioids carries the risk of increasing tolerance, hyperalgesia, and adverse effects (respiratory depression, nausea, constipation, pruritis, etc.) that are associated with larger doses of opioids. Thus, nerve block techniques, when paired with appropriate patient selection, help circumvent suboptimal pain treatment during opioid refractory pain episodes.

The fourth case report by Vuong et al. underscores the importance of patient variability and tailoring SCD pain crisis treatment regimens in the case of this 12-year-old girl who was intolerant of both morphine and hydromorphone PCAs. In patients with true opioid allergies where alternative pharmacologic treatments are inadequate, nerve block techniques can be an invaluable tool in the armament of the pediatric pain team.

Thoughtful patient selection is important in maximizing treatment success. Patients who suffer from distant multifocal pain, or a more global pain picture, are unlikely to reap the extent of analgesia attained in patients who have pain in a single limb or a localized area. In patients who have localized pain that is perceived to be amenable to a nerve block/continuous nerve block catheter, consent must be obtained from the parents or guardians in the case of non-emancipated minors less than 18 years old following an informed consent discussion on the risks, benefits, and alternative treatment modalities available. Patient cooperation during the block procedure is also important given the fact that most blocks will be performed under local anesthesia alone.

To the author's knowledge, no large robust clinical trials on nerve block and pain control in SCD patients during VOC currently exist. Although the authors acknowledge that the current mainstay treatment for moderate to severe pain during sickle cell episode is opioid-based analgesia, included articles may suggest utility of regional/neuraxial techniques with regard to potentially improving patient pain control, reducing opioid requirements, and decreasing the length of hospital stay. As highlighted in the case reports, these modalities were effective in

select cases of refractory pain where progressively larger doses of PCA opioids associated with increased risk of adverse medication effects (apnea, constipation, nausea/vomiting, pruritis) were used. Thus, more research is urgently needed in this realm, especially when considering the impact the opioid epidemic has had on the US population.

8. Bias, limitations, and areas for future study

As noted above, we undertook the current scoping review with the goal of determining whether peripheral nerve blocks or neuraxial anesthetics are effective adjuncts in treating pain during SCD pain crises. Given the lack of robust randomized control trials/cohort studies/other larger multi-center studies, the investigators needed to rely on lower quality evidence studies (case reports and case series) that are more prone to confounding, involve lower degrees of external validity, and are unable to establish a cause-and-effect relationship between treatments and outcomes [29]. As such, the potential for publication bias is certainly possible and should be considered when examining the case reports discussed.

Another limitation of the study relates to regional anesthesia as a treatment modality. Namely, not all hospitals have anesthesiologist or other providers trained in pain medicine or regional anesthesia. If there are no available providers trained, credentialed, and willing to provide the nerve block at the receiving facility, then this treatment adjunct is not an option without patient transfer to a qualifying facility. In addition, an absolute contraindication for a nerve block is lack of patient consent (or parental/guardian consent in the case of a minor). If relevant caregivers are unwilling to consent to the procedure for a nerve block after the informed consent process, then this treatment approach is not a viable adjunct for refractory pain.

Although the above limitations exist, the evidence extracted from the 6 included studies provides preliminary evidence to facilitate creation of larger controlled studies (proof of concept). Furthermore, given the formerly discussed rise in hospitalization rates for SCD acute painful episodes novel approaches aimed at cost containment and reduced length of hospital stays has never been timelier. With that said, in centers that do relatively few regional blocks for SCD pain crises, larger controlled studies with adequate statistical power would likely require research collaboration among several larger tertiary care centers to achieve adequate study size enrollment.

9. Conclusion

Neuraxial and peripheral nerve blocks are an understudied treatment approach for SCD acute pain crises. Targeted blocks based on the anatomical location of discomfort have the potential to reduce the pain experienced during hospitalization as well as emergency room work-up and management. Overall, future research will be necessary to increase the confidence in this treatment modality for acute pain episode management in SCD. With that said the current study sheds light on the potential benefit that blocks may provide beneficial for patients with localized medication-refractory SCD-related pain.

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