Clinical Evaluation of the New Topical Anesthetic Formulation in β-Thalassemia Major Patients

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ABSTRACT

Background

Iran is among the most prevalent areas of major β-thalassemia. As thalassemic patients need repeated blood transfusion and deferoxamine injection, which is painful. This study was performed to compare the effects of two new anesthetics products, (B4 and B6) with eutectic Mixture of Local Anesthetics (EMLA).

Methods

In a double-blind randomized, prospective, self-controlled trial, a total of 106 patients with an age range of 10-33 years who were referred to Shiraz Thalassemia Clinic, were enrolled in this study. In different referrals, 60 minutes after application of 2 gr EMLA, B4 and B6, the pain associated with insertion of a sterile 22 gauge needle into a depth of 2 mm of right forearm skin were assessed by visual analog pain scale.

Results

In deferoxamine injection, pain sensation was evaluated after application of 0.5 gram EMLA, B4 and B6. Mean ± SD intensity of pain sensation at the site of application of EMLA, B4 and B6 was 0.32(±1.41), 0.5 (±1.67) and 0.1 (±0.71) respectively. So, B6 was more potent than B4 and EMLA in pain reduction. In blood transfusion, pain sensation was evaluated after application of 0.5 gram of EMLA, B4 and B6. Mean intensity of pain sensation at the site of application was 0.57 (±1.62), 0.52 (±1.6) and 0.46 (±1.71) for EMLA, B4 and B6 respectively. Thus, B6 was more potent than B4 and EMLA, and B4 was more potent than EMLA in pain reduction.

Conclusion

B4 and B6 are low-priced and when considering their minor adverse effects compared to EMLA. Therefore, they can be substituted for EMLA in developing countries that have economical problems to provide EMLA.

INTRODUCTION

Pain and anxiety caused by invasive procedures are common findings in children and insertion of needle into the skin is accompanied with pain. [1,2] Topical anesthetics can decrease the pain sensation via anesthetizing pain nerve endings of intact skin. The use of topical anesthetics before invasive procedures,[3] particularly venepuncture and venous cannulation, has become a routine standard care in children. [4-6].

Major β-thalassemia is one of the most prevalent diseases in Iran. These patients, who are mostly children, need repeated blood transfusions and Desferal injection, which are painful procedures. Eutectic Mixture of Local Anesthetics (EMLA) cream is one of these anesthetics. Since its introduction, it has been found to be an effective topical anesthetic agent, with a high degree of efficacy, particularly for venepuncture and venous cannulation.[7-9] In addition, it has an impressive tolerability profile. It consists of a mixture of 2.5% Lidocaine base, and 2.5% Prilocaine base in an emulsifier (polyoxyethylene) with added carboxy polymethylene to thicken the consistency and render it more suitable for transdermal application. Reports of adverse effects are remarkable for their rarity. However, metabolites of Prilocaine have been shown to cause methemoglobinemia, especially in the presence of fetal hemoglobin.[10] The high degree of efficacy of EMLA makes the use of EMLA a routine standard of care before blood transfusion and Desferal injection in major β-thalassemic patients.[11] However, its cost and unavailability in developing countries, and increasing reports of its side effects, [12-14] encouraged us to find a less expensive and more readily available substitute with less complications and with equal efficacy.

In our country, researches in the Pharmacy School of Shiraz University of Medical Sciences, led us to find two new formulations using a lidocaine base without prilocaine to avoid methemoglobinemia. The attempt to formulate such an agent exists in part due to inadequate diffusion and delivery of lidocaine through the intact skin. [15]

The improved efficacy of EMLA, as compared to conventional topical formulation was attributed to the high drug concentration in its oil phase [11, 15-17]. In this regard two same formulations with different oil content were evaluated (B4 and B6). As well as we compared these two new products with EMLA. Due to the EMLA expenses, an alternative product with similar anesthetic properties but with lower cost was considered.

METHODS

Study Design

This is a double-blind, randomized, prospective, self-controlled trial study. It was carried out using three different drugs on major β-thalassemic patients during a 6- month period in Shiraz, south of Iran.

In different referrals, 60 minutes after application of 2 gr EMLA, B4 and B6, the pain associated with insertion of a sterile 22-gauge needle into a depth of 2 mm of right forearm skin were assessed by visual analog pain scale. The needle size, technique of injection, and technician that conducted the injection were the same for each group.

Patients

A total of 106 patients with an age range of 10-33 years among 1,200 thalassemic patients in Shiraz, who referred to Shiraz Thalassemia Clinic, were selected. All were major β-thalassemic patients. The patients were visited individually, and the patients and their parents were informed about the standard pain scale, how they should attain the pain score, and about the rarity of the side effects, and a written consent were provided.

Our colleagues in Shiraz Pharmacy School prepared three tubes of A (EMLA), B (B4) and C (B6). Each time, when a patient came to the Thalassemia Clinic for blood transfusion or Desferal injection, an individual expert nurse applied 2gr of one of the tubes: A, B, and C, in turn, at the site of needle insertion and covered them by an occlusion dressing.

Table1: *Mean intensity of pain sensation at the site of application of EMLA, B4 and B6 in both of procedures.*

Drugs procedures	EMLA	B4	B6
DESFERAL INJECTON	0.32 (SD=1.41)	0.50 (SD=1.67)	0.10 (SD=0.71)
BLOOD TRANSFUSION	0.57 (SD=1.62)	0.52 (SD=1.69)	0.46 (SD=1.71)

Thus, every patient was tested by each preparation for both blood transfusion and Desferal Injection. Neither the examiner nor the objects knew the real compounds of each tube. After 60 minutes, dressing was removed, and the site of the application was cleaned by alcohol and an assessment perceived pain associated with the insertion of needle, which was made by the subject using a previously validated 10 cm visual analogue pain scale (V.A.S).

Anesthetic Ointments

An Eutectic Mixture of Local Anesthetics (EMLA) cream is one of these anesthetics, since its introduction has been found to be an effective topical anesthetic agent [3, 5-7], [10]. New products named B4 which is the combination of lidocaine 10 %, DMSO (Dimethyl sulfoxide) as permeability enhancer 10% and castor 20 % as oil phase, and B6 which is the combination of lidocaine 10 %, DMSO 10% and castor oil 10 %. The improved efficacy of EMLA, as compared to conventional topical formulation was attributed to the high drug concentration in its oil phase. In this regard B6 contains half of the B4 oil phase to maximize the thermodynamic activity of lidocaine in this formulation [11, 18-20].

Pain Assessment

Pain is one of the most common concerns of patients entering the health care system. Pain is whatever the experiencing person says and he or she is feeling at a specific time. Pain is subjective; therefore, the only way to ensure that patients receive equally high quality pain relief is to rely on the patient's self report.

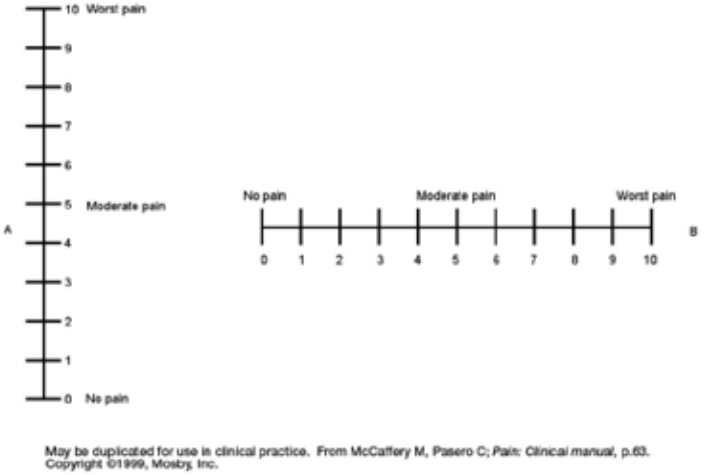
Pain rating scales are used to help the patient to communicate the intensity (severity) of pain and to be a guide in the treatment of pain. Commonly used scales include the visual analogue, graphic rating, simple descriptor, numerical rating, and face rating scales. In this study the visual analogue scale (V.A.S) was used, because (VAS) often considered as the golden standard in pain assessment [21].

An assessment perceived pain associated with the insertion of needle was made by the subject using a previously validated 10 cm visual analogue pain scale (V.A.S) as follows: Score of maximum pain at the site of

Table2: *Difference between mean of pain reduction ability of EMLA, B4 and B6 in both of procedures.*

Drugs Severity of pain	EMLA	B4	B6
Drugs procedures	EMLA-B4 (score)	B6-EMLA (score)	B6-B4 (score)
DESFERAL INJECTON	0.18 (P=0.3271)	0.22 (P=0.2604)	0.40 (P=0.054)
BLOOD TRANSFUSION	0.05 (P=0.4042)	0.11 (P=0.5595)	0.06 (P=0.96)

Figure1: *Visual Analogue Scale*



needle insertion =10, minimum or no pain = 0, and the other intensity of pain is ruled among 1 to 9 (Figure 1).

Statistical analysis

For comparison of pain reduction ability by EMLA, B4 & B6 with each other, Paired sample T-test was used for statistical analysis and a p value less than 0.05 was considered significant.

Results

The results are presented in two separated categories for deferoxamine injection and blood transfusion.

Deferoxamine Injection

Comparison of the effects of EMLA, B4, and B6 revealed that 92.5 % of the patients had no pain 60 minutes after application of EMLA, while just 0.9% expressed maximum pain (VAS=10). These values for B4 were 88.6% and 0.9% respectively. None of the patients felt maximum pain (VAS=10) with B6, while 98.1% had no pain (Figure 2).

Mean ± SD intensity of pain sensation (pain score) at the site of application of EMLA, B4 and B6 was 0.32 (±1.41), 0.5 (±1.67) and 0.1 (±0.71) respectively (Table 1). In other words, potency of EMLA to reduce pain was as much as 9.68 scores, as it was 9.5 for B4 and 9.9 for B6 (Figure 3).

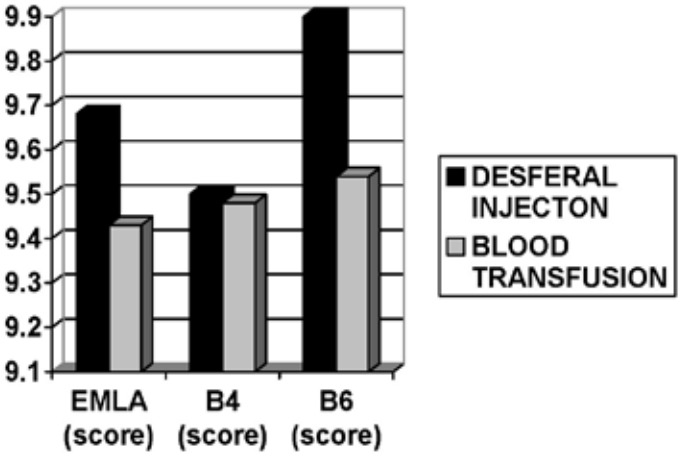
We compared EMLA and B4, EMLA and B6 as well as B4 and B6 separately. The differences between mean of pain reduction ability were 0.18 for EMLA and B4 (P=0.3271), 0.22 for B6 and EMLA (P=0.2604) and 0.4 for B6 and B4 (P=0.054) (Table 2).

Blood transfusion

The same values mentioned above for deferoxamine injection were also calculated for blood transfusion. Comparison of the effects of EMLA, B4, and B6 revealed that the patients, who had no pain at the site of injection (60 minutes after application), were 84.9% for EMLA, 86.7% for B4 and 89.3% for B6. Only 0.9% of patients for whom

Figure2*: Severity of pain sensation associated with insertion of needle in Desferal injection by using VAS in patients after application of EMLA, B4 and B6.*

Figure3: *Potency of EMLA, B4 and B6 to reduce pain of needle insertion in both of procedures.*



EMLA preparation was used experienced maximum pain (VAS=10), while this increased to 1.9% for preparations of B4 or B6 (Figure 4).Mean intensity of pain sensation at the site of application was 0.57 (±1.62), 0.52 (±1.6) and 0.46 (±1.71) for EMLA, B4 and B6 respectively (Table 1).Therefore, the potency of EMLA to reduce pain at the site of needle insertion for blood transfusion was 9.43 and was 9.48 for B4 and 9.54 for B6 (Figure 3). Comparison of the ability of pain reduction showed a 0.05 difference between B4 and EMLA (P=0.4042), and 0.11 difference between B6 and EMLA (P=0.5595). When the preparation of B4 and B6 were compared, this difference was 0.08 (P=0.96) (Table 2).

Complications

During this organized study, we did not record any complication with application of EMLA or our new anesthetic ointments of B4 and B6.

DISCUSSION

Our two new local anesthetic creams were as effective as EMLA but with lower costs and more availability. The only differences between these formulations were the percent of the oil phase ratios.

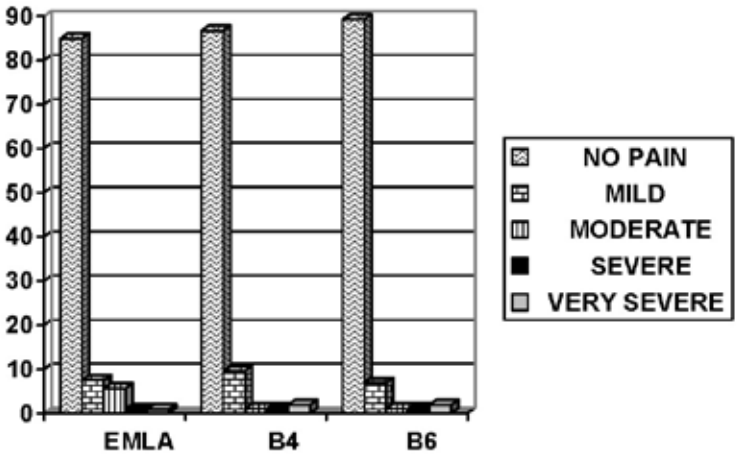
The effectiveness of EMLA has been proved previously by several studies during venepuncture, vaccination, cancer, and lumbar puncture [9, 15-17, 22].

All of the preparations (EMLA, B4 and B6) are potent enough to decrease pain of needle insertion, when compared with each other.

Also, the results revealed that there was no significant difference in pain reduction ability of EMLA and B4 (P=0.3217) as well as EMLA and B6 (P=0.2604) before desferal injection, while B6 was more potent than B4 (P=0.054). It is in agreement with other studies that reveal lower oil phase potentiate faster penetration of lidocaine through the intact skin [11, 15-17].

There was no significant difference between the use of preparation EMLA, B4

Figure4: *Severity of pain sensation associated with insertion of needle in blood transfusion by using VAS in patients after application of EMLA B4 and B6.*



and B6 as local anesthetics before blood transfusion.

Clinically these results are virtual because conforming the numerical visual analogue and descriptive pain scales, indicate that EMLA is able to reduce the pain intensity from very severe to a mild range during deferoxamine injection (10 vs. 0.32) and in blood transfusion (10 vs. 0.57).

Conforming the numerical visual analogue scale and descriptive pain scale, indicates that B4 is able to reduce the pain intensity from very severe to mild during desferal injection (10 vs. 0.5) and in blood transfusion (10 vs. 0.52) and for B6 from very severe to mild during deferoxamine injection (10 vs. 0.1) and in blood transfusion (10 vs. 0.46).

Otherwise, the risk of methemoglobinemia, which is a potential side effect of prilocaine in patients with hypersensitivity to this drug or in patients with congenital or idiopathic methemoglobinemia, is decreased by B4 and B6.

Application of local anesthetic drugs at the site of any procedure, which needs skin penetration of anesthetic drug, not only to decrease the pain of procedures, but also to reduce the patient's anxiety and makes them more cooperative.

In conclusion, our results showed that B4 and B6 are low-priced, effective in reducing pain and easy available and when considering their minor adverse effects, they are recommended to be substituted for EMLA especially in developing countries.

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