

Randomized Trial of Hypnosis as a Pain and Symptom Management Strategy in Adults with Sickle Cell Disease

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ABSTRACT: Sickle cell disease (SCD) is the most common genetic disease in African-Americans, characterized by recurrent painful vaso-occlusive crises. Medical therapies for controlling or preventing crises are limited because of efficacy and/or toxicity. This is a randomized, controlled, single-crossover protocol of hypnosis for managing pain in SCD patients. Participants receive hypnosis from a trained hypnosis therapist followed by six weeks of self-hypnosis using digital media. Those in the control arm receive SCD education followed by a six-week waiting period before crossing over to the hypnosis arm of the study. Outcome measures include assessments of pain (frequency, intensity and quality), anxiety, coping strategies, sleep, depression, and health care utilization. To date, there are no published randomized, controlled trials evaluating the efficacy of hypnosis on SCD pain modulation in adults. Self-hypnosis for pain management may be helpful in modulating chronic pain, improving sleep quality, and decreasing use of narcotics in patients with SCD.

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Background

Sickle cell disease (SCD) is the most common genetic disease in African-Americans, characterized by recurrent painful vaso-occlusive crises. The disease is caused by a mutated form of hemoglobin that results in red blood cell (RBC) rigidity during low oxygen states. The most common types of SCD are sickle cell anemia (Hb SS), sickle cell hemoglobin SC (Hb SC), and sickle beta thalassemia (Hb S β thal). When the defective hemoglobin gives up its oxygen, it is prone to polymerize, causing RBC rigidity and accelerated RBC lysis. These phenomena lead to recurrent vaso-occlusive “crises” that are usually accompanied by disabling pain. The pain episodes are commonly termed “crises” as they are unpredictable, frequent, and debilitating.¹ The severity and

frequency of the crises presents a significant impact on self-determination, independent living, and overall quality of life.² The symptomatology that drives the SCD patient to medical care falls into three major categories: anemia, pain, and infection.³

The management of SCD in the past was predominantly palliative in nature, using symptomatic and preventative approaches. The standard of care for SCD patients during vaso-occlusive crisis is pharmacologic analgesia, typically with opioids. While this approach is effective for some patients, many are inadequately treated because of high dosage requirements that are difficult to meet over time, and this approach does little to prevent pain crises from occurring. Patients with SCD have a range of frequencies and intensities of painful



vaso-occlusive episodes. Acute episodes often require the individual to be hospitalized for aggressive pain management. Characteristically, the management regime involves narcotic administration. Estimates of pain frequency, based on medical records in hospitals, emergency rooms, and sickle cell clinics, indicate that 10–20% of SCD patients have frequent pain, while 40–50% have some pain, and 30–40% have no pain.^{4,5} Yet, it remains unclear how many pain episodes associated with SCD may not involve hospitalization and are managed with a variety of opioid and non-opioid medications at home.^{6,7} Previous studies show that discharge follow-up was often deficient and ineffective with the patient going home without any pain medication at all. Pain coping strategies were rarely taught.⁸

Impact of chronic pain in SCD. Pain in SCD is not limited to acute pain; SCD pain can also be classified as chronic pain or a mixture of both chronic and acute pain.⁹ Chronic pain is not merely the continuation of the acute vaso-occlusive pain; it is often a result of vascular necrosis of bone particularly at the hips, shoulders, and ankles. SCD patients with more frequent or severe pain often have similar pain patterns throughout the lifespan. Pain has also been shown to be associated with sleep deprivation, poor school or work attendance, and decreased daytime functioning.^{7,10} Ideally, SCD patients with pain should learn to cope with the pain, with as little negative impact on daily function as a result of the pain or its treatment as possible. Evidence focuses on the frequency of pain resulting in emergency department use and number of hospitalizations because of pain crisis in SCD patients; however, few studies focus on these pain manifestations outside the typical health-care delivery system or how patients manage their pain apart from their physician. Furthermore, it is unclear what percentage of patients are able to self-manage their crises at home without accessing health-care professionals.¹¹

Smith and colleagues¹¹ have conducted The Pain in Sickle Cell Epidemiology Study (PiSCES), a longitudinal, etiologic study of pain with an emphasis on non-biologic variables. These investigators vividly describe the frustrations and barriers for both providers and patients related to pain assessment and relief in SCD. Chief among these barriers is that “red cell vaso-occlusion has no observable clinical correlates to validate subjective descriptions of painful crises, which results in physician skepticism and patient dissatisfaction.”¹¹ In addition to measuring psychosocial variables such as stress, mental health status, coping and social support, Smith and colleagues have developed a conceptual explanatory model of pain and utilization in SCD, which examines the relationship of individual demographics, disease-related variables, psychosocial variables, and readiness variables and their effects on distress disability, health care utilization, and pain. We used this conceptual model (Fig. 1) to guide us in the selection of measures evaluating the process and outcome variables of interest.

Therapeutic hypnosis as an intervention. A published review summarized trials of psychosocial interventions as adjuncts to treating SCD.¹² These interventions included cognitive-behavioral techniques, hypnosis, and social support procedures wherein self-empowerment and education are strong facets of the supportive care approach. The effects of these techniques on pain control, quality of life, and health care utilization were inconsistent, perhaps because of inadequate study designs (eg, a lack of suitable control groups and non-standardized scripts).

Evidence exists supporting the efficacy of hypnotic analgesia in a variety of experimental^{13–15} and clinical settings, including pain associated with medical or surgical procedures.^{16–19} Gil and colleagues²⁰ demonstrated a direct correlation between daily use of pain-coping skills and less major health care contacts. Thus, cognitive measures that influence attitudes and improve pain-coping skills appear to have a significant impact on sleep, functional outcomes such as work and school attendance, use of analgesics, and major health care utilization. Since hypnosis is a cognitive-behavioral strategy that has been shown to have a powerful effect on pain management in a number of settings, it is postulated that a program designed to teach and encourage the use of self-hypnosis may positively impact the pain perception, sleep quality, functional outcomes, quality of life, and satisfaction of SCD patients.

As with other acute and chronic pain conditions, a goal in SCD pain management is to maximize function with the least amount of medication. Hypnotic training may offer an effective approach toward improving coping strategies and lessening focus on pain and its interference in functional outcomes. Hypnosis is a natural state of consciousness characterized by highly focused concentration with a relative suspension of global awareness.²¹ In addition to addressing conscious processes, as in traditional cognitive-behavioral therapy, hypnosis can also access subconscious and unconscious processes. Hypnosis involves a change in the brain’s perception.²² A study by Rainville and colleagues (2002) using positron emission tomography (PET) provides supportive evidence that distinct brain changes occur during hypnosis particularly in the anterior cingulate cortex, the thalamus, and the pontomesencephalic brainstem during the production of hypnotic states. Furthermore, hypnotic relaxation is distinguished by a decrease in cortical arousal and disinhibition.²³

The efficacy of hypnosis has been demonstrated in treating numerous conditions including acute pain, chronic pain, burn injury progression, pulmonary diseases, and hemophilia, to name a few.²⁴ Hypnosis has also become part of a broader model of integrative mind–body interventions for breast cancer²⁵ and palliative care.^{26,27} Hypnotherapy, including self-hypnosis, has proven particularly effective in pain and symptom management for pediatric pulmonary patients^{28,29} and pediatric functional abdominal pain.³⁰ For those with clinically significant pain episodes, learning a cognitive-behavioral

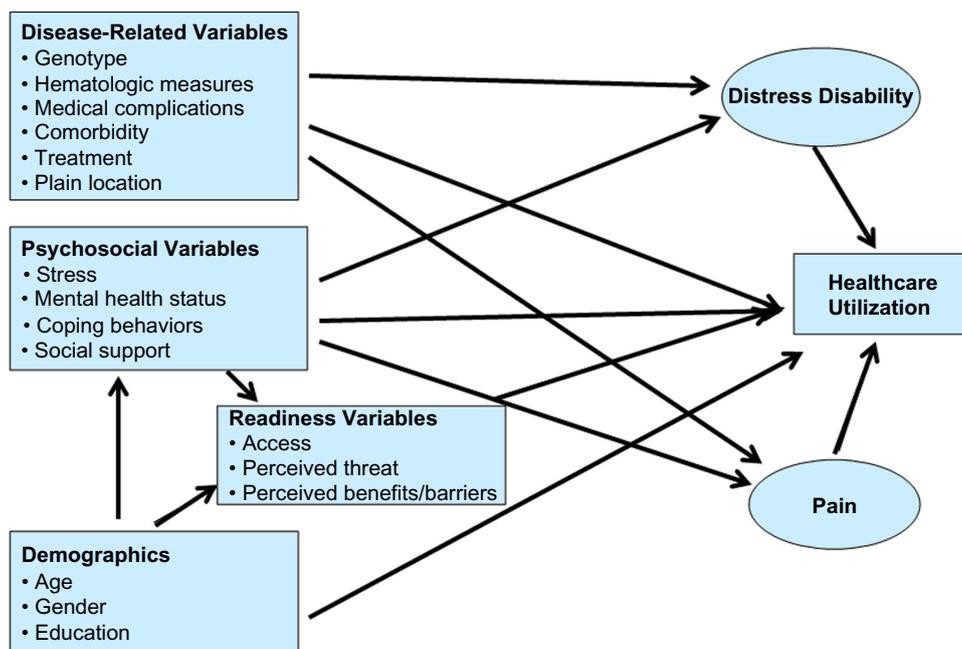


Figure 1. Explanatory model of pain and utilization in SCD. Conceptual explanatory model of pain and utilization over time in sickle cell disease.¹¹

intervention centered on self-hypnosis for pain management has proved helpful in reducing pain frequency, improving sleep quality, and decreasing use of narcotic pain medications.³¹ In a 12-month non-randomized prospective trial, Dinges et al.³¹ demonstrated a reduction in both SCD pain days and non-SCD-related pain days. Analgesic use decreased proportionately in patients who experienced a decrease in pain frequency. The majority of this decrease resulted from a reduction in days with mild pain yet there was no significant reduction in the number of severe-pain days or length of vaso-occlusive episodes. This reduction of mild-pain frequency indicates that self-hypnosis may be most helpful for eliminating mild or moderate pain episodes of vaso-occlusive pain, and less helpful for the management of severe SCD pain episodes. Self-hypnosis training also decreased the frequency of poor-sleep nights, primarily by reducing the frequency of mild-pain nights. These improvements persisted over 12 months.³¹ Additionally, two case studies have also been published supporting the use of hypnosis for pain management in SCD patients.^{32,33}

Purpose of study protocol. To date, there are no published randomized, controlled trials evaluating the efficacy of hypnosis in SCD pain modulation in adults. Furthermore, there is a need to explore dosing of the hypnosis intervention with limited therapist time, and a model of home-based therapy has yet to be accomplished. This protocol is aimed at longitudinally assessing the effects of hypnosis in such a manner. The major advantage of conducting a longitudinal analysis is the ability to observe and separate changes over time within the study participants from differences among the participants in their baseline characteristics. Using repeated measures allows us to study the trajectory of psychosocial behaviors and pain intensity changes over time after controlling for intrapersonal correlations

in order to draw valid scientific inferences regarding the impact of the hypnosis intervention.

Methods/Design

Recruitment. Patients with known or suspected SCD were recruited into this study through referrals by physicians from the National Heart Lung and Blood Institute (NHLBI) Vascular Therapeutic Section of the Cardiovascular Branch. Because Hb SC and S- β -plus-thalassemia patients typically have less pain than hemoglobin SS patients, for this pilot study we enrolled only hemoglobin SS patients.

Participants first underwent a screening history and physical examination to evaluate the presence and severity of SCD. Blood sample results from medical record source documents were utilized to establish hemoglobin genotype and baseline clinical characteristics. Participants had to meet all of the following criteria to be eligible for study enrollment:

Inclusion criteria:

- ≥ 18 years of age;
- Diagnosis of hemoglobin SS SCD;
- Patient identifies history of pain as a significant problem during at least 2 days in the month prior to enrollment; Written informed consent/assent has been obtained.

Exclusion criteria:

- Less than 18 years of age;
- Unwilling to experience hypnosis or to have hetero-hypnosis sessions recorded;
- Non-fluency in written and spoken English;
- Physical or other disabilities that prevent adequate participation in hypnotic susceptibility testing;



- Does not wish to be video and audiotaped;
- Psychosis or psychotic depression;
- History of seizures or epilepsy.

There has been one published report of a serious consequence related to hypnosis, a seizure in an 18-year-old with a history of epilepsy.³⁴ For this reason, individuals with a history of seizures or epilepsy were excluded from this study. Reports also suggest that hypnosis in individuals with a history of psychosis or psychotic depression may trigger psychiatric illnesses or produce decompensation or recurrent dissociative episodes.³⁵ Based on these reports, this pilot study excluded individuals with a history of psychosis or psychotic depression. Although we do not expect that hypnosis will mask the onset of acute vaso-occlusive pain crisis, participants will be monitored and any unexpected adverse events reported to the clinical team as well as the institutional review board. The study complies with the principles of the Declaration of Helsinki and was approved by the institutional review board of NHLBI (NCT00393250).

Sample size. A meta-analysis conducted by Montgomery et al.³⁶ of hypnotically induced analgesia exists estimating an average effect size of 0.74 across 18 studies. However, as previously noted, to date there have been no published randomized studies examining the efficacy of hypnosis-induced pain and symptom control in SCD patients. Because of this lack of evidence for accurately estimating an appropriate effect size for sample size selection, we proposed to conduct this study as a pilot with 20 participants in each group for a total of 40 participants. Based on the feasibility of undertaking this time- and resource-intensive intervention study and the possibility that some patients will be lost to follow-up, we requested an additional five participants in each group as our accrual ceiling.

Design. This is a randomized, controlled, single-crossover, repeated measures study (Fig. 2). After completing the intake interview, each participant was asked to begin daily pain diaries for one week. One week following enrollment, participants were randomized to the treatment or control groups. A random allocation scheme was computer-generated to provide participant group assignments. The study principal investigator (PI) and designees were initially blinded to the patient assignments, which were placed in individual, consecutively numbered, sealed envelopes. When the participant returned for their one week clinic visit, the study PI or designee opened the next numbered envelope to obtain that patient's assignment.

One week after enrollment, participants returned to the outpatient clinic and were randomized to the initial hypnosis (Group A) or control arm (Group B) of the study. Participants returned to the outpatient clinic as follows:

Interventions. Hypnosis interventions were conducted in four weekly sessions by an investigator certified in hypnosis (hetero-hypnosis). It is important to note that the sessions were conducted in a two-person-contact format in an outpatient

clinic patient room rather than a group setting away from the clinic. Interventions consisted of a hypnotic induction followed by individualized suggestions for analgesia, reducing anxiety, improving sleep hygiene, promoting ego-strengthening (self-efficacy), and enhancing health and well-being (see Table 1 for sample scripts). When appropriate, participants also received therapeutic suggestions specific to other symptoms. Sessions lasted about one hour and were conducted typically in a clinic room. After completion of the self-hypnosis, an assessment was conducted to measure hypnotic ability, using the Stanford Hypnotic Susceptibility Clinical Scale for Adults.³⁷ Hypnosis sessions were videotaped and audiotaped for documentation purposes. Participants were excluded from the study if they did not wish to be video and audio taped because this was the method by which a standard, blinded hypnosis susceptibility score was obtained by an independent rater other than the hypnosis therapist. This hypnosis susceptibility rating was for documentation purposes and as a potential variable that may be associated with the outcomes of the treatment.

Following these hetero-hypnosis sessions, participants entered a self-guided hetero-hypnosis phase. Participants were provided a digital video disc (DVD) for self-guided hetero-hypnosis and a DVD player. Each DVD had four selections from which participants can choose. Each selection had a scene from nature with the hypnotist's voice overlying the accompanying music from the scene. We hypothesized that scenes from nature that were recommended by SCD patients at an open house would provide additional interest and visual focus for the self-guided hetero-hypnosis. The participant only needed to watch one of these selections during a session. Participants were instructed to watch the DVD recording 3–7 times a week for six weeks. Participants were asked to evaluate their self-guided hetero-hypnosis experience in their daily diary (see Appendix C).

Therapeutic use of media. In addition to experiencing therapeutic hypnosis during face-to-face encounters in this study (hetero-hypnosis), participants also experienced self-guided hetero-hypnosis through digital media. The use of media technology for this study was twofold. The first reason was that videos allowed for a visual focus. While listening to the hypnotist, the patient was able to watch a scene from nature, thus complementing the audio and further removing them from their environment with the intent of making them more sensitive to suggestion. The other factor was closely tied to self-guidance. The patient had a choice of scenes to select from and therefore could match how they were feeling to what would assist them in visualizing relief.

Study processes for the control group were designed to control for the attention, interpersonal exchange, and positive expectation inherent in the therapeutic hypnosis experiences. Participants in the control group received age-appropriate education on SCD pathophysiology, inheritance, prevalence, common complications, and management in four

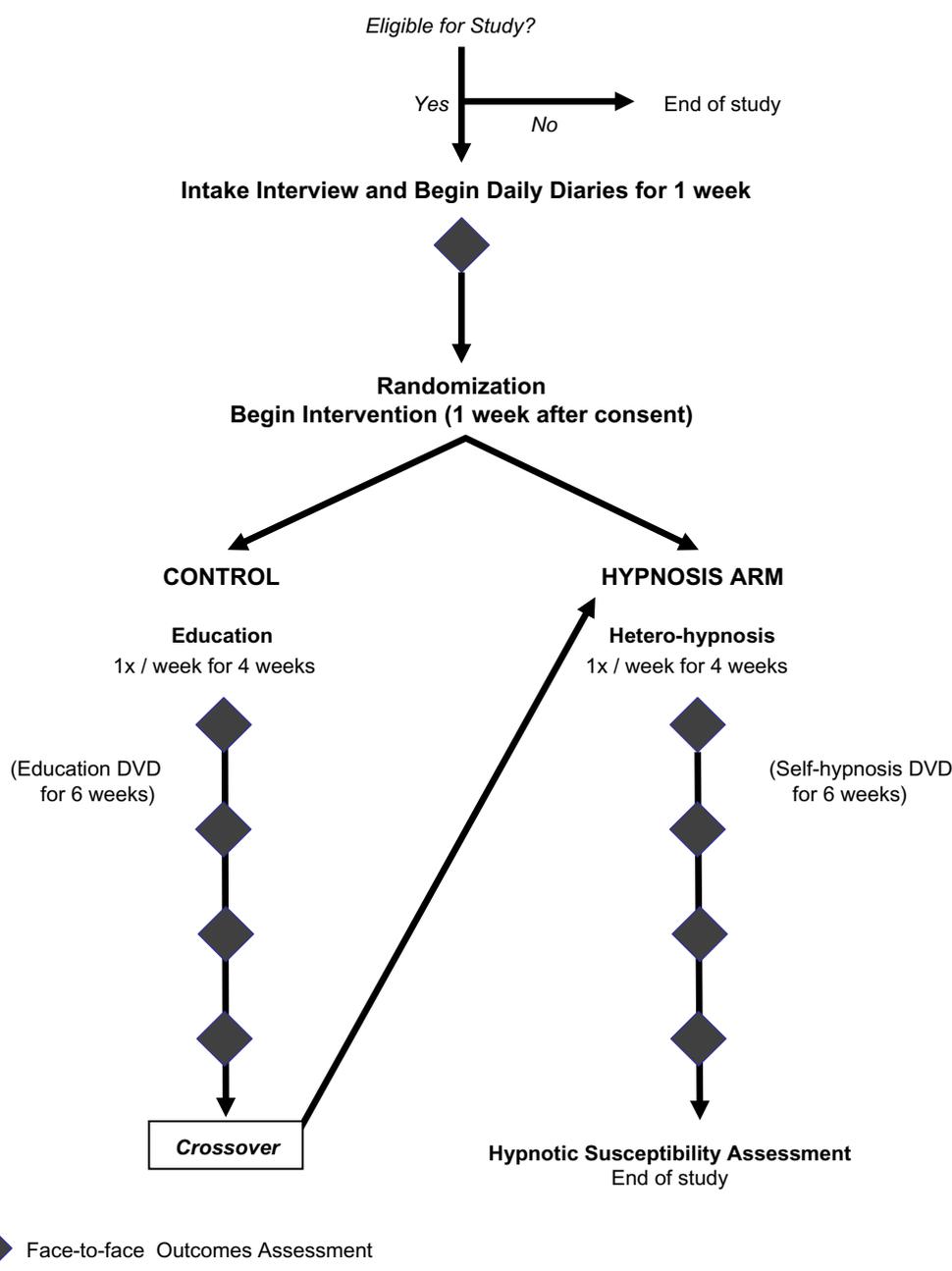


Figure 2. Hypnosis protocol design and randomization.

weekly sessions. Education was delivered by a qualified nurse investigator. Sessions lasted about one hour and were typically conducted in a clinic room. Participants in the control arm received a DVD with educational material that they could use during the six weeks following the face-to-face education sessions. Following the 11th week, participants in the control arm crossed over to the hypnosis arm of the study and completed both the four weeks of hetero-hypnosis and the six weeks of self-hypnosis. All patients could receive standard medical therapy while on the study regardless of study group assignment.

Outcome measures. The primary outcome measures in this study were patients' diary reports of pain severity

and pain intensity as measured by the pain numerical rating scale during follow-up clinic assessments. Participants were instructed on daily documentation of pain incidence, pain severity, sleep quality, medications taken, visits to a hospital, emergency room, or physician's office, and absence from school or work. Secondary outcome measures (pain impact, mood, anxiety, sleep, and coping) were collected during face-to-face interviews prior to randomization, at the end of the four-week education or hypnosis interventions, and at two-week intervals until the end of the six-week self-hypnosis (intervention) or education (control) CD/DVD phases. See Table 2 for a list of validated outcome measures.^{11,31,38-55}



Table 1. Self-hypnosis DVD categories and sample hypnotic excerpts.

SESSION / THEME	EXCERPTS FROM HYPNOTIC SCRIPT
1. Sensing Calm	<p>As you HEAR my voice...you may simply...begin noticing how much more relaxed those muscles are beginning to feel as you pay attention to my voice...automatically...allowing you to feel RELAXED in your face and your eyes. Your eyes can focus...on an image behind your eyelids...or some OTHER place carrying you DEEPER and DEEPER into a STRONG sense of CALM.</p> <p>Maybe, in your safe place you are reminded of other safe and comfortable experiences...that you may find yourself visiting easily to safe and happy experience, and you mind may wander ONLY to safe and special experience...or in your imagination...to new experience...reminding you of safe and comfortable feelings...drifting easily...and isn't it nice...notice how you feel much more comfortable and relaxed, as you settle back in that experience...</p>
2. Restful Sleep	<p>As you drift into sleep, you may hear a sound in the background...a rustle of a breeze perhaps...waves on a shore...or something else...that almost sounds like words...or a phrase...in the background...DEEP...as your breathe in... SLEEP...as you breathe out...and each word lasts for the full length of that stroke of your breathing...and as you drift comfortably in trance...you can hear that phrase continuing to flow along with each breath: DEEP...SLEEP...</p> <p>If at any point you should happen to awaken during the night, you'll easily fall back to sleep after taking care of any important business. As your head returns to its sleep position, you will quickly drift into a comfortable, deep sleep for the remainder of your rest.</p>
3. Strong Calm	<p>Perhaps you can imagine that there's a balloon in your tummy. As you notice what color it is, you may find yourself settling in deeper...deeper into imagining that with each in-breath, you are comfortably breathing <i>into that balloon</i>... so that with each time you breathe in...the balloon inflates and gets a little bigger... and with each out-breath, the balloon becomes a little smaller. Notice how the color of that balloon changes as it gets bigger...with each in-breath...that's right...deeper breath...bigger balloon...changing as the color stretches and thins to cover the larger balloon...</p> <p>You might even hear a phrase in the background...as you breathe in: STRONG, As you breath out: CALM. Each word lasts the particular length of that breath...and, since each breath is different, each word lasts a different length of time. So filling each in-breath...you'll hear that word S...T...R...O...N...G, and with each out-breath hear the word C...A...L...M...M..., STRONG...CALM...settling more and more with each sound...each breath <i>filling</i> with those words...</p>
4. Deeper Comfort	<p>And there you may find a peaceful sense of quiet free from bother or pain. Free to explore the depths of relaxation. You may find yourself settling NOW into a feeling free to experience a cooling numbness...a quieting feeling spreading over any area that has been bothered. Allow that feeling to proceed further, deeper into the tissues, as they quiet into a really <i>comfortable</i> state, <i>completely free</i>. Free to feel free of bother...more and more comfortable with each breath...more and more comfortable...</p> <p>Feelings of anxiety, doubts, fear, panic, and the sense of loss of control often arise from flashbacks... of reliving aspects of past pain...or from other past experiences which have brought out those kinds of feelings. All of these feelings and behaviors have interfered with your growth, your sense of oneness, and your natural healing processes...and even your appreciation of your own uniqueness and goodness. If you experience any of those negative feelings as you are listening, either you can allow yourself to choose to look at what is causing those feelings when you experience them, or you can imagine putting them into my locked file cabinet, where they will <i>safely</i> be stored. These feelings will <u>not</u> surface and can <u>not</u> be touched unless you <i>choose</i> to retrieve them to work on, to help you learn to live and enjoy life.</p>
5. Pain and Sleep	<p>Now, there may be a part of your body that you wish could become more comfortable. A part that, if only it could feel more comfortable, things would be better. <i>Much better</i>. As soon as you have decided where you want to start feeling comfortable, you will begin to notice how that comfort increases more and more in whatever part of your body...<i>you want to be comfortable</i>. The comfort might set in slowly or it may appear more quickly; the comfort may begin right in the center of where you want it most, or it may spread in from around the edges. It doesn't really matter how...<i>that comfort grows and spreads</i>.</p> <p>And it is always satisfying to return home after having been on an enjoyable ride in a comfortable car at the end of a long day, looking forward to deep and relaxing sleep. Everyday can be like a ride in a comfortable car, and every night can be like a homecoming, when you prepare for bed and drift off to comfortable and deep sleep. You can practice doing this in your imagination now, so that the next time you actually go to sleep, you'll be able to go to sleep easily, and sleep deeply and comfortably until it is time for you to wake up.</p>

Analysis plan. Initial analysis will be descriptive and exploratory. Our hypotheses for the analysis phase of the protocol are as follows:

- Therapeutic hypnosis, guided by a hypnotherapist (hetero-hypnosis) and followed with self-hypnosis using customized digital media, improves disease-related pain, anxiety, coping strategies, sleep, and depression compared to an education control intervention in patients with SCD.
- Therapeutic hypnosis, guided by a hypnotherapist (hetero-hypnosis) and followed with self-hypnosis using customized digital media, reduces health care utilization compared to an education control intervention in patients with SCD.

Statistical analysis for each of the main outcomes will involve comparing the patients assigned to the hetero- and self-guided hetero-hypnosis intervention to patients who do not initially receive hypnosis using the appropriate scale/instrument for that outcome. Each scale/instrument will be analyzed separately and the general statistical approach will employ multiple-way analysis of covariance (ANCOVA) to compare the mean scores of the two groups. The analyses will control for specific patient factors (eg, genotype, hematologic measures, treatment, co-morbidity, age, gender, education) as indicated by the conceptual model. Mixed linear modeling will be used to account for some of the expected missing data in this repeated measures study.

**Table 2.** Measures.

Pain Impact Questionnaire (PIQ-6™)	<ul style="list-style-type: none"> • 6-item, patient-reported health outcomes assessment designed to measure pain severity and the impact of pain on an individual's health-related quality of life (HRQOL) • Measures the impact of pain on work and leisure activities as well as on emotional well-being • Brief, easy to use, reliable assessment of pain severity and pain impact³⁸
Pain Numerical Rating Scale	<ul style="list-style-type: none"> • Verbally administered or written 11-point scale from 0 to 10, with 0 representing no pain and 10 equaling the worst possible pain • Well-established validity^{39–41}
Sickle Cell Pain Diary	<ul style="list-style-type: none"> • Examines painful crises and utilization events within a given SCD patient on a given day • Includes both the entire Dinges et al diary³¹ with the addition of health care utilization items as proposed by Smith et al.¹¹
Beck Depression Inventory (BDI)	<ul style="list-style-type: none"> • 21-item questionnaire which screens for presence and severity of depression in adults⁴² • Each item assess particular aspect of experience/symptomatology of depression rated on a four-point intensity scale • Higher scores indicate that the individual is more depressed⁴³ • Reliable and valid with adults, including the elderly⁴⁴
State-Trait Anxiety Inventory (STAI)	<ul style="list-style-type: none"> • Includes two distinct self-report anxiety concepts: state (transitory emotional state) and trait (habitual predisposition to anxiety)^{45,46} • 40-item inventory, takes approximately 10 minutes to complete⁴⁶ • Reliability and validity supported in studies of both patients and normal volunteers^{46–48}
Coping Strategies Questionnaire (CSQ)	<ul style="list-style-type: none"> • Measures frequency of use of six different cognitive / behavioral coping strategies⁴⁹ • Patients rate how often they use each strategy on a 7-point scale⁵⁰ • Acceptable internal reliability^{49,51,52}
Pittsburgh Sleep Quality Index (PSQI)	<ul style="list-style-type: none"> • Self-rated questionnaire which assessed sleep quality and disturbances over a one-month time interval • 19 individual items generate seven component scores and a global score⁵³ • Acceptable internal homogeneity, consistency, and validity; score >5 indicates “poor” sleepers
Stanford Hypnotic Clinical Scale for Adults (SHCS: Adult)	<ul style="list-style-type: none"> • Hypnotic susceptibility scale^{54,55} • Takes 20 minutes to complete • Designed for clinical use; reliable³⁷

Discussion

Previous research related to SCD patients has focused on the frequency of pain resulting in emergency department use and number of hospitalizations because of pain crisis in SCD patients. Few studies focus on these pain manifestations outside the typical health-care delivery system or on how patients manage their pain apart from their physician. Little is known about the percentage of patients who are able to self-manage their crises at home without accessing health-care professionals.

Recent findings suggest that patients may have two types of positive outcomes following hypnosis treatment: 1) a reduction in the severity of ongoing daily pain intensity; and 2) the ability to use self-hypnosis to experience greater intervals of comfort.⁵⁶ However, to date, there are no published randomized, controlled trials evaluating the efficacy of hypnosis in SCD pain modulation. This protocol is aimed at longitudinally assessing the effects of hypnosis in such a manner. The design of this study provides information related to daily diary reports of pain incidence, pain severity, sleep quality, medications taken, as well as visits to a hospital, emergency room, or physician's office, and absence from school or work. Additional secondary outcome measures (pain impact, mood, anxiety, sleep, and coping) were collected during face-to-face interviews.

The major advantage of conducting a longitudinal analysis is its capacity to observe and delineate changes over time within the study participants from differences among the participants while controlling their baseline characteristics. Therefore, repeated measures and mixed linear modeling will allow us to study the trajectory of psychosocial behaviors and pain intensity changes over time after controlling for intrapersonal correlations in order to draw valid scientific inferences regarding the impact of the hypnosis intervention. Limitations exist in this protocol including the lack of qualitative inquiry to explore the patient experience while utilizing hypnosis as a self-care strategy for pain and symptom management. Although this is a randomized, controlled, crossover design, the sample size will not yield conclusive results in terms of treatment or dose efficacy, but rather will serve as a proof of concept for future randomized controlled trials (RCTs) testing hypnosis as a potential non-pharmacological approach to managing chronic pain and symptoms in adults with SCD.

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Author Contributions

Conceived and designed the experiments: GW, DH, NA. Wrote the first draft of the manuscript: GW, KM, AB. Contributed to the writing of the manuscript: GW, KM, AB, DH. Agree with manuscript results and conclusions: GW, KM, NA, AB, DH. Jointly developed the structure and arguments for the paper: GW, KM. Made critical revisions and approved final version: GW, KM, NA, AB, DH. All authors reviewed and approved of the final manuscript.

Supplementary Files

Appendix A. This file shows the format for subjects' morning diary entries.

Appendix B. This file shows the format for subjects' nightly diary entries.

Appendix C. This file shows the format for subjects' diary entries evaluating self-hypnosis exercises.

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