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Patient controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomised controlled trial

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Abstract

Intravenous morphine is the treatment of choice for severe pain during vaso-occlusive crisis in sickle cell disease (SCD). However, side-effects of morphine may hamper effective treatment and high plasma levels of morphine are associated with severe complications such as acute chest syndrome. Furthermore, adequate dosing remains a problem since no objective measurement of pain severity exists and analgesia should be titrated upon the patient's reported pain. Patient-controlled analgesia (PCA) may therefore be an interesting alternative since patients can titrate the level of analgesia themselves.

In this randomized controlled study, the efficacy of intravenous morphine administration with PCA was compared with continuous infusion (CI) of morphine in patients with SCD during vaso-occlusive crisis.

Twenty five consecutive episodes of vaso-occlusive crisis in 19 patients with SCD were included in the study. Patients in the PCA-group had a markedly and significant lower mean and cumulative morphine consumption as compared to the patients in the CI-group (0.5 mg/h versus 2.4 mg/h ($P<0.001$) and 33 mg versus 260 mg ($P=0.018$) respectively). The mean daily pain scores were comparable (4.9 versus 5.3). The lower mean and cumulative morphine consumption in the PCA-group led to significant less nausea and constipation during treatment as compared to the CI-group (area under the curve respectively 11 versus 18 ($P= 0.045$) and 30 versus 45 ($P= 0.021$)). Furthermore, a non-significant reduction in the duration of hospital admission of 3 days was observed in the PCA-group.

Patient controlled analgesia results in adequate pain relief at a much lower morphine consumption and should considered to be first choice in morphine administration to sickle cell patients admitted with vaso-occlusive crisis.

Introduction

Recurrent painful episodes due to vaso-occlusive crises are the hallmark of sickle cell disease (SCD) and the most common cause for hospital admission in these patients.[1] The episodes of severe pain are caused by local vaso-occlusion within the bone marrow leading to bone infarction and the release of inflammatory mediators. The incidence of painful episodes requiring hospital admission is estimated at once a year for the whole group of patients with SCD but may vary highly between and within individual patients. Approximately 5% of the patients with SCD are responsible for more than a third of all hospital admissions with vaso-occlusive crises. Frequent admission with vaso-occlusive crises is an important prognostic factor and has been associated with mortality in SCD. An acute vaso-occlusive crisis is generally treated with hyperhydration and analgesia.[2] Although most episodes of vaso-occlusive crisis in patients with SCD are treated at home with oral analgesics such as acetaminophen and/or nonsteroidal anti-inflammatory drugs (NSAIDs), many patients are eventually admitted for intensive pain treatment requiring intravenous morphine.[3] Despite its good analgesic efficacy, morphine has many dose-related side–effects including nausea, constipation, pruritus, sedation and hypoventilation. Moreover, morphine administration has been related to the development of acute chest syndrome. A post-hoc analysis of a study comparing oral morphine administration with continuous intravenous infusion (CI) of morphine in patients with SCD showed that the incidence of acute chest syndrome was directly related to the plasma levels of morphine and its active metabolites.[4] Therefore, strict regulation of the administered morphine dose is advocated in patients with SCD. In general, there are no objective measurements of pain severity and analgesia has to be titrated upon the patient's reported pain, preferably with the use of pain-measurement scales to guide the intensive treatment.[3;5] Patient-controlled analgesia (PCA), which allows patients to take control over the treatment of pain, was successfully introduced in the management of postoperative pain. Although PCA has also been used in patients with SCD, no controlled trials in patients with vaso-occlusive crisis have been performed so far.[6]

The aim of our study was to determine the efficacy of PCA in vaso-occlusive crisis in a prospective randomized controlled trial in patients with SCD. Here we show that, morphine administration with PCA lead to markedly lower morphine consumption than dose-adjusted CI of morphine while both methods resulted in comparable pain relief.

Methods

Subjects

This randomized clinical trial was conducted at the Academical Medical Centre in Amsterdam, the Netherlands. The study was approved by the local medical ethics committee and all participating patients gave written informed consent. Consecutive patients with SCD requiring parenteral analgesia for pain during a vaso-occlusive crisis were considered eligible for the study. Inclusion criteria were: SCD (HbSS, HbSC, HbSβ^0 and HbSβ^+); the presence of an episode of pain caused by vaso-occlusive crisis necessitating treatment with intravenous morphine; age more than 17 years. An episode of pain caused by vaso-occlusive crisis was defined as the occurrence of pain in the extremities, back, abdomen, chest, or head that led to a clinic visit, and could not be explained except by SCD.[29] All patients received a pain flow-chart on the outpatients-clinic. With use of this flow-chart patients self administer pain medication, starting with 500 mg acetaminophen 6 times daily and adding 50 mg diclofenac 3 times daily, when needed. To be admitted for intravenous morphine treatment pain scores had to be more than 4 during at least four hours with maximum self-administered pain medication (500 mg acetaminophen 6 times daily and 50 mg diclofenac 3 times daily). Excluded from the study were patients who already received opioids for more than 24 hours or patients that were allergic or intolerant to morphine.

Study Protocol

Patients were randomized between treatment with intravenous morphine using a PCA-pump (Perfusor® fm, Braun, Melsungen, Germany; PCA-group) or dose-adjusted CI administration of morphine (CI-group). Patients who met the inclusion criteria on a subsequent admission were crossed over to the alternative study arm. Randomization was performed in blocks of six with closed envelopes, containing the designated morphine delivery regimen. Data were analyzed on an intention to treat basis. In both intervention groups, the aim of treatment was to establish an adequate level of pain relief. A pain score of five or less on an 11-point verbal response scale (0 = no pain, 10 = worst pain) was accepted as an adequate level of pain relief.[30;31] Pain scores were collected four times a day. To get an estimate of mean pain intensity during treatment all verbal response pain scores during treatment were averaged. The change between a single pain measurement on a visual analogue scale (VAS) at baseline and a single measurement after two days of treatment was used to measure difference in pain relieve (0 mm = no pain, 100 mm = worst pain).

Patients randomized to the PCA-group received a single bolus injection of 5 mg morphine followed by patient-controlled bolus of 0.01 mg/kg. The PCA device allowed patients to self-administer an intravenous bolus of morphine by pressing a button which was attached to their bed.

Maximal one bolus every 5 minutes could be administered (a lockout of 5 minutes). If this dosage did not result in adequate pain relief, the bolus dose was increased to 0.02 mg/kg with a lockout of again 5 minutes. Patients in the PCA-group did not receive any continuous infusion (background infusion) on top of the self-administered boluses of morphine. Patients in the CI-group received a single bolus injection of 5 mg followed by CI of 0.03 mg/kg/h. After pain assessment by the attending nurse the morphine dose was increased when needed with cumulative steps of 1 mg/h until adequate pain relief was obtained or side-effects became intolerable. The continuous morphine dosage was decreased in steps of 1 mg/h if pain scores where five or lower or at the patient's request.

Next to their designated morphine delivery regimen, all patients received additional oral pain treatment consisting of 500 mg acetaminophen 6 times daily and 50 mg diclofenac 3 times daily during the whole admission. Patients with contra-indications or intolerance for diclofenac received tramadol 50 mg, 3 times daily in combination with acetaminophen.

Outcome

The primary outcome of this trial was the cumulative and mean hourly morphine consumption, pain intensity score and cumulative side-effects during treatment with intravenous morphine. Length of hospital stay, duration of treatment, and quality of life were secondary outcomes. Hourly and cumulative daily dose were registered during admission. Pain intensity was assessed and recorded four times a day with a verbal response pain scale on an 11-point scale. To account for variances in verbal response pain scales during vaso-occlusive crisis also the worst and least daily painscore were analyzed.[32] Because the experience of pain may vary from person to person in perception, response and reported intensity also individual change in pain intensity, importance of pain control, and perceived pain control were assessed separately from the other measurements between the day of admission and two days later.[33] Perceived pain intensity, importance of pain control and perceived control of pain was also assessed with a VAS, with 0 mm designated "not at all important" or "not at all under control" and 100 mm "very much important" or "completely under control", respectively. In addition to above measurements change in quality of life was assessed between the day of randomization as a baseline measurement and two days later. Quality of life was measured using the Medical Outcomes Study 36-item Short Form Health Survey (SF36).[34;35] Scores on the SF-36 items were aggregated into a Physical Health Summary (PHS) and a Mental Health Summary (MHS) to compare physical and mental health QoL outcomes.

Side-effects and adverse events

Side-effects of morphine, consisting of nausea, pruritus and sedation, were scored daily on an 11-point scale (0= no symptoms, 10= worst symptoms). A day without defecation or the need for a

rectal enema scored 10 points on the constipation-scale. The need for medical intervention for side-effects (anti-emetics, antihistamines) was scored plus 5 points on the appropriate scale. To quantify the cumulative experienced side-effects, the area under the curve (AUC) for the separate side-effect scores during treatment of each individual admission was calculated. Mean oxygen saturation was measured daily with a pulse oximeter (Datascope Accutorr Plus; Datascope Corporation. Paramus, NJ. USA). All adverse events were registered. Acute chest syndrome was defined as a new pulmonary infiltrate on a chest x-ray in the presence of chest pain, temperature >38.5°C, tachypnea, wheezing or cough.[36]

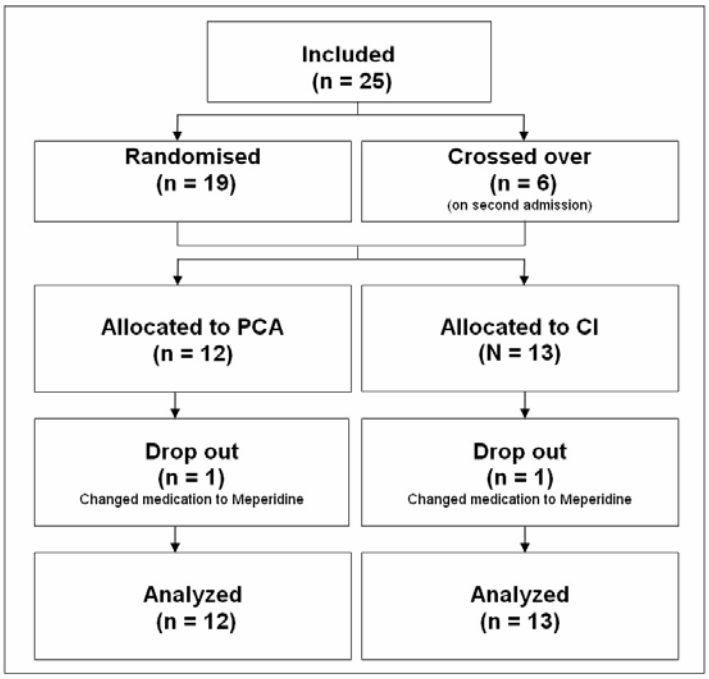

Figure 1. Trial profile.

Patients who met the inclusion criteria on a subsequent admission were crossed over to the alternative study arm.

Statistical analysis

An episode of vaso-occlusive crisis was the unit of analysis of the study. Because of the mixed unpaired and paired observations as a result of the study-design, group differences were analyzed with mixed models (compound symmetry). In each model individual patients were subject variables and episodes of vaso-occlusive crisis were repeated variables. Dependent variables were the primary outcomes of the study with way of morphine administration (PCA or CI) as main factor. We further analyzed these differences using area under the curve (AUC) to adjust for duration of experienced side-effects. To that end, AUC variables were square root transformed so that normal distributions were obtained.

Change from baseline in QoL was a secondary outcome and was calculated by subtracting two days-outcomes in QoL from baseline-outcomes. All physiological and haematological parameters in this study are presented as medians and interquartile ranges (IQR). Since previous studies have demonstrated conflicting results on the effect of PCA on morphine consumption, the sample size of the study was calculated to detect a clinical relevant reduction of 50% in the mean hourly morphine consumption between the PCA-group and the CI-group. With a power of 0.90, we had to include at least 12 episodes of vaso-occlusive crisis in each study arm. Data were double entered into the study database and analyzed in SPSS version 11.5.1 for Windows.

Results

Patients

Twenty-five episodes of vaso-occlusive crisis in 19 patients were included in the study. Two patients (one randomized to CI and one to PCA) withdrew consent and requested treatment with meperidine after randomization (Figure 1). The base-line characteristics (Table 1) between the two groups were comparable except for the leukocyte count (15.2 (11.7-17.8) versus 11.3 (7.9-13.4) in the CI- and PCA-group, respectively). Homozygous SCD was the most common genotype in both groups (8/13 and 8/12 in the CI- and PCA-group, respectively). Median percentage of fetal haemoglobin, a major prognostic factor in SCD, was 3.7% in the CI-group and 3.2% in the PCA-group. Four episodes of vaso-occlusive crisis developed in patients taking hydroxyurea (two episodes in both groups). Of the six patients who crossed over, four received PCA and two received CI as initial treatment. The mean time between the first and second inclusion was five months.

Table 1. Baseline characteristics

	Treatment group	
	CI morphine	PCA morphine
N	13	12
Age (y)	25 (20-33)	27 (23-42)
No. Female*	7	7
Hydroxyurea treatment*	2	2
Haemoglobin genotype		
SS*	8	8
SC*	3	3
Sβ*	2	1
Baseline blood parameters		
Haemoglobin (mmol/L)	5.8 (5.3-6.9)	5.5 (4.4-7.0)
Leukocyte count (x10^9/L)	15.2 (11.7-17.8)	11.3 (7.9-13.4)
Neutrophils (%)	73 (55-79)	61 (50-78)
C-reactive protein (mg/L)	12.7 (3.2-17.5)	9.0 (1.6-20.5)
HbF (%)	3.7 (2.1-8.1)	3.2 (2.2-4.9)
HbS (%)	72 (47-85)	78 (62-90)

Data are presented as medians with interquartile ranges. *Number of patients.

Morphine dose and duration of treatment

The morphine dose in the PCA-group was significantly lower than the CI-group. The mean daily morphine consumption during treatment was 0.5(0.3-0.6)mg/hr in the PCA-group versus 2.4(1.4-4.2)mg/hr in the CI-group (P<0.001; figure 2) and median cumulative dose of morphine during vaso-occlusive crisis was lower in the PCA-group (33 (10-68)mg) than in the CI-group (260(204-529)mg; P=0.018; Table 2). This was partly explained by a relevant, but not statistically significant, reduced duration of morphine administration in the PCA-group compared to the CI-group (4.5(3.3-6.0) days versus 7.0(5.0-8.5) days; P=0.21) which was directly correlated to the total morphine dosage (P< 0.001). Assessment of the mean daily morphine consumption during the first three days of admission resulted in a median morphine dose of 0.5(0.3-0.8) mg/h in the PCA-group versus 3.5(2.0-4.5) mg/h in the CI-group (P<0.001). The patients in the PCA-group pressed the button to self-administer a dose of morphine on average 14 (9-16) times a day. Six of the patients in the PCA-group and five in the CI-group needed a dose increase because of inadequate pain relief. The median duration of admission in the PCA-group was 6.0(4.3-9.3) days and in the CI-group 9.0(6.0-12.0) days (P=0.15). Assessment of the morphine consumption if consecutive patients were unit of analysis in stead of an episode of vaso-occlusive crisis resulted in similar results (mean morphine consumption of 0.5(0.3-0.8) mg/hr in the PCA group versus 2.5(1.5-4.7) mg/hr in the CI-group; P<0.001). The usage of additional oral pain medication was evenly distributed between the groups. In the CI-group three patients received tramadol and in the PCA-group two patients received tramadol.

Table 2. Outcome on morphine consumption, pain score and quality of life.

	Treatment group		
	CI morphine	PCA morphine	P value
Morphine consumption and pain			
Morphine dosage (mg/h)	2.4 (1.4-4.2)	0.5 (0.3-0.6)	0.001
Total morphine dosage (mg)	260 (204-529)	33 (10-68)	0.018
Mean verbal response pain score	4.9 (3.9-5.8)	5.3 (4.5-6.9)	0.09
Mean side-effect score and pain (AUC)*			
Nausea	18 (3-55)	11 (3-21)	0.045
Constipation	45 (36-59)	30 (10-40)	0.021
Pruritus	14 (0-28)	5 (0-25)	0.42
Sedation	12 (6-33)	18 (0-20)	0.52

Data are presented as medians with interquartile ranges.* = Symptoms of side-effects are presented as area under the curve (AUC) during treatment.

Pain and Quality of Life

The range of pain scores were comparable in the two arms of the study (Figure 2B). In the CI-group the least verbal response pain score was 4.2(3.1-5.1), the mean score 4.9(3.9-5.8) and the worst score 5.8(4.5-6.2). These scores did not differ significantly from the least, mean and worst scores in the PCA-group, 4.2(3.4-5.8), 5.3(4.5-6.9) and 6.3(5.5-7.8) respectively. (P=0.14 P=0.09 and P=0.39). The mean pain score if patients were unit of analysis was 5.2(4.3-5.8) in the PCA-group versus 4.9(3.9-6.9) in the CI-group (P=0.85). Baseline pain-scores were comparable in both groups, 59(51-85) in the CI-group and 72(63-84) in the PCA-group and change from baseline after two days of treatment were also comparable respectively -24(-57 to -11) and -38(-52 to 4). Assessment in quality of life remained unchanged in both groups (Table 3). There was a statistically significant difference in change over time in perceived importance of pain control between the PCA-group and the CI-group. Perceived importance of pain control increased in the PCA-group, whereas it decreased in the CI-group.

Table 3. Individual response in pain score and quality of life after two days.

	Baseline		Change after two days		
	CI	PCA	CI	PCA	P**
Pain score (VAS)	59 (51-85)	72 (63-84)	-24 (-57 to -11)	-38 (-52 to 4)	1.00
Importance of pain control (VAS)	98 (93-100)	98 (69-98)	-12 (-29 to -1)	2 (-7 to 10)	0.02
Perceived pain control (VAS)	39 (13-53)	48 (19-52)	22 (-8 to 44)	15 (-32 to 51)	0.79
Quality of Life*					
Physical Health Summary	31 (23-37)	24 (21-36)	0 (-5 to12)	1 (-7 to 9)	0.94
Mental Health Summary	40 (34-56)	44 (37-56)	4 (-7 to 14)	4 (-2 to 9)	0.94

All numbers are medians (inter quartile ranges).*= Short Form Health Survey (SF36) **= P-value of difference in change after two days between continuous infusion (CI) and patient controlled analgesia (PCA) of morphine.

Side-effects and adverse events

The AUC of experienced nausea and constipation side-effect scores were significant lower in the PCA-group compared to the CI-group (respectively 11(3-21) versus 18(3-55) (P=0.045) and 30(10-40) versus 45(36-59) (P=0.021) (Table 2). No significantly difference in pruritus or sedation was found. After post hoc adjusting for morphine consumption no difference in side-effects were found between the two groups. Medians of mean oxygen saturation in the PCA-group and CI-group were respectively 98(95-99)% and 97(94-98)%. One patient in the CI-group experienced an episode of severe hypoxia due to hypoventilation and received an opioid antagonist (naloxone). Two intestinal pseudo-obstruction syndromes were reported in this study. Both occurred in the same patient (once in the PCA- and once in the CI-group). During eight episodes of vaso-occlusive

crisis acute chest syndrome was diagnosed. Five episodes were diagnosed in the CI-group (three before and two after randomization) and three episodes were diagnosed in the PCA-group (two before and one after randomization). None of these episodes required mechanical ventilation or resulted in hypoxia.

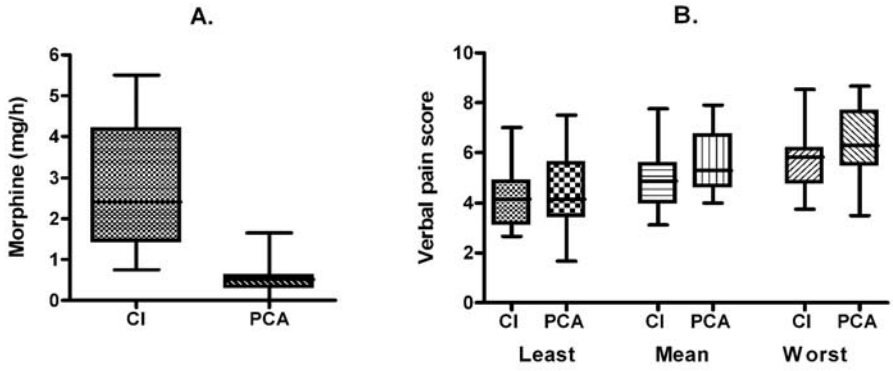

Figure 2. Morphine dosage and range of painscores.
(A): Mean morphine dosage (mg/h) during treatment in the CI-group was 2.4 (1.4-4.2) and in the PCA-group 0.5 (0.3-0.6) (P<0.001). (B): In the CI-group the least verbal response pain score was 4.2 (3.1-5.1) the mean score 4.9 (3.9-5.8) and the worst score 5.8 (4.5-6.2). These scores did not differ significantly from the least, median and worst scores in the PCA-group, 4.2 (3.4-5.8), 5.3 (4.5-6.9) and 6.3 (5.5-7.8) respectively (P=0.14, P=0.09 and P=0.39).

Discussion

Vaso-occlusive crisis in patients with SCD is characterized by intense and severe pain often requiring intravenous morphine. In this open randomized clinical trial morphine administration with PCA resulted in markedly and significantly lower morphine consumption as compared with CI with a similar effect on pain or other scales of relief. Patients in the CI-group needed about 5 times more morphine per hour as compared to the PCA-group. Additionally, the difference in total cumulative morphine consumption was even larger since the duration of treatment tended to be shorter in the PCA-group. Total experienced nausea and constipation depicted in the AUC of the corresponding side-effects scores during treatment were significant lower in the PCA-group compared to the CI-group. This difference disappeared after correcting for morphine consumption confirming that these side-effects are related to the cumulative morphine consumption. No differences in pruritus and sedation were observed between the groups. The results of this trial are in accordance with the observation of Gonzalez et al. demonstrating that PCA was effective and safe in patients with SCD with vaso-occlusive crisis in a day care setting as compared to intermittent morphine injections for maximal 8 hours, although no difference in the total amount of morphine was demonstrated in that study.[7] Besides this study, no other comparative trials have been performed with PCA in patients with SCD. A retrospective chart review in 26 children with SCD and vaso-occlusive crisis demonstrated that children treated with a PCA-regimen with low basal rate infusion and high bolus dose used significantly less morphine during their hospitalization, had a shorter length of hospital stay, and reported lower pain scores as compared to a PCA regimen with a high basal rate infusion and a low bolus dose.[8] A possible explanation for this effect, which also could explain the low morphine consumption in the PCA-treated patients in the present study, may be that a more rapid analgesic effect is induced by bolus administration of morphine rather than CI. However, comparative trials with PCA in patients with other causes of pain have demonstrated conflicting results on the cumulative morphine consumption. [9-20]

We also analyzed quality of life during treatment to assess response on other outcomes than verbal response pain scale. No difference in response in quality of life was observed between the intervention groups. A statistically significant difference was demonstrated in perceived importance of pain control. Patients assigned to PCA showed a slight increase in perceived importance of pain control while patients assigned to CI showed a decrease. This may indicate that patients treated with PCA experience the direct control of morphine administration to be more important than patients in the control group, despite similar pain intensity scores in the two groups. An alternative explanation for this finding may be "post decision justification bias".[21] This is a cognitive adaptation mechanism by which patients justify the way they were managed. Since pain control is a key-characteristic of PCA, patients who were managed with PCA are expected to value pain control

as more important than patients who were managed with CI. Psychological factors which influence response to treatment in the context of illness and pain are complex. Control may have a positive influence on these factors.[22] This factor may be particularly important for patients with SCD and may be a possible explanation for the fact no difference in pain or quality of life was found between the CI-group and PCA-group despite the large difference in the amount of morphine used. [23;24] Furthermore, patients in the PCA-group appeared to accept a pain score of 5.5 and did not titrate to achieve a pain free state, while most health professionals titrate pain medication to reduce even mild pain. This was observed in previous studies in children as well as adults.[25-27] The analgesia-induced side effects as perceived by the patient may be an important reason for this phenomenon. Hypothetically, patients balance their pain with the side-effects of morphine administration.[28] In the study, we found that the higher consumption of morphine in the CI group resulted in significant more morphine-related side-effects like nausea and constipation. Although no significant difference in sedation and pruritis was demonstrated it is likely that also these side-effects would be significantly less if a larger samples size would have been studied.

Some aspects of our study require comment. Firstly, the limited sample size of our study improves the chance of unevenly distributed confounders. However, after post-hoc correcting for possible confounders as age, gender, leukocyte count or genotype the difference in morphine usage stays clinical and statistical significant. Furthermore, the study design of mixed paired and unpaired observations decreases unevenly distribution of unknown confounders. Although our study is of comparable size as other trials with PCA a larger trial will be needed to demonstrate whether the use of PCA in vaso-occlusive crisis will result in a reduction in length of hospital stay and complications such as acute chest syndrome.[9-20] Secondly, the patient-controlled-analgesia design of our study made a complete blinding of the study impossible and could therefore be subject to bias. Thirdly, we took episodes of vaso-occlusive crisis as unit of analysis. To prevent multiple enrolments of a few patients with frequent vaso-occlusive crises, patients were only allowed to participate in the study twice and were treated according to the opposite arm of the study upon second admission. However, if patients were the unit of analysis, our study resulted in similar conclusions.

In conclusion, the present study demonstrates that the use of PCA in patients with SCD with vaso-occlusive crisis results in a significant reduction in morphine consumption with equivalent response on measurements of pain and quality of life. A significant difference in morphine-induced side-effects was found and PCA may therefore be considered the first choice for adequate morphine administration in patients with SCD with vaso-occlusive crisis.

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