Which strategy to manage severe vaso-occlusive crisis in patients with sickle cell disease in countries with limited healthcare capacities?

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Abstract

We evaluated the treatment of morphine by intravenous patient controlled analgesia versus intermittent subcutaneous routes on patients with sickle cell disease developing severe vaso-occlusive crisis.

Objectives: The primary objective was to compare intravenous patient controlled analgesia (PCA) versus intermittent subcutaneous injection of morphine (SC) on sickle cell patients developing severe vaso-occlusive crisis during the first 24 hours of admission. The secondary objective was to assess the side effects of morphine in both regimens.

Methods: A randomized controlled trial of 77 patients in the PCA and 81 in the SC group was conducted at the Sickle Cell Center of Brazzaville in the Republic of Congo. Participants aged from 15 to 45 years old with severe vaso-occlusive crisis were included in the study.

Results: Both regimens provided pain relief. However, a significant pain reduction was observed 30 minutes after the administration of morphine in the PCA group (P= 0.001). The mean scores in the PCA and SC regimens were respectively: 1.16±1.40 and 4.30±2.32. The total median dose of morphine administered in the PCA regimen was markedly lower: 24,6±4,16 mg versus 36.6±3.1 mg in the SC group (P=0.01). Morphine administered by PCA provided pain relief during 24 hours while intermittent severe pain was experienced in the SC group (P=0.014). Sedation score S2, S3 was significantly observed in the SC group (P< 0.05).

Keywords: severe pain, sickle cell disease, morphine, patient controlled analgesia, subcutaneous

Introduction

Sickle cell disease is the most common inherited blood disorder with varying severity and clinical features [1,2]. Vaso-occlusive crisis (VOC) is the most common acute complication of the

disease. VOC requires immediate analgesia which is commensurate with the intensity of the pain developed by patients. Pharmacological treatment of VOC involves the use of non-opioid, opioid analgesics, and adjuvants. When the VOC is severe it constitutes a medical emergency that requires opioid use such as morphine [3]. The choice of routes, dosage, and frequency of administration of morphine depends on the patient's clinical presentation. Despite clear guidelines for the management of severe VOC, most patients with sickle cell disease have a long history of pain not adequately managed [4]. That statement is particularly true for severe VOC in low and middle-income countries where access to affordable and consistent supplies of morphine are limited. Physicians are reluctant to prescribe morphine because of its numerous side effects. They also express their concern to induce drug addiction even though it has never been demonstrated [4]. In the Congo, severe VOC is the second cause of admission, with a high lethality rate of 17.02% [5]. Before 2017, the combination of subcutaneous (SC) tramadol and intravenous (IV) non-steroidal anti-inflammatory (NSAIDs) were the main drugs of choice in the treatment of severe VOC. While the combination was effective, it was associated with a high frequency of adverse effects as such as nausea and vomiting. Additionally, the high rate of kidney failure probably associated with the long-term use of NSAIDs led us to change our strategy. Since 2018, morphine is available in the Congo at an affordable cost. Morphine administered subcutaneously is the mainstay of pharmacotherapy in treating severe VOC. A donation of a PCA (Patient Controlled Analgesia) device to our unit allowed us to experience the intravenous route. In that context, we wanted to assess the efficacy of PCA versus SC of morphine during severe episodes of VOC in sickle cell patients.

Methods

We conducted an observational randomized study for 6 months. We included in the study, sickle cell patients aged 15 years and more, weighing at least 50 Kg with severe VOC. All nurses and internists in the Hematology unit had been trained to assess pain with the Visual Analog Scale (VAS), to perform morphine titration, and to use the PCA device. THE VAS scale we used was a straight horizontal line of fixed length of 100mm oriented from the left (best) to the right (worst)

The VOC was defined as severe when the pain intensity measured scored at least 7/10, moderate: 4-6, mild: 1-3, and no pain: 0/10. The allocation of morphine administration routes was determined by lot for each patient. The randomization process made it possible. There were 2 arms. Arm A for the Intravenous (IV) PCA route and arm B for the SC route.

In the PCA group, we had administered a morphine loading dose of 0.1mg/kg (maximum dose of 4 mg) then sequential and repeated (titration) administration every 5 minutes of 0.02mg/kg until pain relief (VAS <4). Then the titration was relayed by IV PCA. Morphine PCA orders included a basal rate, intermittent dose lockout interval, and a 1 hour and 4-hour limit.

In arm B, the morphine was administered subcutaneously with a catheter 25 gauge over the lateral aspect of the right or left deltoid muscle at a dosage of 0.15mg/kg, maximum every 6 hours.

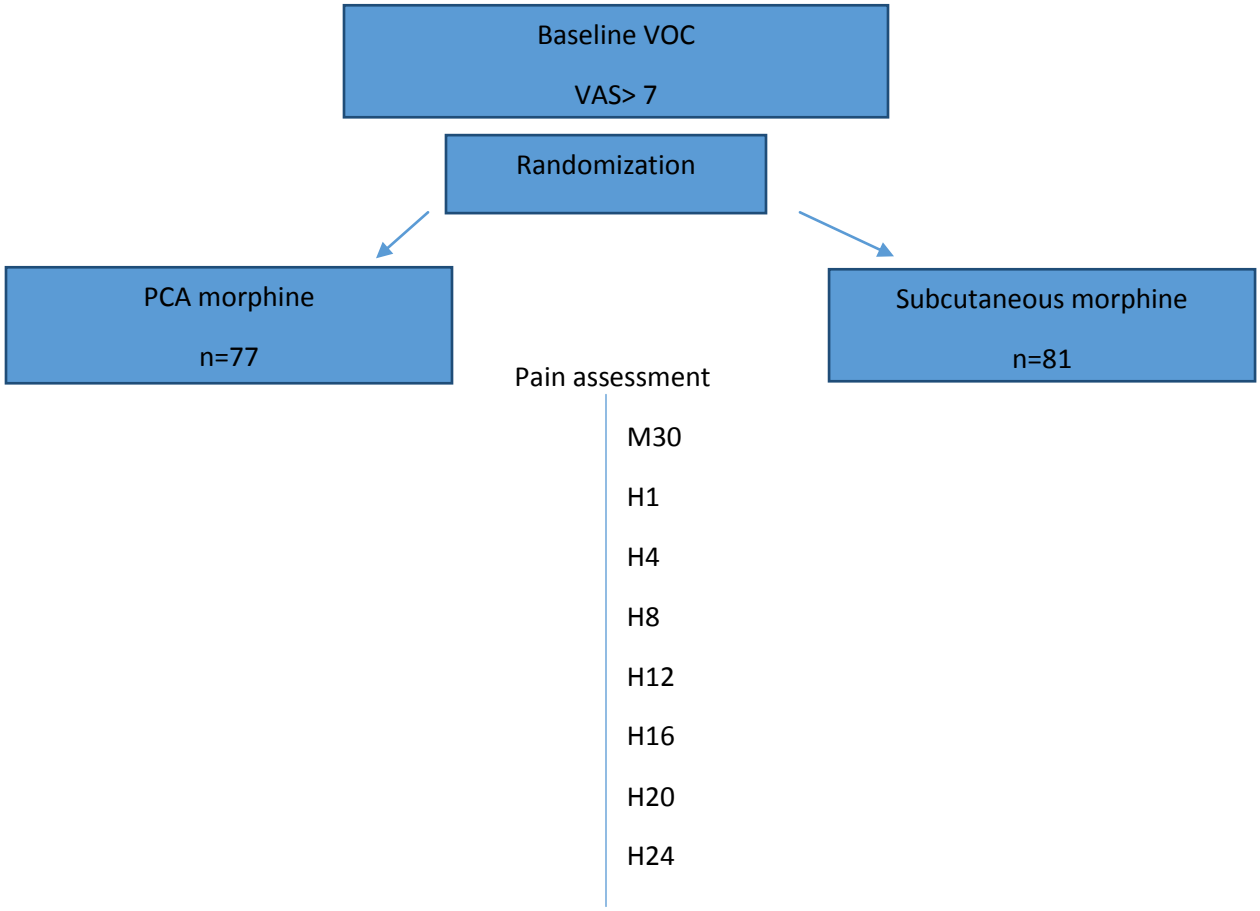
We collected in both groups: age, weight, temperature, heart rate, respiratory rate, oxygen saturation, blood pressure, side effects, morphine use, and pain score. We monitored respiratory rate measurements as well as sedation according to the Ramsay score [6]. The patient's level of sedation was divided into seven categories as detailed in the table below

Table I. Ramsay score

Ramsay score	Level of sedation
0	Awake, orientated
1	Agitated, anxious or restless or both
2	Co-operative , oriented and tranquil
3	Responding to command only
4	Brisk response to light glabellar tap or loud auditory stimulus
5	Sluggish response to light glabellar tap or loud auditory stimulus
6	No response to stimulus

We assessed control of the pain intensity after the administration of morphine. The control was effective when there was no pain or the intensity was mild. The control was ineffective when the pain was moderate or severe. In case of severe ventilatory depression (respiratory rate< 10 breaths/min), naloxone (intravenous bolus of 0.04mg) was administered until the respiratory rate was greater than 12 breaths/min. It was defined as a severe adverse effect.

Fig. 1. Flow chart of baseline VOC



Statistical analysis

Data are expressed as means ±SD. Student t test and repeated measures ANOVA were used for continuous Gaussian variables. The chi-square test or Fisher's exact method were used for categorical variables. Correlation between two variables were performed by use.

Results

We have received 158 participants during the study period. There were 89 males (59.26%) and 99 females (40.47%). 77 were randomized in arm A while 81 in arm B. The median age was 22.83± 4.93 for the PCA group and 21±4.57 for the SC group. Clinical baselines are detailed in table II.

Table II. Clinical baselines

Clinical baselines	Arm A (n=77)	Arm B (n=81)	P
Temperature (Celsius)			0.13
Weight (Kg)	61.90±7.60	62.29±7.60	0.76
O2sat (%)	95.94±7.0.79	95.81±0.92	0.33
HR (beat/min)	78.66±8.41	81.16±7.11.28	0.11
RR (breath/min)	25.97±7.3.62	27.25±3.11	0.01
Systole	116±10.8	116±10.7	0.39
Diastole	68.5±8.14	69.6±8.54	0.20
VAS	8.55±1.25	8.59±1.59	0.91

O2sat: saturation of oxygen

Six patients in the PCA group (7.79%) auto-injected morphine on an average of 5 times during 24 hours (range: 1 to 8). The median dose of morphine administered in arm A was 24,6±4,16 mg versus 36.6±3.1 mg in arm B (P=0.01). Both routes provided analgesic effects. However, the range of VAS was significantly lower in arm A with a minimum score of 0.53. The VAS highest score was 1.41± 1.16 for arm A versus 4,30±2,32 for arm B. The lowest score was 0.53±0.89 for

arm A and 0.88±1.40 for arm B. The delay in having an analgesia status was shorter in arm A: Thirty minutes (VAS: 1.16±1.40) versus 1 hour (VAS: 1.87±1.73) for arm B. Table III.

Table III. Pain score among patients in the first 24 hours in the PCA and SC groups

	Arm A PCA (n=77)	Arm B SC (n=81)	P
Dose of morphine (mg)	24,6±4,16	36.6±3.1	0.01
Pain score			
VAS M30	1.16±1.40	4.30±2.32	0.001
VAS H1	0.72±0.86	1.87±1.73	0.001
VAS H4	0.53±0.89	0.88±1.40	0.06
VAS H8	0.88±1.08	1.39±1.79	0.03
VAS H12	0.75±1.00	1.40±1.08	0.005
VAS H16	0.68±0.94	1.13±1.45	0.024
VAS H20	0.62±0.94	1.93±2.25	0.001
VAS H24	1.03±1.06	1.71±1.91	0.007

H: hour M: minute

Thirty minutes after the administration of morphine, 22.22% of patients in the SC group were still developing severe pain while relief was noticed in PCA group for all patients. Severe pain reoccurred in the subcutaneous group respectively at H4, H20 and H24. Table IV.

Table IV. Pain assessment among patients in the PCA and the SC groups

	No pain (%)	Mild pain (%)	Moderate pain (%)	Severe pain(%)	P
M30					<0.005
PCA	32.47	67.53	0	0	
SC	11.11	20.99	45.68	22.22	
H1					<0.005
PCA	50.65	49.35	0	0	
SC	33.33	48.15	18.52	0	
H4					0.69
PCA	67.53	31.17	0	0	
SC	55.56	38.27	4.94	1.23	
H8					0.02
PCA	54.55	45.45	0	0	
SC	51.85	32.1	16.05	0	
H12					0.02
PCA	55.8	44.2	0	0	
SC	49.4	33.3	17.3	0	
H16					0.027
PCA	57.14	42.86	0	0	
SC	53.09	35.8	11.11	0	
H20					0.014
PCA	63.6	36.4	0	0	
SC	45.7	32.1	14.8	7.41	
H24					0.014
PCA	42.86	57.14	0	0	
SC	39.51	40.74	17.28	2.47	

Adverse effects of morphine are detailed in the table V.

Table V. Side effects and adverse events among patients in the PCA and SC groups

Side effect	Arm A	Arm B	P
Nausea/ vomiting	40.27	85.17	0.22
Pruritus	00	11.19	0.18
bladder retention	34.63	4.93	0.27
Ramsay score (2,3)	12.99	60.49	<0.05

Discussion

The morphine administered by PCA devices has become the most popular procedure for pain management [8,13]. IV PCA reduces morbidity and length of hospitalization [14]. However, few studies are describing the use of PCA in patients with sickle cell disease. A meta-analysis of 32 studies by Walder et al, found that the PCA route is slightly more effective than the conventional approaches [15]. Our results are in accordance with the studies published [8,15]. In contrast, a recent study in Saudi Arabia did not find any significant advantage of the PCA in the control of pain [14}. In our trial, the efficiency of the PCA route was significantly observed 30 minutes after the administration of morphine. It results from the sequential administration of morphine [8,16].

What strategic approaches for the management of severe VOC when PCA device is not available? Despite the numerous critics on the ground that morphine should not be administrated subcutaneously since its absorption may be erratic [16]; our study has shown that the SC route can be considered for the management of severe VOC. However, supplementary analgesic requirements of morphine noted at H4, H8, H20 in the SC group. The benefit of that route would have been improved if we subcutaneously titrated patients. Indeed, the benefit of the titration can as well be noticed and performed in the SC route with a catheter in place. Elner et al, reported that the titration of the morphine offered similar analgesia in both routes:

subcutaneous and intravenous morphine [17]. That study opens up options for low and middle resource countries where PCA device is not available or rare. The procedure is simple, easily accomplished by nursing staff, and does not require the intervention of physicians. The permanent presence of nurse staff in units during the day ensures the implementation and continuity of care.

The PCA is a very interesting procedure as it empowers patients to manage their pain [14]. Our Patients self-administered morphine only four times while Beers et al reported an average of 14 times [8]. The perception and expression of pain vary. They are influenced by culture and environment. Patients in Africa with sickle cell show higher tolerance of pain thus might have reduced the frequency of self-administration of morphine. Additionally, the PCA device was used for the first time by many of our participants. It could have restrained the number of auto-injections. Finally, the fear of an overdose expressed by our participants contributed to limit the number of bolus of morphine.

Thus, the total of morphine administered in the IV PCA group was lower compared to the subcutaneous group. That finding is controversial and varies depending on the studies [14]. Our findings indicated that there was no significant difference in term of side effects in both routes even though the number of episodes was higher in the SC group. The sedation score was markedly higher in the SC group ($P<0.05$). Reducing in that group by 25% the dosage of morphine when pain relief was obtained as did Rouss et al, would have reduced the frequency of adverse effects and sedation score [18].

Our study has some limits. As we said previously, many of our patients have used the PCA device for the first time. Doing a pilot study to test the feasibility of the trial would have reduced some bias in data selection and analysis. However, it is the first study on the topic in the region. It introduces a feasible procedure for countries where health capacities are limited: the subcutaneous PCA for which further studies are needed.

Conclusion

Both subcutaneous and intravenous PCA of morphine induce analgesia. For the low resources countries where the PCA device is not available, subcutaneous PCA can be an option to the intravenous PCA and needs to be evaluated.

Disclaimer regarding Consent and Ethical Approval:

As per university standard guideline, participant consent and ethical approval have been collected and preserved by the authors

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of interest

The authors declare no conflicts of interest.

Authors contributions

Ngolet Lydie coordinated field study and conducted the study and analyzed the data. Chelsea Jayne Bango, Peggy Mawandza and Alexis Elira Dokekias reviewed the draft. All the authors read and approved the final manuscript.

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