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# Patient-controlled analgesia improves pain control in a vaso-occlusive crisis in sickle cell patients

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**ABSTRACT** A critical appraisal and clinical application of van Beers EJ, van Tuijn CF, Nieuwkerk PT, Friederich PW, Vranken JH, Biemond BJ. Patient-controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomized controlled trial. *Am J Hematol.* 2007;82(11):955-60. doi: [10.1002/ajh.20944](https://doi.org/10.1002/ajh.20944)

**Keywords:** *sickle cell disease, patient controlled analgesia, vaso-occlusive crisis*

## Clinical Context

A 20-year-old African American woman with past medical history of sickle cell (HbSS) disease, avascular necrosis of right hip bone, and cholelithiasis presented complaining of pain in her back, legs, and elbows that had been going on for one and a half weeks. She had come to the emergency department two more times during the past ten days, with this being her second admission in a week.

On presentation, she had scleral icterus with a hemoglobin level of 6 and reticulocyte count of 370,000. She was admitted for a sickle cell vaso-occlusive crisis and started on intravenous (IV) fluids with half normal saline and half D5W (5% dextrose in water). Her pain was not controlled on fixed scheduled IV hydromorphone with rescue doses of oral (PO) morphine as needed for breakthrough pain. She stated that her pain was still 10/10 in severity, and she was still having breakthrough pain in between hydromorphone doses. She inquired about the possibility of receiving hydromorphone in a continual manner in order to maintain an adequate, sustained level of analgesia. As a result, we considered placing the patient on continuous hydromorphone therapy, either via a patient-controlled analgesia (PCA) pump or a continuous infusion (CI).

## Clinical Question

Is patient-controlled analgesia a better choice for pain control than continuous infusion for a vaso-occlusive crisis in a sickle cell patient?

## Research Article

van Beers EJ, van Tuijn CF, Nieuwkerk PT, Friederich PW, Vranken JH, Biemond BJ. Patient-controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomized controlled trial. *Am J Hematol.* 2007;82(11):955-60. doi: [10.1002/ajh.20944](https://doi.org/10.1002/ajh.20944)

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## Related Literature

A search for research studies that evaluated the clinical question was conducted on PubMed and Google Scholar using the key phrases “patient-controlled analgesia” and “sickle cell disease.” UpToDate was also used to search for links to relevant research studies. Articles regarding the hospital management of sickle cell crises were examined for connection to this case. It is important to note that we were unable to find a randomized controlled study in adolescents that examined all three therapeutic options of PCA, CI, and intermittent scheduled dosing. Therefore, our goal was to find a study that would guide our future therapeutic plan for our patient. Specifically, studies that compared PCA and CI in adolescent patients were deemed of greatest relevance.

Six pertinent studies were found that examined the use of PCA in sickle cell patients with vaso-occlusive crises.<sup>1-6</sup> Three of these were nonrandomized studies.<sup>4-6</sup> The investigation by Melzer-Lange et al. was a nonrandomized pilot study that reviewed patient records and found that a protocol to initiate early PCA in the emergency department shortened inpatient length of stay and improved patient satisfaction.<sup>6</sup> Shapiro et al. conducted a retrospective review of patient records to examine dose ranges and patterns of PCA use for vaso-occlusive pain and found significant variations in patterns of PCA use and patient satisfaction.<sup>4</sup> Trentadue et al. examined patient records to compare two different PCA regimens that were used in pediatric patients during vaso-occlusive crises and found that a high dose PCA & low dose CI combination was superior to a low dose PCA & high dose CI combination with regards to total morphine consumption, length of stay, and pain control.<sup>5</sup> The remaining three experiments were randomized controlled trials.<sup>1-3</sup> Of the three randomized controlled trials, the one conducted by Schechter et al. was a pilot study with a small sample of three adolescent patients demonstrating that PCA was a feasible modality for pain control and that patients used less opioids with each successive day of treatment.<sup>2</sup> The study by Gonzalez et al. compared PCA and intermittent injections in vaso-occlusive crises in an older patient population in the setting of the emergency department, concluding that both low- and high-dose PCA regimens were as safe and effective as intermittent injections.<sup>3</sup>

The study performed by van Beers et al.<sup>1</sup> was the most relevant to our 20-year-old patient, as it was a prospective randomized controlled study that compared the use of PCA to CI of morphine for sickle cell crisis pain control in an inpatient setting, with inclusion criteria of patients with known sickle cell disease older than age 17. In addition to comparing pain control, the study examined the incidence of opioid adverse effects and hospitalization duration between the experimental and control groups.<sup>1</sup> Out of the six pertinent papers, the study conducted by van Beers et al. was the most recent, published in 2007. It has been cited 35 times and was most recently cited in 2016, demonstrating its continued relevance in ongoing research.

## Critical Appraisal

This un-blinded, randomized controlled study conducted by van Beers et al. included 25 episodes of vaso-occlusive crisis observed in 19 patients.<sup>1</sup> During the first vaso-occlusive episode of each patient, they were randomized to either the patient-controlled analgesia (PCA) morphine group or the continuous-infusion (CI) morphine group. Six of the 19 patients presented with a repeat episode and were subsequently crossed-over to the other treatment group. The crossover consisted of four patients who received PCA and two patients who received CI initially. Ultimately, 12 patient episodes were allocated to the PCA group while 13 were allocated to the CI group. Two separate patients withdrew consent during the trial (one from each group) and requested to have their medication changed from morphine to meperidine. Baseline parameters including age, gender, current treatment with hydroxyurea, hemoglobin genotype, and baseline blood parameters were comparable between the two groups with one notable exception: baseline leukocyte count was higher in the CI group relative to the PCA group (15.2 versus 11.3, respectively).<sup>1</sup> Data from the study was analyzed on an intention to treat basis.

Both the PCA group and CI group received an initial 5 mg morphine bolus. Patients in the PCA group were allowed self-administration of 0.01 mg/kg IV morphine bolus with a 5-minute lockout. If pain control was inadequate, the dosage was increased to 0.02 mg/kg, again with a lockout of 5 minutes. The PCA group did not receive any background infusion on top of these self-administered boluses. Patients in the CI group received a morphine infusion of 0.03 mg/kg/hr. If pain control was inadequate, the morphine dose was increased by 1 mg/hr until pain control was satisfactory or side effects became intolerable.

The primary outcomes examined were pain relief, mean daily morphine consumption, and mean cumulative morphine consumption. The secondary outcomes included duration of hospitalization, adverse effects, and quality of life. The mean verbal pain scores (scale 0-10, 10 being worst pain) were comparable for the PCA group (5.3) and the CI group (4.9). The mean daily morphine consumption



for the PCA group was 0.5 mg/hr, compared to 2.4 mg/hr in the CI group. The mean cumulative dose of morphine during the vaso-occlusive crisis for the PCA group was 33 mg, compared to 260 mg in the CI group. This significant difference in cumulative morphine consumption was partly explained by a reduced mean duration of hospitalization for the PCA group (6.0 days) relative to the CI group (9.0 days). This reduced duration of admission was not statistically significant ( $p$ -value = 0.15). Adverse effects of nausea and constipation were significantly lower for the PCA group relative to the CI group, but no significant difference was found in pruritus and sedation between the two groups. The discrepancy in the incidence of nausea and constipation was eliminated when adjusting for morphine dose, indicating that the increased nausea and constipation experienced by the CI group was dose-related. The two groups reported no significant differences in regards to the perceived quality of life.

In conclusion, the study showed that the PCA group achieved comparable pain relief with significantly lower daily and cumulative morphine consumption relative to the CI group. The CI group, on average, used nearly five times as much morphine each day compared to the PCA group. In addition, the PCA group experienced, on average, a lower incidence of nausea and constipation when compared to the CI group. However, the study is not without limitations. One of the major shortcomings is that there is no data given on the ethnicity or race of the study participants, and thus it is difficult to gauge whether the participants are representative of the entire sickle cell disease population. The study was conducted at a medical center in the Netherlands. Our patient was an African American woman residing in Detroit, and thus may have differed in significant ways from the study population. Another drawback of the study is the small sample size of 19 participants, which increased the likelihood of the nonrandom distribution of confounding variables. A larger study is warranted to make more definitive conclusions in regards to pain control and length of hospitalization. Finally, the authors noted that the lack of blinding was a significant drawback to their study.<sup>1</sup> The use of PCA pumps made it impossible for them to conduct a double-blind study, and this may have introduced some bias in their findings. Double-blinding in future studies may be possible by incorporating a control group that receives a CI treatment from a PCA device that has the button-press dose set at zero.

The study conducted by van Beers et al. can be designated as a level 2 study per the Strength of Recommendation Taxonomy (SORT) scale. The strengths of the study are evident in the fact that its outcomes are patient-oriented, addressing the patient's pain level and cumulative side effects of treatment as well as secondary outcomes such as length of hospitalization and quality of life. There is statistically significant evidence in this study to indicate that treatment via PCA is superior to CI in key aspects, and therefore PCA should be considered as a first-line therapy when around-the-clock opioid analgesia is required. However, the study's quality is decreased by the small sample size, low statistical power, and lack of blinding. Future research designs should attempt to build on the findings of van Beers et al.

## Clinical Application

The decision to start a sickle cell patient with a vaso-occlusive crisis on PCA should be carefully considered, especially in patients who chronically use opioids at home. Previous research studies in post-operative patients have demonstrated the safety and efficacy of patient-controlled analgesia under appropriate dose strengths and schedules. This study provides evidence of comparable pain control at lower doses of morphine and fewer adverse events in patients with PCA. However, PCA may not be appropriate for all sickle cell patients, such as patients who are opioid-naïve or who have demonstrated adverse side effects to opioid use in the past. The risks and benefits must be weighed in each individual case. In the case of our patient, we decided to start her on PCA since traditional dosing schedules were not managing her pain. Our reasoning was that by allowing her to control analgesic administration, the patient could better manage her breakthrough pain.

We met with our patient and discussed our plan to start her on a PCA pump. Given her chronic use of opioids at home, which included oral (PO) hydromorphone and PO sustained-release morphine, we decided to place her on hydromorphone PCA rather than morphine PCA. Patient was agreeable to our suggestion. After consulting with hematology, we started hydromorphone patient-controlled analgesia pump at 1.0 mg at 6-minute lockout for pain control, along with morphine sustained-release 600mg twice a day. Patient subsequently stated her pain was being well controlled on the PCA. Our patient improved over the next couple days and was discharged with outpatient hematology clinic follow-up.

Take Home Points:



1. Patient-controlled analgesia (PCA) provides comparable pain relief to continuous-infusion (CI) at significantly reduced morphine consumption.
2. The PCA group experienced significantly less nausea and constipation relative to the CI group in a dose-dependent manner, but there was no significant difference in pruritus and sedation.
3. PCA is a strong candidate to be considered first-line therapy over CI in a vaso-occlusive crisis in sickle cell disease patients. However, each patient's previous history with opioids and individual risks and benefits must be weighed in each case.

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