Supplementary Material

Appendix 1:

Characteristics of included studies

Fein 2016,[54]

Methods	Randomized double-blind placebo-controlled parallel study Single center (ED) Drop-outs described.
Participants	Sample of 161 children approached for study. 124 children consented. 9 withdrew their consent. 115 were eligible and randomized from which there were a total of 130 PED visits for VOC. 70 were excluded. 11 were lost. 49 children received study drug, included and analyzed: 24 in intranasal fentanyl group and 25 in intranasal placebo group Age: between 3 - 20 years Gender: both Disease status: having any SCD genotype (sickle cell anemia, hemoglobin C disease, sickle beta thalassemia) Inclusion criteria: participants had painful vaso-occlusive crisis who presented to the PED and did not take daily opiates Exclusion criteria: patients who had a known allergy to fentanyl, had been on daily opiate use (for instance, methadone), patients had pain score < 6 on the modified WBFPRS at presentation in PED with pain crisis, having previously received the study drug, hypotension (systolic blood pressure < 5^{th} percentile for age), oxygen saturation < 92% on room air, temperature > 102° F, respiratory distress, recent trauma, priapism, isolated headache, isolated abdominal pain, severe rhinorrhea or epistaxis, new neurological signs or symptoms, pregnancy (a point-of-care urine pregnancy test was performed on female subjects ≥ 13 years to ensure they were not pregnant prior to the administration of the study drug), or having started daily opiates since consent
Interventions	Treatment group: a single dose of intranasal fentanyl citrate 2μg/kg, maximum 100 μg (half of volume administered in each naris) Control group: normal saline placebo (intranasal, half of volume administered in each naris) The study drug was split equally into two 1 mL syringes and the contents of each syringe were administered into each naris using a nasal mucosal atomization device.
Outcomes	Primary objective ─ Pain relief rating at 10, 20, and 30 min by comparing change in the ladder of pain after the administration of the study drug (assessed with WBFPRS) in children, the *a priori* primary time point of interest was 20 min.

	Secondary objective ─ Adverse events in children related to the medication and the delivery method.	
Notes	Setting: Hospital; large urban quaternary children's hospital, PED, Montefiore, New York, United States. ClinicalTrial.gov identifier: NCT01482091 Awaiting answer from the authors study to supply additional details of results of outcome measures	
Risk of bias		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by a research pharmacist according to randomization tables in block of six" Study design was stated as randomized double-blind, placebo-controlled study. Vials were labeled to maintain blinding and were numbered to correspond to the specific randomization assignment Randomization code and blinding were not broken until after study completion
Allocation concealment (selection bias)	Low risk	Quote: "Vials containing either 2 mL of standard IV formulation fentanyl citrate (concentration 50 µg/mL) or 2 ml of 0.9% NaCl were prepared in a sterile environment. Vials were labeled to maintain blinding and were numbered to correspond to the specific randomization assignment known only to the research pharmacist"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Physicians, nurses, subjects, parents were blinded to study drug allocation. Vials were labeled to maintain blinding and were numbered to correspond to the specific randomization assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Physicians, nurses, subjects, parents were blinded to study drug allocation" Comment: the study was registered on clinicaltrials.gov and it described that the quadruple masking included the participant,

		care provider, investigator, and outcomes assessor (search on clinicaltrials.gov for NCT01482091)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "49 children resulted in administration of the study drug" Comment: All of 49 participants completed the study
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were reported
Other bias	High risk	The targeted sample size intended for this study was 161 children from which was approached for enrollment, 124 consented, 9 participants afterward withdrew their consent, and 115 were eligible to receive the study drug upon 130 future ED visits. But only 49 children received the study drug (24 in intranasal fentanyl and 25 intranasal placebo) so the target was not achieved

Goldman 2013,[55]

Methods	2-armed randomized double-blind placebo-controlled parallel study. Single center (ED) Drop-outs described.
Participants	Total of 159 children approached for study. 106 children (67%) consented 2 children (2%) withdrew their consent. 104 children included and examined: 51 in the $MgSO_4$ arm, 53 in the placebo arm Age: mean (SD) 12.4 (3.8) years, range 4-18 years, median 12.9 years Gender partition: 56 (54%) female SCD genotype: 61 (58.6%) homozygous sickle cell anemia; 33 (31.7%) sickle hemoglobin C disease; 10 (9.6%) sickle beta thalassemia Pain started a median of 24 hours before arrival at ED (range 4-240 hours; SD 37 hours) Elapsed times from last visit to ED until study admission: mean of 7.3 months in the $MgSO_4$ arm and 8.7 months in the placebo arm Included criteria: participants with known SCD (documented on hospital files) and who had experienced a vaso-occlusive crisis. Excluded criteria: patients who had fever (> 38.5 °C) during the 24 hours before ED visit, transfused within 90 days of study entry, with known renal disease, heart block or myocardial damage, any calcium channel blocker, or who took a magnesium-containing medication on a regular basis, received anesthetics, cardiac glycosides, and neuromuscular blockers during the acute illness in the past 24 hours,

	patients or parents incapable of communicating in English, pregnancy, known allergy to magnesium, admission to the ICU, and enrolment to the study in the last 30 days	
Interventions	Treatment group: IV $MgSO_4$, 100 mg/kg, maximum 2 g/dose, 8 hourly until discharge Control group: IV normal saline placebo, 100 mg/kg maximum 2 g/dose, normal saline equivalent amount to $MgSO_4$, 8 hourly until discharge	
Outcomes	Primary outcome ─ LOS in the hospital (measured as number of hours from the first study drug dose until the physician's decision to discharge) Secondary outcome ─ Reduction mean daily pain intensity during an admission for VOC (assessed by using the Faces Pain Scale-Revised and VAS) ─ Cumulative drug use (analgesic required to manage the crisis during admission, measured as micrograms per kilogram of body weight per hour for their LOS) ─ Adverse events, such as changes in vital signs and other appearance of clinical signs.	
Notes	Setting: Hospital; The PED at the hospital for sick children, Toronto, Canada. ClinicalTrial.gov identifier: NCT00313963 (MAST, Magnesium for Sickle Cell Acute Crisis in Children, study)	
Risk of bias		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization and dispensing were conducted by research pharmacy using a preset randomization table (block of 4) " Study design was addressed as 2-armed randomized, double-blind, placebo-controlled study. Participants children with families providing consent were randomly assigned by the research
Allocation concealment (selection bias)	Low risk	Quote: "Randomization and dispensing were conducted by research pharmacy. Families providing consent were randomly assigned by research pharmacist to receive IV $MgSO_4$ (100 mg/kg, maximum of 2 g/dose) 8 times hourly or IV placebo (normal saline in a volume equivalent to $MgSO_4$) 8 times hourly"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators, physicians, nurses, parents, and patients were blinded to the treatment arm. Study drug and placebo looked

		exactly the same (volume and appearance)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Investigators, physicians, nurses, parents, and patients were blinded to the treatment arm." Comment: insufficient information to make a judgment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "106 (67%) consented, with 2 children (2%) withdrawn from the study because of withdrawal of consent. A total of 98 unique patients who had 104 episodes in which they were recruited to the study: 51 (49%) in the $MgSO_4$ group and 53 in placebo group"
Selective reporting (reporting bias)	Low risk	The study's pre-specified outcomes were described
Other bias	High risk	From the protocol of this study, the intended simple size was not accomplished. A total of 159 participants were analyzed; only 106 consented and 2 individuals later withdrew their consent

Morris 2013,[56]

Methods	Prospective randomized double-blind placebo-controlled single group study Single-center (ED, hematology clinic, day hospitals, and wards) Phase 2 trial Drop-outs described.
Participants	A total of 38 patients with 56 distinct vaso-occlusive episodes (VOE) 54 completed randomization and received study drug or placebo 28 in each arm (arginine versus placebo) 2 excluded from analyses (after the unblinded study and calculation of total opioid), then 54 VOE were analyzed and included in total: 26 in arginine arm, 28 in placebo arm 47 episodes (85.5%) evaluated in the ED, 7 admitted to ward Age: mean (SD) 13.9 (4) years, range 3.6 - 19 years Gender split: 53 females Disease status: pain episodes involved children with homozygous sickle cell anemia (Hb-SS) 73 %; sickle hemoglobin C disease (Hb-SC) 18%; sickle beta thalassemia (S-beta thalassemia) 9% Time between triage in the ED or presentation to clinic, and delivery of first randomized study drug dose was 20.4 (11) hours 5 individuals (9%) withdrew from study after initiation of study drug (3 in arginine arm, 2 in placebo arm);3 adolescents were no longer interested in participating and asked to withdraw from study without providing a particular reason (2 in arginine arm, 1 in placebo arm)

	2 patients withdrawn by principal investigator for adverse events (1 in arginine arm, 1 in placebo arm) Erroneously crossed over for three doses of arginine due to a pharmacy medication error: 1 participant in placebo arm Included criteria: children with an established diagnosis of SCD and VOE requiring parenteral opioids throughout their hospital stay and admission to hospital Excluded criteria: patients who had hemoglobin less than 5 g/dL or immediate needed for red cell transfusion, known hepatic (increased in SGPT to > 2x normal value) or renal insufficiency (increased in creatinine to > 2x normal value or > 1.5), pregnancy, > 10 hospitalizations per year or history of dependence to narcotics, mental status or neurological changes (concern for stroke), inability to take oral medications or to use a PCA device or a known allergy to arginine	
Interventions	Treatment group: intravenous or oral 100 mg/kg/ dose 3 times/day L-arginine hydrochloride (maximum dose of 10g for 15 doses or until discharge) Control group: capsule placebo identical to study drug, 700 mg (sugar pill), normal saline for intravenous administration	
Outcomes	Primary outcome – LOS in the hospital (days) (participants will be followed foe the duration of hospital stay an expected average of 3-6 days) Secondary outcomes – Pain score (assessed with 10-cm linear VAS and Faces Pain Scale) – Total of narcotic used (mg/kg)	
Notes	Setting: Hospital, Children's hospital research center Oakland, California United State. ClinicalTrial.gov identifier: NCT01796678	
Risk of bias		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization and dispensing were performed by the hospital research pharmacist using block randomization" Study design was described as phase 2 trial, a prospective, randomized, double-blind, placebo-controlled study. Participants consented within 24 hours of admission to hospital and were randomized
Allocation concealment (selection bias)	Low risk	Quote: "Patients were consented within 24 hours of admission to the hospital and randomized to receive IV or oral (PO) study drug, L-arginine hydrochloride (100 mg/kg/dose three times per day with maximum dose of 10 g for 15

		doses or until discharge, whichever occurred first) or placebo. Placebo capsules appeared identical to the study drug (700 mg capsules) and were matched to the study drug by Tyson Pharmaceuticals for color and size"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Entry on clinicaltrials.gov for NCT01796678 states there was double-blind masking (participant, care provider, investigator). Quote: "Placebo capsules appeared identical to the study drug (700 mg capsules) and were matched to the study drug by Tyson Pharmaceuticals for color and size, while normal saline was used for the IV placebo"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Entry on clinicaltrials.gov for NCT01796678 states there was double-blind masking (participant, care provider, investigator); however, the method of blinding the outcome assessors was not mentioned Comment: insufficient information to make a judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of 110 pain events assessed for eligibility, 57 were randomized into placebo-controlled trial and 56 received either arginine therapy or placebo per protocol with 28 events in each arm. Two excluded after randomization (in arginine arm). A total of 5 patients were withdrawn from the study and intervention discontinued; however, their data were included in the intent-to-treat analysis"
Selective reporting (reporting bias)	Low risk	Study pre-specified outcomes procedure of interest were reported
Other bias	High risk	The targeted sample size expected for the study was not obtained. 110 individuals were assessed for study participation, 57 pain events were randomized; a total of 38 patients with 56 received either arginine or placebo (one patients

		in placebo arm received three doses of arginine). In 56 patients, 54 were analyzed in total (2 patients excluded in arginine arm received IV ketorolac only for pain and no parenteral narcotics throughout their hospital stay). Five patients (9%) withdrew after initiation of study drug, 3 of them without providing a particular reason, later 2 participants withdrew by adverse events

Weiner 2003,[57]

Methods	Prospective randomized double-blind placebo-controlled study. Pilot study (ED) Drop-outs described.
Participants	79 patients assessed for eligibility. 25 participants were randomized. 5 patients did not meet eligibility criteria after randomization but before initiation of inhalation. 20 participants included and analyzed: 10 in inhaled nitric oxide group, 10 in placebo group Age: 10 to 21 years Gender: both Disease status: sickle cell anemia (HbSS), hemoglobin SC (HbSC), or HbS-β-thalassemia (HbS-βthal) Included criteria: participants were experiencing uncomplicated severe acute VOC (score ≥ 6-cm on a 10-cm VAS) Excluded criteria: patients who were included in ED treatment for VOC within the previous 24 hours, VOC concomitant with other acute processes including but not limited to ACS and potential serious infection, transfusion or use of investigational drugs other than hydroxyurea within the last 30 days, a known allergy to morphine, smoking more than 1/2 pack per day, and pregnancy
Interventions	Treatment group: Inhaled nitric oxide (80 ppm with 21% final concentration of inspired oxygen by face mask) + morphine (0.1 mg/kg, maximum dose 6 mg by patient-controlled administration = PCA) + fluids (isotonic sodium chloride solution, 10 mL/kg, over 30 minutes) Control group: 21% inspired oxygen placebo by face mask + morphine (0.1 mg/kg, maximum dose 6 mg by PCA) + fluids (isotonic sodium chloride solution, 10 mL/kg, over 30 minutes)
Outcomes	Primary outcome measure—Change in pain score at 4 hours of inhalation (evaluated by VAS, 10 cm horizontal, undemarcated, with 0 = no pain and 10 = worst pain) Secondary outcomes measures—Amount parenteral narcotic used at 4, 6, and 24 hours after initiating inhalation—LOS in the hospital—Adverse events

Notes	Setting: Hospital, urban, tertiary care academic children's hospital in United States.	
Risk of bias		
Bias	**Authors' judgment**	**Support for judgment**
Random sequence generation (selection bias)	Unclear risk	Mentioned as randomized, but no details provided for how the sequence was generated Insufficient information to judge
Allocation concealment (selection bias)	Unclear risk	There was insufficient information to judge
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Investigators, patients, parents of patients remained blinded throughout the study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Investigators, patients, parents of patients remained blinded throughout the study" The method of blinding the outcome assessors was not mentioned Comment: insufficient information to make a judgment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "79 patients assessed for eligibility. 25 participants were randomized. 5 patients did not meet eligibility criteria after randomization but before initiation of inhalation. 20 participants included and analyzed"
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes procedure were reported
Other bias	High risk	The targeted sample size expected for this study was not achieved. 79 patients assessed for eligibility. 25 participants were randomized. 5 patients did not meet eligibility criteria. 20 participants included and analyzed

SCD: sickle cell disease

HbSS: sickle cell anemia,

HbSC: hemoglobin SC

HbS-βthal: HbS-β-thalassemia

VOC: vaso-occlusive crisis

VOE: vaso-occlusive episodes

WBFPRS: Wong-Baker FACES Pain Rating Scale

VAS: Visual analog pain scale

LOS: length-of-stay

IV: intravenous

Mg: magnesium

MgSO4: magnesium sulfate

SD: standard deviation

PCA: patient-controlled analgesia

ED: emergency department

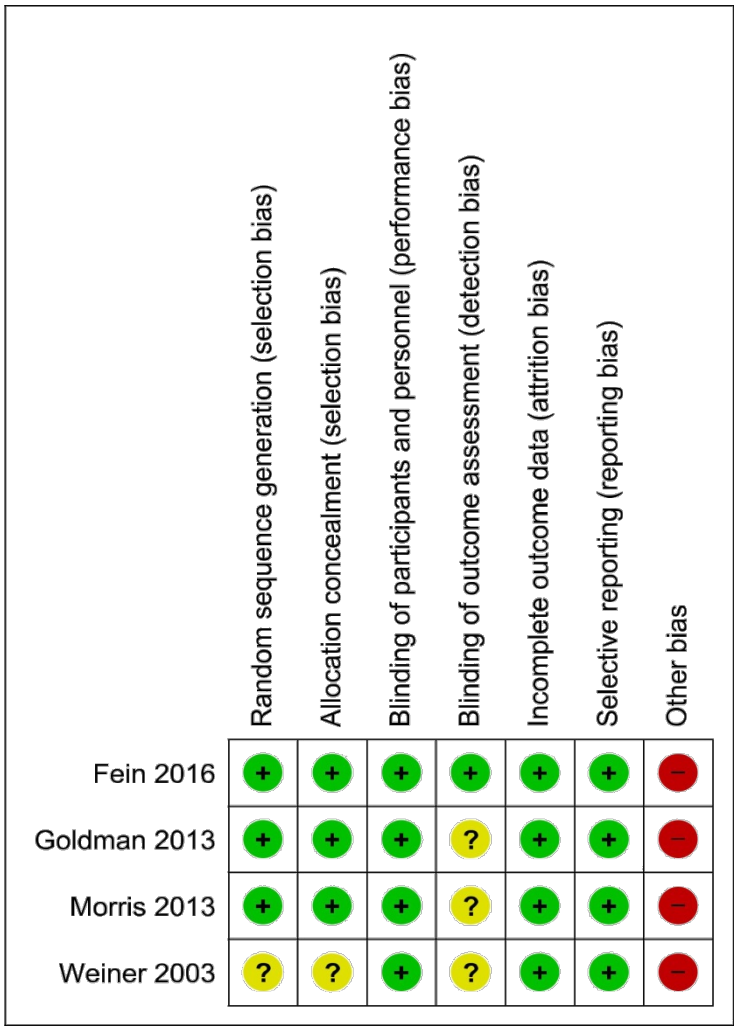
PED: pediatric emergency department

PO: *per os*

SGPT: serum glutamic pyruvic transaminase

ACS: acute chest syndrome

Risk of bias summary: review authors' judgments about each risk of bias item for each included study



Risk of bias graph: review authors' judgments about each risk of bias item, presented as percentages across all included studies.