

## ISOXSUPRINE IN THE TREATMENT OF SICKLE CELL PAINFUL CRISES: A DOUBLE-BLIND COMPARATIVE STUDY WITH NARCOTIC ANALGESIC

Ali H. Al-Jam'a, CABIM; Ibrahim A. Al-Dabbous, CABP; Muhammad S. Rafiq, MBBS;  
Adil Al-Khatti, FRCPC; Ahmed H. Al-Salem, FRCS; Abdalali Al-Baharna, BPharm;  
Mohammed Boholaiga, BPharm

**Background:** Isoxsuprine is a tocolytic agent which improves erythrocyte deformability. It was accidentally found to be effective in the management of sickle cell disease (SCD) painful crises. The experience with the drug in the treatment of sickle cell disease is limited. This double-blind randomized comparative study was undertaken to test its efficacy and safety in the treatment of SCD painful crises.

**Patients and Methods:** Forty-three SCD patients (33 males and 10 females) with 44 episodes of pain were included in the study (i.e., one patient was included twice). Only those with painful crises requiring hospital admission were included. Patients were randomized to receive either isoxsuprine 5-10 mg, or meperidine 50-100 mg intramuscularly, according to body weight, every four hours. A random selection of 23 patients received isoxsuprine, and 21 received meperidine. Pain score, duration of crisis, hospital stay, and side effects were monitored.

**Results:** No significant difference was found in any parameter except for pain score at 30 and 60 minutes.

**Conclusion:** We conclude that isoxsuprine appears to be effective in the treatment of sickle cell painful crises. Confirmation of its efficacy in studies involving a larger number of patients is warranted.

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**Key Words:** Isoxsuprine, sickle cell disease, painful crisis.

Sickle cell anemia is the most common inheritable disease affecting man.<sup>1</sup> It is characterized by the formation of an abnormal hemoglobin (HbS) which results from the replacement of normal glutamic acid by valine at position 6 of the  $\beta$ -globin polypeptide.<sup>2</sup> In addition to chronic hemolytic anemia, the disease is characterized by repeated episodes of musculoskeletal pain and acute ischemia in other organs.<sup>3</sup> These episodes are called vaso-occlusive crises to denote the underlying pathophysiologic process which produces them. The painful episodes are thought to be the result of bone marrow ischemia/infarction.<sup>2,4</sup>

The extensive knowledge of pathophysiology of vaso-occlusion at the cellular and molecular levels has not resulted in an improvement in the treatment of painful crises. Hydration and analgesia, usually with narcotic analgesics, remain the cornerstones of management.<sup>5</sup> Narcotic analgesics have many attendant risks, the most important of which are suppression of ventilation and drug addiction. An alternate safe and effective therapy for treating painful crises is still awaited. Some agents that

affect the rheology of the erythrocytes have been tested with variable results. Isoxsuprine hydrochloride is one such agent. It is a smooth muscle relaxant and a potent uterine relaxant. It has also been found to improve the deformability of red blood cells and reduce platelet adhesion to damaged vessel walls. Experience with isoxsuprine in sickle cell disease (SCD) is limited.<sup>6,7</sup> This was a prospective randomized double-blind comparative study to test the safety and efficacy of isoxsuprine hydrochloride in the treatment of sickle cell painful crises, as compared to the conventional treatment with narcotic analgesics.

### Materials and Methods

The study was conducted at Qatif Central Hospital over 10 months, from July 1993 to April 1994. All patients 12 years or older with sickle cell disease (homozygous sickle cell disease or sickle  $\beta$ -thalassemia) presenting to the Emergency Department during the day with musculoskeletal painful crisis were eligible for enrolment in the study. Exclusion criteria included evidence of infection or temperature  $>38.3^{\circ}\text{C}$ , pregnancy or possibility of conception and lactation, recent arterial hemorrhage, use of  $\beta$ -blockers, and likelihood of the patient receiving general anesthesia in the next 24 hours. None of the

From the Qatif Central Hospital, Qatif, Dhahran Health Center, Dhahran and Dammam Central Hospital, Dammam, Saudi Arabia.

Address reprint requests and correspondence to Dr. Al-Jam'a: P.O. Box 627, Qatif 31911, Saudi Arabia.

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patients was on hydroxyurea or on chronic transfusion program.

Patients were evaluated by an Emergency Department physician and referred to a specified Senior Medical Resident who evaluated the patient for eligibility. An informed written consent was obtained once the patient agreed to participate.

One pharmacist was responsible for the preparation of sets of six ampoules of the study drug (isoxsuprine) 10 mg/2 mL and the conventional drug (meperidine) 100 mg/2 mL ampoules. The ampoules were masked so that they looked alike. Each set was given a code number which was known only to the pharmacist. The evaluator would pull a number from an envelope and the corresponding set of medication was dispensed.

Prior to giving any medication (0 time), blood was extracted for complete blood count (CBC), reticulocyte count and total and direct bilirubin, which was repeated after 24 hours.

Patients with body weight of less than 60 kg were given 1 mL of the study medication (5 mg of isoxsuprine or 50 mg of meperidine), and those weighing 60 kg or more were given 2 mL of the medication (10 mg of isoxsuprine or 100 mg of meperidine). The injections were given intramuscularly every four hours for 24 hours. After 24 hours, further management was left to the treating physician.

During the first 24 hours, any need for extra analgesics was assessed and recorded. All patients received intravenous fluids in the form of 5% dextrose alternating with normal saline at a rate of 120 cc/hour. The severity of pain was assessed on a visual pain scale from 0-10 (0

indicating absence of pain, 10 indicating maximum pain experienced). The assessment was done at baseline (pre-treatment), then at 30 minutes, 60 minutes, 2 hours, 6 hours and 24 hours post-treatment.

Other parameters which were evaluated were: 1) degree of mobilization from the bed, which was graded from 0-4 (0=asymptomatic; 1=symptomatic, fully ambulatory; 2=symptomatic, in bed <50% of the day; 3=symptomatic, in bed >50% of the day; 4=confined to bed); and 2) side effects of medication, as indicated by palpitation, somnolence, nausea, vomiting, tachycardia and hypotension. Mann-Whitney test was used to compare continuous variables, and chi-squared and Fisher's exact test were used for categorical variables. All statistical analyses were done by BMDP statistical software.<sup>8</sup>

## Results

The 43 patients included in the study comprised 33 males aged 13 to 40 years (mean, 21 years), and 10 females aged 2.5 to 25 years (mean, 17 years). They experienced 44 episodes of pain (one male patient was treated twice). After opening the code, it was found that 23 patients had received isoxsuprine and 21 patients had received meperidine. There were 16 males and 7 females in the isoxsuprine group, and 18 males and three females in the meperidine group. The mean age was 18.5 years and 21.6 years in both groups, respectively. There was no statistically significant difference among the two groups in terms of the sex, age, height or weight.

The control of pain was better with conventional treatment (meperidine) only at 30 and 60 minutes. There was no statistically significant difference at 2, 6, or at 24 hours between the two groups. Also, the degree of mobilization from the bed was the same in the two groups at 24 hours (Table 1). The duration of crisis and the length of hospital stay did not differ in the two groups (Table 2).

There was no significant side effect in either of the two groups, as there was no significant difference in the pulse or BP at the various periods of assessment. There was no difference regarding the subjective symptoms of palpitation or somnolence, and no one reported nausea or vomiting, or any unusual side effects. Isoxsuprine did not seem to improve the degree of hemolysis, as there were no significant differences in the level of total hemoglobin, reticulocyte count or the total bilirubin in both groups after 24 hours of treatment. There was no statistically significant difference in the use of extra analgesic. Six patients in the isoxsuprine group and eight in the meperidine group required extra analgesia ( $P=0.6$ , chi-squared test). Five patients in each group required extra analgesia in the first two hours ( $P=0.58$ , Fisher's exact test).

## Discussion

Acute painful episodes are the most frequent complica-

TABLE 1. Pain assessment and mobilization of patients pre- and post-treatment.

	Isoxsuprine mean±SD	Meperidine mean±SD	P-value*
Pain score			
0 min	10**	10**	
30 min	8±2	6±2	0.01†
60 min	7.6±2	6±2.5	0.05†
2 hrs	7.2±2.3	6.5±3	0.48
6 hrs	6±3	5±3	0.3
24 hrs	5±3	5±3	0.9
Mobilization score			
0 min	3±0.3	3±0.4	0.7
24 hrs	2.6±0.9	2.7±0.6	0.8

\*Mann-Whitney test (two-tailed); \*\* maximum pain for the present painful episode; † statistically significant.

TABLE 2. Duration of crisis and hospitalization (hours).

	Isoxsuprine mean±SD	Meperidine mean±SD	P-value*
Crisis			
Median	24	48	0.44
Range	8-120	24-168	
Hospitalization			
Median	72	72	0.7
Range	24-288	24-216	

\*Mann-Whitney test (two-tailed).

tion of sickle cell disease and the most common reason for emergency room visits and hospital admissions.<sup>9</sup> The process once thought to be a simple passive occlusion of the microcirculation by the rigid, poorly deformable sickle cell<sup>10</sup> appears to be more complex.<sup>11</sup> Adhesions of sickle cells to the endothelial surface of vessel wall cause damage and intimal proliferation that perpetuates vaso-occlusion. The sickle erythrocytes have also been found to adhere abnormally to monocytes and macrophages.<sup>12</sup> The understanding of the underlying pathophysiology of vaso-occlusion in sickle cell disease has not yet been translated into improved management of painful crises.

The treatment remains frustratingly symptomatic and supportive. Several attempts to find an effective therapy to abort the vaso-occlusive episodes have failed to provide a method that can replace the present method of management. These attempts included the use of cetiedil,<sup>13</sup> piracetam and pentoxifylline.<sup>14</sup> Other methods include the use of high-dose intravenous methyl prednisolone<sup>15</sup> and isoxsuprine hydrochloride.<sup>6</sup>

Isoxsuprine hydrochloride is a tocolytic agent. Attention was incidentally drawn to this drug when it was given to a pregnant woman with sickle cell disease, and severe generalized painful episode occurred, resulting in developed premature labor. Not only did the uterine contractions cease, but the pains completely disappeared after about two hours of IV infusion.<sup>6</sup> The drug was found to have several properties that may be beneficial in the setting of sickle cell vaso-occlusive crises. It improves red cell deformability, decreases adhesion of the platelets to damaged vessel walls,<sup>16,17</sup> decreases blood viscosity,<sup>18,19</sup> dilates deep peripheral vessels, and stimulates the myocardium.<sup>20-22</sup> The drug may exert other actions at the cellular or molecular level, such as the effects on polymorphonuclear leukocytes and inflammatory mediators. Further studies in this regard are needed.

This study showed that isoxsuprine was as effective as the conventional treatment with narcotic analgesic at 2, 6 and 24 hours. Narcotic analgesics were more effective in pain control during the initial 60 minutes. This finding may suggest the initial use of narcotic analgesic alone or concomitant with isoxsuprine, followed by continuation of isoxsuprine alone. Further studies with larger numbers of patients to reproduce these findings are needed. The treatment protocol was limited to the first 24 hours of admission. We anticipate that the drug would be more effective if it were to be continued for 2 to 3 days, as the crisis tends to resolve after 48-72 hours in most patients. It was recommended that 2-3 intramuscular doses of isoxsuprine per day for the next 2-3 days might prevent relapse of the pain.<sup>6</sup> This seems to be a reasonable recommendation. Some patients may require more frequent administrations, depending on the severity of pain.

We could not confirm the superiority of the drug in decreasing hospital stay, as has been suggested in other

reports.<sup>6</sup> This was due to the fact that we included only patients with severe crises in our study. If it is effective for moderate crises in the emergency room, it may reduce the rate of hospital admissions.

In summary, our study confirms the potential effectiveness of this relatively safe drug for the treatment of acute painful crises of sickle cell disease. This may be an important addition to the supply of drugs against this devastating problem. Many questions still remain to be answered. These include the optimal dosage, route of administration, duration of treatment and the mechanism of action during the vaso-occlusive episodes. The potential use of isoxsuprine in preventing painful crisis requires long-term placebo-controlled trial.

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