Published in final edited form as:

Pain Pract. 2015 November ; 15(8): E90–E97. doi:10.1111/papr.12336.

Dexmedetomidine as an adjuvant to analgesic strategy during vaso-occlusive episodes in adolescents with sickle cell disease

Kathy A. Sheehy, RN, MSN¹, Julia C. Finkel, MD¹, Deepika S. Darbari, MD², Michael F. Guerrero, MD², and Zenaide M.N. Quezado, MD¹

¹The Sheikh Zayed Institute for Pediatric Surgical Innovation, Divisions of Pain Medicine, Children's National Health System, Children's Research Institute, George Washington University School of Medicine and Health Sciences,, Washington, DC, 20010

²Hematology and Oncology, Children's National Health System, Children's Research Institute, George Washington University School of Medicine and Health Sciences,, Washington, DC, 20010

Abstract

Patients with sickle cell disease (SCD) can experience recurrent vaso-occlusive episodes (VOE), which are associated with severe pain. While opioids are the mainstay of analgesic therapy, in some SCD patients, increasing opioid use is associated with continued and increasing pain. Dexmedetomidine, a α_2 -adrenoreceptor agonist with sedative and analgesic properties, has been increasingly used in the perioperative and intensive care settings and has been shown to reduce opioid requirement and to facilitate opioid weaning. Therefore, there might be a role for dexmedetomidine in pain management during VOEs in SCD patients. Here we present the hospital course of three patients who during the course of VOEs had severe pain unresponsive to opioids and ketamine and were treated with dexmedetomidine. Dexmedetomidine infusions that lasted for three to six days were associated with marked reduction in daily oral morphine-equivalent intake and decreases in pain scores (numeric rating scale). There were no hemodynamic changes that required treatment with vasoactive or anticholinergic agents. These preliminary findings of possible beneficial effects of dexmedetomidine in decreasing opioid requirements support the hypothesis that dexmedetomidine may have a role as a possible analgesic adjuvant to mitigate VOE-associated pain in patients with SCD.

Keywords

sickle cell; pain; opioid; α_2 -agonist; opioid-induced hyperalgesia; muscle pain; case report

Introduction

Pain resulting from vaso-occlusive episodes (VOE) is the principal reason for hospital admission among sickle cell disease (SCD) patients^{1–5}. During VOEs, while opioids are the

Corresponding Author: Zenaide M.N. Quezado, MD, The Sheikh Zayed Institute for Pediatric Surgical Innovation, Center for Neuroscience Research, Children's National Health System, School of Medicine and Health Sciences, George Washington University, 111 Michigan Avenue, Washington, DC 20010, zquezado@childrensnational.org.

Conflict of interests: The authors have no conflicts of interest to report

mainstay of analgesic therapy, some patients despite receiving escalating doses of opioids have continued and increasing pain. Many believe that this phenomenon results from opioid-induced hyperalgesia or tolerance, or indicates that VOE-related pain might be partially unresponsive to opioid modulation^{3, 6}. Consequently, some patients have severe pain throughout hospitalization and after hospital discharge, pain-related re-hospitalization rates are high^{3, 7, 8}. Currently, clinicians caring for SCD patients mostly treat symptoms because mechanism-based strategies for SCD-associated pain are sorely lacking^{9, 10}. Further, most approaches to treat SCD pain have poor levels of evidence, being based on observational studies and on expert opinions rather than on clinical trials^{9, 10}. Therefore, new therapies to more effectively treat SCD pain are needed.

Dexmedetomidine, a specific α_2 adrenoreceptor agonist without respiratory depressant effects¹¹, has been used as a sedative and/or analgesic during the perioperative period¹² and in intensive care units to treat children and adults¹³. Dexmedetomidine decreases opioid consumption and pain intensity^{12, 14}, and in settings where patients are on high-dose opioids, dexmedetomidine halts escalation of opioid intake and facilitates opioid weaning^{15, 16}. There are a few reported cases of dexmedetomidine use in SCD patients in emergency rooms and during the perioperative period^{17, 18}. Therefore, given its favorable therapeutic index and the salutary effects in decreasing opioid requirement, one might argue that dexmedetomidine might have a role in SCD pain. We report preliminary data that supports the conduct of clinical trials of dexmedetomidine as an adjunct to opioid therapy for pain management of SCD patients requiring and not responding to escalating doses of opioids during VOEs.

METHODS

Case series and data collection

Patients' hospitalization records review and waiver of informed consent were approved by the Children's National Institutional Review Board. We reviewed the hospital course of SCD patients who had been admitted to the hospital with VOEs and had been treated with dexmedetomidine between November 2010 and April 2014. We also reviewed records of SCD patients treated at the same time with similar analgesic therapy (opioids and subanesthetic doses of ketamine) who had not received dexmedetomidine. The patients treated with dexmedetomidine were identified by the authors who had cared for those patients. For the purpose of this report, we defined high-dose opioid as those exceeding 2mg/kg/day of oral morphine-equivalent. This definition is based on a study indicating that patients requiring those doses of opioid were often treated with ketamine¹⁹. For the present investigation, we examined patient demographics, SCD genotype, analgesic therapy, self-reported pain scores (numeric rating scale 0–10) and treatment related hemodynamic changes requiring intervention.

Opioid administration

SCD patients admitted with VOEs received morphine or hydromorphone patient controlled analgesia. Patient controlled morphine was administered at a basal rate of 0.02 mg/kg/h with bolus doses of 0.02mg/kg up to every 8 min. Patient controlled hydromorphone was

administered at a basal rate of 0.003 mg/kg/h and boluses of 0.003 mg/kg up to every 10 min. If uncontrolled pain required escalation in opioid dosing, patients could be given additional opioid by order of the Pain Medicine team by either increasing basal and/or bolus doses or by nurse administered opioid boluses.” Daily oral morphine equivalent opioid doses (per body weight) were calculated as previously described²⁰ using the conversion tool at website www.globalrph.com/narcoticonv.htm.

Dexmedetomidine administration

Administration of dexmedetomidine was directed by the Pain Medicine team in consultation with hematologists. The reasons to initiate dexmedetomidine included: increasing opioid requirements associated with opioid-related undesirable side effects (e.g., respiratory depression), pain unresponsive to high-dose opioid as defined above, and/or the clinical impression that in part, opioid-induced hyperalgesia was contributing to the patient’s pain. In keeping with our institutional guidelines at the time, in order to receive dexmedetomidine infusions patients were transferred to the pediatric intensive care unit. Dexmedetomidine (Precedex™ Hospira) was initiated and maintained as a continuous infusion (starting dose 0.2–1 µg/kg/hour), which was titrated for pain. Once the decision to discontinue dexmedetomidine was made, it was weaned over a few hours by halving the doses every 2 hours. During dexmedetomidine administration, sedation scores (0=awake, 1-minimally sedated, 2-moderately sedated, 3- deeply sedated, and 4-unarousable), heart rate, pulse oximetry, and blood pressure were monitored.

Ketamine administration

The institutional experience with ketamine administration in SCD patients has been previously described¹⁹. Subanesthetic ketamine doses are here defined as those lower than 1 mg/kg/h, as doses greater than 1 mg/kg/h often yield loss of consciousness²¹. At our institution, ketamine can be ordered by the Divisions of Anesthesiology and Pain Medicine and at subanesthetic doses it can be administered by a registered nurse trained on the safe administration of the drug in a setting that provides monitoring of heart rate, pulse oximetry, and blood pressure. The recommended starting dose is 0.1 mg/kg/h, but it is left to the discretion of the attending physician.

Results

Hospital Course

We identified three patients with VOEs who were treated with dexmedetomidine after failing to respond to or displaying detrimental side-effects with escalating doses of opioid and ketamine. Patient demographics, SCD genotype, and analgesic regimen are shown in Table 1. At the time of dexmedetomidine administration, all patients were receiving opioids, non-steroidal anti-inflammatory drugs, and subanesthetic doses of ketamine. Daily oral morphine-equivalent intake and pain scores for each patient from one day before until the day after dexmedetomidine administration are shown in Figure 1A and 2A respectively. When patients reported pain scores above 10, these are shown as 10. Details of dexmedetomidine-treated patients’ hospital course are described below.

Patient 1

An 18-year-old, 58-kg female with a history of sickle cell anemia (HbSS), multiple admissions for chronic pain and opioid use and frequent VOEs was admitted for worsening back, chest, and right leg pain in the setting of increasing opioid intake. Upon arrival to the hospital the patient had a pain score of 8 and had taken 3.7mg/kg/day of morphine-equivalent at home for a few days prior to admission. By hospital day two the patient was receiving 5.9mg/kg/d morphine-equivalent by patient controlled morphine and had no change in pain scores. A continuous infusion of ketamine was initiated at 0.3mg/kg/h. After three days of ketamine continuous infusion, the patient was still receiving approximately 2mg/kg/day of morphine-equivalent and continued to report severe pain. The clinical impression was that the patient had developed opioid-induced hyperalgesia and a continuous infusion of dexmedetomidine was initiated and maintained between 0.2 and 0.4µg/kg/h. Upon initiation of dexmedetomidine, all opioids were discontinued and pain scores reported were between 6 and 7. Ketamine was discontinued (not weaned) on the third day of dexmedetomidine infusion. During dexmedetomidine infusion, the sedation scores were recorded at various times during the day and ranged between 0 and 1. Dexmedetomidine was continued for a total of five days and just prior to its discontinuation, a transdermal clonidine patch (0.2 mg) was placed. The patient was discharged one day later entirely off opioids and clonidine was continued for 14 days.

Patient 2

An 18-year-old, 88-kg female with a history of sickle cell disease (HbSC), asthma, pseudotumor cerebri, frequent episodes of VOEs and acute chest syndrome was admitted with left arm, legs, back, and chest pain. Upon admission she had a pain-score of 9 and was taking approximately 2mg/kg/day of oral morphine-equivalent. A subanesthetic dose infusion of ketamine (0.1mg/kg/h) was initiated along with patient controlled morphine. After 3 days of ketamine infusion, the patient was receiving morphine equivalent of 9mg/kg/day and had increasing chest pain, reported pain scores of 9–10, and increased sedation thought to be partially related to opioids. At that time, the patient was admitted to the ICU for management of acute chest syndrome, had increasing oxygen requirements, and required ventilatory support delivered via BIPAP. Dexmedetomidine was then started at 0.5µg/kg/h and continued for a total of 3 days. Ketamine was discontinued (not weaned) on day 3 of dexmedetomidine infusion. During the administration of dexmedetomidine, sedation scores were recorded at various times during the day and ranged between 0 and 3. After discontinuation of ketamine and dexmedetomidine infusions, and initiation of a transdermal clonidine patch (0.1 mg), the opioid requirement was 2.1 mg/kg/day morphine equivalent and the pain score was 2. The patient was discharged from the hospital on oral opioid (0.87mg/kg/day oral morphine equivalent) and reported a pain score of 2. Clonidine was continued for 7 days.

Patient 3

A 15-year-old, 49-kg male with a history of sickle cell anemia (HbSS), failed cord blood transplant, multiple hospitalizations for chronic pain, frequent acute pain, and acute chest syndrome, silent and subacute cerebral infarcts, and sleep apnea, was admitted to the

intensive care unit with severe chest and abdominal pain. At that time, a patient controlled hydromorphone infusion was started. On the 5th hospital day, the patient continued to have intractable chest pain, had a pain score of “14” (on a numeric rating scale 0–10) and was receiving 5.74 mg/kg/d of morphine-equivalent. At that point, a continuous infusion of dexmedetomidine was started at a dose of 1µg/kg for 5 hours, decreased to 0.5µg/kg/h for 12 h, and maintained between 0.2 to 0.4µg/kg/h. A ketamine infusion (0.2 mg/kg/h) was also initiated at the time of the dexmedetomidine infusion but was discontinued as the patient was disoriented and had irrational fears, which were thought to be related to ketamine. Dexmedetomidine infusion was continued for six days and at time of its discontinuation, the patient was receiving 0.7mg/kg/day of morphine equivalent opioid, required no ventilatory assistance, and had a pain score between 6 and 8. While sedation scores were not recorded during dexmedetomidine administration, the patient was reported to be awake at times and able to play video games. A clonidine patch (0.1mg) was applied and continued for seven days. The patient remained in the hospital for intensive physical therapy and at the time of discharge, the patient reported pain scores of 6–8 on 0.17mg/kg/day of oral morphine-equivalent.

Overall, dexmedetomidine was well tolerated by all three patients and no evidence of hemodynamic instability or bradycardia that required vasoactive or anticholinergic treatment was noted in any of the patients. Anecdotally, in all three patients, VOE-associated pain and opioid requirement appeared to have improved after initiation of dexmedetomidine while opioid analgesia and subanesthetic doses ketamine appeared to have not been effective. Further, as suggested by Figure 1A, in all patients, dexmedetomidine was associated with marked decreases in morphine equivalent opioid intake.

Comparison patient group

For comparison, we also show data on four SCD patients who were admitted for VOE-related pain at the same time of the year as the dexmedetomidine-treated group of patients (Table 1 and Figures 1 and 2) but did not receive dexmedetomidine. These four patients were also treated with opioids, NSAIDs, and ketamine. Demographic data for these four patients is listed in Table 1 and indicates that the comparison group had age, admission weight, and length of stay comparable to those in the dexmedetomidine-treated group. During ketamine infusions, the sedation scores were recorded in three out of the four patients at various times during the day and ranged between 0 and 1. Figures 1B and 2B show daily oral morphine-equivalent intake and pain scores for each of the four patients from one day before until the day after ketamine administration respectively.

Discussion

Here we report three adolescents with SCD who were treated with long-term (lasting several days) dexmedetomidine infusions during VOEs. Given its sedative effects and the reported effects on heart rate (bradycardia) and blood pressure (hypertension and/or hypotension) these patients were admitted to the intensive care unit for hemodynamic and sedation monitoring¹². Reasons to initiate dexmedetomidine included high opioid requirements and development of undesirable side effects, pain unresponsive to escalating doses of opioid,

and the clinical impression that in part, opioid-induced hyperalgesia was contributing to patient's pain. Given previous reports that dexmedetomidine facilitates opioid weaning^{15, 16} and has profound analgesic and sedative effects^{12, 14}, a decision to initiate dexmedetomidine was made. As suggested by Figure 1, daily oral morphine-equivalent intake was markedly reduced after the initiation of dexmedetomidine. In the three patients, dexmedetomidine infusions lasted from three to six days and were followed by administration of transdermal clonidine. While this is a preliminary report, the data suggest that there may be a role for dexmedetomidine as an adjuvant to the analgesic strategy to treat VOEs in SCD patients.

There are a few reports of the use of dexmedetomidine in adults with SCD^{17, 18}. In one report, two patients presenting to the emergency room with VOE were treated with a bolus dose and a continuous infusion of dexmedetomidine for a total of four hours. Those patients were discharged pain-free and off opioids¹⁷. In another report, an adult SCD patient undergoing total hip replacement received dexmedetomidine infusion as an adjuvant for intra- and post- operative analgesia along with a continuous epidural infusion of local anesthetics¹⁸. In those reports, dexmedetomidine was tolerated and decreased opioid requirements. Here we show that prolonged dexmedetomidine infusions, used as an adjuvant to treat three adolescents with VOE and severe pain unresponsive to escalating doses of opioid and ketamine, was well tolerated, decreased opioid requirement, and allowed discontinuation of ketamine infusion.

A number of animal studies also support the hypothesis that dexmedetomidine may have a role for the treatment of SCD pain. For example, in models of SCD, subcutaneous injections of dexmedetomidine ameliorates nocifensive behavior as it increases tolerance to noxious thermal stimuli and ameliorates muscle hyperalgesia as it increases grip force in SCD mice²². Further, in neuropathic pain models, the antinociceptive effect of dexmedetomidine appears to be opioid-independent and to be associated with supraspinal facilitation of inhibitory postsynaptic currents, as well as inhibition of input from sensory neurons located in the substance gelatinosa²³. Thus, dexmedetomidine may also be useful in neuropathic pain, which is frequently experienced by SCD patients^{24, 25}. Further, in models of visceral pain, dexmedetomidine has antinociceptive effects unrelated to opioid receptor activation and are associated with increased nitric oxide production, which is reportedly reduced in SCD²⁶. Also of great relevance to SCD, dexmedetomidine has protective effects in several models of ischemia/reperfusion injury^{27–31}. These effects are particularly relevant as researchers propose that endothelial dysfunction, acute chest syndrome, arterial vasculopathy, and pain associated with inflammatory mediators during vaso-occlusive phenomenon are examples of SCD-associated ischemia/reperfusion injury³². Therefore, given the mounting evidence that ischemia/reperfusion injury might underlie several complications of SCD, and that dexmedetomidine has beneficial effects in such settings, one could postulate that further evaluation of the role for dexmedetomidine in SCD is warranted.

We must consider the possibility that despite the sympatholytic effects of dexmedetomidine, the use of α_2 agonists in SCD patients could be associated with undesirable vasoconstriction which can result from activation of peripheral α_2B adrenoreceptors^{33, 34}. In fact, increasing doses of dexmedetomidine are associated with a biphasic dose-response on mean arterial pressure and vascular resistance in normal human volunteers. At lower doses, as used in the

patients reported here, dexmedetomidine decreases, and at higher doses, it increases mean arterial pressures as well as systemic vascular resistance³⁴. Noticeably, these vasoconstrictive effects are exacerbated in settings in which there is decreased sympathetic tone such as general anesthesia or vasodilation related to denervation of vascular bed caused by experimental peripheral nerve block³⁵. In such settings, even lower doses of dexmedetomidine are associated with vasoconstriction³⁵. In contrast, such vasoconstriction was not observed in awake volunteers³⁵. These data suggest that overall, because of its sympatholytic effects, the vasoconstrictive effects of dexmedetomidine may in fact vary depending on the degree of ongoing sympathetic activity³⁵. Therefore, future studies should elucidate the overall effect of dexmedetomidine on the systemic vasculature in SCD patients.

Another theoretical concern about the use of dexmedetomidine in SCD patients is related to its possible vasoconstrictive effect in the pulmonary vasculature. In SCD, some patients develop pulmonary hypertension, which is known to be an independent risk factor for mortality³⁶. However, one study of the hemodynamic response to dexmedetomidine in children with and without pulmonary hypertension demonstrate that even in the setting of pre-existing pulmonary hypertension, the pulmonary vasculature does not respond with significant vasoconstriction to dexmedetomidine³⁷. Therefore, while the theoretical concern exists, it is unknown if and at what dose range dexmedetomidine might yield clinically relevant systemic or pulmonary vasoconstrictive effects in SCD patients. Nevertheless, given the potential benefits of dexmedetomidine during VOEs, these questions merit further exploration.

We acknowledge the limitations of this report and recognize that we are unable to draw conclusions about safety and efficacy of dexmedetomidine for SCD pain from such few patients with no randomized allocation of patients to dexmedetomidine or placebo administration. Therefore while opioid requirement appeared to have decreased after the initiation of dexmedetomidine, we cannot determine whether those decreases represent a direct effect of dexmedetomidine or simply reflect the course of VOEs. However, in our patients, dexmedetomidine in combination with opioid and ketamine was well tolerated and temporally associated with marked reduction in opioid requirements and improved pain scores. Thus, given the anecdotal reports of the use of dexmedetomidine in SCD patients with VOEs, including those reported here, dexmedetomidine should be further investigated by means of randomized controlled clinical trials in SCD patients with painful VOEs.

Acknowledgements

This work was partially supported by Award UL1RR031988 /UL1TR000075 from the NIH National Center for Advancing Translational Sciences and by an intramural grant from The Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's Research Institute.

REFERENCES

1. Platt OS, Thorington BD, Brambilla DJ, Milner PF, Rosse WF, Vichinsky E, et al. Pain in sickle cell disease. Rates and risk factors. *N Engl J Med*. 1991; 325:11–16. [PubMed: 1710777]

2. Smith WR, Penberthy LT, Bovbjerg VE, McClish DK, Roberts JD, Dahman B, et al. Daily assessment of pain in adults with sickle cell disease. *Ann Intern Med.* 2008; 148:94–101. [PubMed: 18195334]
3. Ballas SK, Gupta K, Adams-Graves P. Sickle cell pain: a critical reappraisal. *Blood.* 2012; 120:3647–3656. [PubMed: 22923496]
4. Yusuf HR, Atrash HK, Grosse SD, Parker CS, Grant AM. Emergency department visits made by patients with sickle cell disease: a descriptive study, 1999–2007. *Am J Prev Med.* 2010; 38:S536–S541. [PubMed: 20331955]
5. Steiner, CA.; Miller, JL. Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. Rockville (MD): Agency for Health Care Policy and Research (US); 2006. Sickle Cell Disease Patients in U.S. Hospitals, 2004: Statistical Brief #21.
6. Brush DE. Complications of long-term opioid therapy for management of chronic pain: the paradox of opioid-induced hyperalgesia. *J Med Toxicol.* 2012; 8:387–392. [PubMed: 22983894]
7. Ballas SK, Lusardi M. Hospital readmission for adult acute sickle cell painful episodes: frequency, etiology, and prognostic significance. *Am J Hematol.* 2005; 79:17–25. [PubMed: 15849770]
8. Brousseau DC, Owens PL, Mosso AL, Panepinto JA, Steiner CA. Acute care utilization and rehospitalizations for sickle cell disease. *JAMA.* 2010; 303:1288–1294. [PubMed: 20371788]
9. Field JJ, Knight-Perry JE, Debaun MR. Acute pain in children and adults with sickle cell disease: management in the absence of evidence-based guidelines. *Curr Opin Hematol.* 2009; 16:173–178. [PubMed: 19295432]
10. Niscola P, Sorrentino F, Scaramucci L, de Fabritiis P, Cianciulli P. Pain syndromes in sickle cell disease: an update. *Pain Med.* 2009; 10:470–480. [PubMed: 19416438]
11. Kamibayashi T, Maze M. Clinical uses of alpha2 -adrenergic agonists. *Anesthesiology.* 2000; 93:1345–1349. [PubMed: 11046225]
12. Blaudszun G, Lysakowski C, Elia N, Tramer MR. Effect of perioperative systemic alpha2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology.* 2012; 116:1312–1322. [PubMed: 22546966]
13. Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA.* 2012; 307:1151–1160. [PubMed: 22436955]
14. Pestieau SR, Quezado ZM, Johnson YJ, Anderson JL, Cheng YI, McCarter RJ, et al. High-dose dexmedetomidine increases the opioid-free interval and decreases opioid requirement after tonsillectomy in children. *Can J Anaesth.* 2011; 58:540–550. [PubMed: 21461792]
15. Finkel JC, Elrefai A. The use of dexmedetomidine to facilitate opioid and benzodiazepine detoxification in an infant. *Anesth Analg.* 2004; 98:1658–1659. , table of contents. [PubMed: 15155322]
16. Finkel JC, Johnson YJ, Quezado ZM. The use of dexmedetomidine to facilitate acute discontinuation of opioids after cardiac transplantation in children. *Crit Care Med.* 2005; 33:2110–2112. [PubMed: 16148487]
17. Phillips WJ, Gadiraju S, Dickey S, Galli R, Lerant AA. Dexmedetomidine relieves pain associated with acute sickle cell crisis. *J Pain Symptom Manage.* 2007; 34:346–349. [PubMed: 17903665]
18. Dhansura T, Kapadia S, Gandhi S. Dexmedetomidine as sedative and analgesic in a patient of sickle cell disease for total hip replacement. *Indian J Anaesth.* 2013; 57:425–426. [PubMed: 24163470]
19. Neri CM, Pestieau SR, Young H, Elmi A, Finkel JC, Darbari DS. Low-dose ketamine for children and adolescents with acute sickle cell disease related pain: a single center experience. *J Anesthe Clin Res.* 2014; 5
20. Mercadante S, Ferrera P, Villari P, Casuccio A, Intravaia G, Mangione S. Frequency, indications, outcomes, and predictive factors of opioid switching in an acute palliative care unit. *J Pain Symptom Manage.* 2009; 37:632–641. [PubMed: 19345298]
21. Langsjø JW, Maksimow A, Salmi E, Kaisti K, Aalto S, Oikonen V, et al. S-ketamine anesthesia increases cerebral blood flow in excess of the metabolic needs in humans. *Anesthesiology.* 2005; 103:258–268. [PubMed: 16052107]

22. Calhoun G, Wang L, Almeida LE, Kenyon N, Afsar N, Nouraie M, et al. Dexmedetomidine ameliorates nocifensive behavior in humanized sickle cell mice. *Eur J Pharmacol.* 2015
23. Funai Y, Pickering AE, Uta D, Nishikawa K, Mori T, Asada A, et al. Systemic dexmedetomidine augments inhibitory synaptic transmission in the superficial dorsal horn through activation of descending noradrenergic control: an in vivo patch-clamp analysis of analgesic mechanisms. *Pain.* 2014; 155:617–628. [PubMed: 24355412]
24. Wilkie DJ, Molokie R, Boyd-Seal D, Suarez ML, Kim YO, Zong S, et al. Patient-reported outcomes: descriptors of nociceptive and neuropathic pain and barriers to effective pain management in adult outpatients with sickle cell disease. *J Natl Med Assoc.* 2010; 102:18–27. [PubMed: 20158132]
25. Brandow AM, Farley RA, Panepinto JA. Neuropathic pain in patients with sickle cell disease. *Pediatr Blood Cancer.* 2014; 61:512–517. [PubMed: 24167104]
26. Rangel RA, Marinho BG, Fernandes PD, de Moura RS, Lessa MA. Pharmacological mechanisms involved in the antinociceptive effects of dexmedetomidine in mice. *Fundam Clin Pharmacol.* 2014; 28:104–113. [PubMed: 22924641]
27. Dong X, Xing Q, Li Y, Han X, Sun L. Dexmedetomidine protects against ischemia-reperfusion injury in rat skeletal muscle. *J Surg Res.* 2014; 186:240–245. [PubMed: 24007817]
28. Bell MT, Puskas F, Bennett DT, Herson PS, Quillinan N, Fullerton DA, et al. Dexmedetomidine, an alpha-2a adrenergic agonist, promotes ischemic tolerance in a murine model of spinal cord ischemia-reperfusion. *J Thorac Cardiovasc Surg.* 2014; 147:500–506. [PubMed: 24035379]
29. Bell MT, Puskas F, Smith PD, Agoston VA, Fullerton DA, Meng X, et al. Attenuation of spinal cord ischemia-reperfusion injury by specific alpha-2a receptor activation with dexmedetomidine. *J Vasc Surg.* 2012; 56:1398–1402. [PubMed: 22832266]
30. Yoshitomi O, Cho S, Hara T, Shibata I, Maekawa T, Ureshino H, et al. Direct protective effects of dexmedetomidine against myocardial ischemia-reperfusion injury in anesthetized pigs. *Shock.* 2012; 38:92–97. [PubMed: 22552015]
31. Sahin T, Begec Z, Toprak HI, Polat A, Vardi N, Yucel A, et al. The effects of dexmedetomidine on liver ischemia-reperfusion injury in rats. *J Surg Res.* 2013; 183:385–390. [PubMed: 23321519]
32. Hebbel RP. Ischemia-reperfusion injury in sickle cell anemia: relationship to acute chest syndrome, endothelial dysfunction, arterial vasculopathy, and inflammatory pain. *Hematol Oncol Clin North Am.* 2014; 28:181–198. [PubMed: 24589261]
33. Link RE, Desai K, Hein L, Stevens ME, Chruscinski A, Bernstein D, et al. Cardiovascular regulation in mice lacking alpha2-adrenergic receptor subtypes b and c. *Science.* 1996; 273:803–805. [PubMed: 8670422]
34. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colino MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology.* 2000; 93:382–394. [PubMed: 10910487]
35. Talke P, Lobo E, Brown R. Systemically administered alpha2-agonist-induced peripheral vasoconstriction in humans. *Anesthesiology.* 2003; 99:65–70. [PubMed: 12826844]
36. Parent F, Bachir D, Inamo J, Lionnet F, Driss F, Loko G, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. *N Engl J Med.* 2011; 365:44–53. [PubMed: 21732836]
37. Friesen RH, Nichols CS, Twite MD, Cardwell KA, Pan Z, Pietra B, et al. The hemodynamic response to dexmedetomidine loading dose in children with and without pulmonary hypertension. *Anesth Analg.* 2013; 117:953–959. [PubMed: 23960035]

Figure 1.

The points indicate daily oral morphine-equivalent intake for each patient. Daily oral morphine-equivalent intake in three patients admitted with vaso-occlusive episodes from the day before (−1) to the day after dexmedetomidine infusion (Panel A, N=3). The down arrow in panel A indicates initiation of dexmedetomidine. All patients in panel A were receiving high dose opioid and subanesthetic doses of ketamine before dexmedetomidine administration. For comparison, panel B (N=4) shows daily morphine-equivalent intake [from the day before (−1) to one day after ketamine] in four patients admitted with vaso-occlusive episodes, at the same time of year as patients in A, who were not treated with dexmedetomidine. The down arrow in panel B indicates initiation of ketamine. The duration of dexmedetomidine and ketamine infusions varied according to patient response. Panel A suggests that after dexmedetomidine infusion was commenced, there were marked decreases in morphine-equivalent intake, which is in contrast to the findings in B which suggest no significant changes in morphine equivalent intake.

Figure 2.

The points indicate the highest reported pain score (numeric rating scale 0–10) in SCD patients treated for vaso-occlusive episodes (VOEs). Daily pain score in three patients admitted with VOEs from the day before (–1) until the day after dexmedetomidine infusion (Panel A, N=3). The down arrow in panel A indicates initiation of dexmedetomidine. All patients in panel A were receiving high-dose opioid and subanesthetic doses of ketamine before dexmedetomidine administration. For comparison, panel B (N=4) shows daily pain scores [from the day before (–1) to one day after ketamine] in four patients admitted with VOEs, at the same time as patients in A, who were not treated with dexmedetomidine. The down arrow in panel B indicates initiation of ketamine. The duration of dexmedetomidine and ketamine infusions varied according to patient response. Panel A suggests that at variable times after initiation of dexmedetomidine infusion, there were decreases in pain scores. In instances when patients reported pain scores above 10, they were recorded as 10.

Table 1
Demographics and analgesic therapy for sickle cell disease patients during hospital admissions for vaso-occlusive episodes*

Patient	Sex	Age (y)	Genotype	Preadmission opioid dose (mg/kg/day)	Admission Weight	NSAIDs	Ketamine	Dexmedetomidine	Discharge opioid dose (mg/kg/day)	Length of stay (days)
1	Female	18	HbSS	3.7	58	Yes	Yes	Yes	0.0	10
2	Female	18	HbSC	2	88	Yes	Yes	Yes	0.87	9
3	Male	15	HbSS	0.4	49	Yes	Yes	Yes	0.17	20
4	Female	15	HbSS	0	50	Yes	Yes	No	0.7	11
5	Male	17	HbSS	0.5	58	Yes	Yes	No	1.7	8
6	Male	11	HbSβ0	0.8	30	Yes	Yes	No	1.4	16
7	Male	6	HbSS	0.5	23	Yes	Yes	No	0.5	9

* Patients were admitted for vaso-occlusive episodes at approximately the same time of the year. All patients received opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and sub-anesthetic doses of ketamine during admission and patients 1, 2, and 3 received a continuous infusions of dexmedetomidine