Efficacy and Safety of Delivery Timolol Maleate via Nanometer Microneedles among Superficial Infantile Hemangioma: a retrospective study in China

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Research Article

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Abstract

Background:

Infantile hemangioma is common and affects multidemensionally. Drug therapy is a commonly used method in clinical practice, but its effect needs to be improved. The main challenge derives from the drug penetration and safety. The emergence of nanometer microneedle technology seems to solve these problems. The proposed study aims to review the efficacy and safety of the nano-microneedle by comparing with other drug therapy methods.

Methods:

A retrospective study reviewed patients with infantile hemangioma who were admitted to a tertiary stomatological hospital from January 2014 to October 2021. The cases were divided into three groups according to the different drugs and the different methods of drug administration, namely timolol maleate solution introduced by nanometer microneedle technology (NM), timolol maleate drops dipped with a medical swab (MS), and propranolol orally (PO). The effective rate, the cure rate, the rate of adverse reactions, and the time for treatment to be effective were recorded and compared.

Results

A total of 307 cases were reviewed in the study (NM=97, MS=107, PO=103). The total effective rate, total cure rate, total rate of adverse reactions were 87.6%, 65.2%, 9.4%, respectively. There was statistically significant difference in the effective rate, the cure rate, the rate of adverse reactions, the time for treatment to be effective between the three groups. The results of the pairwise comparison showed that the effective rate of NM was higher than that of MS (P0.05), the cure rate of NM was higher than that of MS (P0.05), the rate of adverse reactions of OP was higher than that of MS (P0.05), the time for treatment to be effective of NM was shorter than that of MS and OP (P0.05).

Conclusions:

Our study revealed that delivery timolol maleate via nanometer microneedle is an efficacy and safety in infantile with superficial hemangioma. It has the highest effective rate and cure rate, lower incidence of adverse reactions, and shortest time for treatment to be effective.

Background

Infantile hemangioma (IH) is the most common benign vascular tumor among infants and young children [1], with an incidence of about 4% ~ 5%. The incidence rate of male versus female was 1:3 ~ 1:5, and about 60% occurred in the head and neck [2]. Hemangiomas usually appear in the first few days to one month postnatally and are characterized by small red spots in the early stage, then their volume increases rapidly, and they proliferated rapidly in the first month and 4–5 months, reaching 80% of their final volume[3]. After the age of 1 year, the natural regression process is beginning and can last 3 to 8

years or even longer. However, it is worth noting that although some hemangiomas can resolve spontaneously, erythema, pigment changes, telangiectasias, atrophic scars and fibro-fatty tissue growths are often left locally after the resolution, which affects the appearance to varying degrees [4]. In addition, while waiting for observation, hemangioma, especially head and neck hemangioma, brings obvious socio-psychological harm to children and their parents during the growth and development period. In addition, about 10% of hemangiomas grow rapidly. If not actively treated, various complications may occur, such as obstruction of the respiratory tract, affecting vision, ulcers, infections, bleeding of hemangiomas, affecting appearance, etc; a few are even life-threatening [3]. Therefore, in addition to hemangioma that grows in a hidden area, is small or is in a stable state, which can be “waiting for observation”, active treatment is required in other cases [5].

Many approaches have been utilized to treat IH, such as surgery, laser, cryotherapy and drug therapy, etc. When it comes to the clinical setting, drug therapy gets the highest priority as its conservatism. At present, various types of receptor blockers have been used in clinical practice and have become a hot spot in clinical research. Relevant studies on the application of these drugs have shown that propranolol and timolol maleate can indeed effectively treat hemangioma. Propranolol has been marketed in the United States and Europe for the treatment of infantile hemangioma; Guo et al[6] reported that the topical use of 0.5% timolol maleate eye drops can effectively treat eyelid vascular tumors, opening up the treatment of hemangioma a new path since 2010. At present, the expert consensus or expert advice on the use of hemangioma tumor drugs is “off-label use” [7, 8]. Therefore, the application of Timolol maleate is another revolutionary change in the treatment of hemangioma. A clinical study conducted in 2012 confirmed this view, also found that the factor restricting the efficacy of topical drugs is skin permeability rather than drug concentration[9]. However, the barrier function of the stratum corneum is the key to drug penetration. According to research, only about 10–30% of the liquid medicine can pass through this layer into the deep tissues of the skin [10]. Therefore, how to promote the penetration of drugs into the deep tissues of the skin is the key to improving the efficacy.

Nanometer microneedle technology, short for nano-microneedle, has emerged in recent years to promote the penetration of drugs into the skin. Nano-fabricated single-crystal silicon nano-permeable wafers can non-invasively and rapidly open a large number of nano-scale microchannels on the skin surface. It can be used for the delivery of drugs and other substances between cells because of their small diameter. The study found that the nano-microneedles can exert their effects while minimizing the damage to the intracellular environment [11, 12]. The nano-microneedle has the advantages of safety, convenience, rapidity, and painlessness which had been used in clinical practice. This study will review and report the clinical application effects and adverse reactions of the three methods: introduction of timolol maleate with nano-microneedle, application of timolol maleate, and oral propranolol. It is expected to provide a reference for improving the clinical treatment effect.

Methods

Study population

This retrospective study reviewed patients with infant hemangioma who were admitted to the Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University from January 2014 to October 2021. The inclusion criteria were as follows: (1) patients were superficial infantile hemangioma in the proliferative stage (1-2months old), (2) patients were hospitalized for treatment, (3) patients were at the initial diagnosis and treating the disease for the first time, (4) patients were treated with timolol maleate solution or propranolol. The exclusion criteria were as follows: (1) patients had systemic disease, (2) patients were allergies to β adrenergic blockers, (3) patients with incomplete data.

Procedure

The study was approved by the Ethical Committee of School and Hospital of Stomatology, China Medical University (No. K2020026), and the retrospective procedures were in accordance with the ethical standards. The general information of cases and tumor, treatment methods, treatment effects, the time for treatment to be effective, and adverse reactions of the cases were obtained by electronic medical records.

Treatments and Grouping

The cases reviewed in the study were divided into three groups according to the different drugs and the different methods of drug administration. Group NM: timolol maleate solution administrated by nano-microneedle technology, once a day, Group MS: timolol maleate drops dipped with a medical swab, twice a day, Group PO: propranolol 1.0 ~ 1.5mg/kg orally, once a day. The detailed treatment process of these three methods is as follows:

The cases in Group NM were treated with timolol maleate solution once a day with nano-microneedle technology. The operation methods are as follows: (1) Wash the surface of the tumor and surrounding skin with normal saline, (2) After the surface is air-dried naturally, timolol maleate drops were dipped in a medical cotton swab, (3) the osmometer is placed vertically on the surface of the tumor and electropuncture point by point. After 1-2 seconds of treatment at each acupuncture point, move 5mm laterally, which is the width of a chip, perform a little acupuncture and puncture the hemangioma lesion area point by point. Repeat this step twice for each treatment, (4) Wet compress with normal saline for 30 minutes.

In Group MS, a small amount of timolol maleate drops were dipped in a medical cotton swab and applied locally to the hemangioma lesion area, with BID once in the morning and evening.

Children in Group PO was given propranolol 1.0□1.5 mg/kg orally, once a day. The general hospitalization is 5 days, during which blood pressure and heart rate are closely monitored, and the electrocardiogram is recorded and evaluated daily. If there is no obvious adverse reaction during hospitalization, the child can be discharged from the hospital for further treatment. Before being discharged from the hospital, the nurses provided health guidance on medication, effect observation and adverse reaction observation to the family members of the children. After being discharged from the hospital, the family members of the

children are required to take medications as required, record the occurrence of adverse reactions, and take the children back to the hospital to check their health and medication conditions every month. At each follow-up, relevant information is collected, and the follow-up nurse understands the patient's condition and gives relevant health guidance.

In the Group NM and MS, it should be noted that for children with periorbital hemangioma, cornea and conjunctiva should be avoided. Besides, the nurse observes the changes in skin, breathing, and heart rate after each medication, and records the changes in heart rate before and after medication and during sleep. If the heart rate is lower than the above lower limit, the medication should be stopped immediately. At the same time, pay attention to whether there are abnormalities in diet and sleep.

Efficacy evaluation criteria

The outcomes of each patient were divided into four levels according to the Achauer' standard analysis [13], which evaluated the outcome based on improvement of volume, color, and texture: I level, poor (0 to 25 percent), II level, fair (26 to 50 percent), III level, good (51 to 75 percent), and 4, excellent (76 to 100 percent).

Drug safety evaluation

The occurrence of systemic and local adverse reactions was recorded according to clinical observation during treatment. The observed adverse reactions mainly included vomiting, diarrhea, hypoglycemia, low blood pressure, low heart rate, and local imitation from medication, etc.

Operating definition

The effective rate, the cure rate and the rate of adverse reactions was calculated as following: The effective rate = the number of cases with outcome II level and above / the number of the all cases. The cure rate = the number of cases with outcome IV level / the number of the all cases. The rate of adverse reactions = the number of cases with adverse reactions / the number of the all cases.

The time for treatment to be effective is defined as the time for the treatment effect to reach III level and above.

Statistical analyses

Statistical Package for Social Sciences (SPSS 22.0 for Windows) was used to conduct data analyses. Significance for all statistical tests was set to be the level of 0.05 (2-tailed). Normality and homogeneity of variances were first tested for each continuous variable. Univariate analysis, Chi-square tests and nonparametric-test were operated to describe distributions in different groups.

Results

Descriptive statistics

This study reviewed 307 cases, including 141 male infants and 166 female infants. The mean age of the cases was 48.45 days (SD=3.28, ranging from 42 to 58). The lesions of 211 patients were on the head and face, and the remaining 97 patients were on the limbs and trunk. The tumor area ranges from 0.6cm*0.7cm to 4cm*12cm. Among them, the thickness of the tumor in 186 cases did not exceed the dermis, 103 cases exceeded the dermis but less than 5 mm, and 18 cases were more than 5 mm. The numbers of cases in Group NM, MS, PO were 97, 107, 103, respectively. The distributions of gender, lesions, tumor area and thickness in the three groups were described in Table 1, and there were no significant differences among the three groups (p□0.05).

Table 1 should appear at this location

Comparisons between three groups

The effective rate and the cure rate:

The treatment outcomes of the cases were described in Table 2. The total effective rate was 87.6%. The effective rates of Group NM, MS, PO were 92.8%, 81.3%, 89.3%, respectively. There was statistically significant difference in the effective rate between the three groups (X^2=6.589, P=0.037). The results of the pairwise comparison showed that the effective rate of Group NM was higher than that of Group MS (P □0.05).

The total cure rate of was 65.2% .The cure rates of Group NM, MS, PO were 76.3%, 57.0%, 63.1%, respectively. There was statistically significant difference in the effective rate between the three groups (X^2=8.613, P=0.013). The results of the pairwise comparison show that the cure rate of Group NM was higher than that of Group MS (P□0.05).

Table 2 should appear at this location

The rate of adverse reactions

The total rate of adverse reactions was 9.4%. “Local irritation from medication” was the only adverse reaction in both Group NM (n=7) and B (n=4), while adverse reactions of the Group PO included hypoglycemia (n=5), low blood pressure (n=4), low heart rate (n=4), diarrhea (n=3) and vomiting (n=2). The rates of adverse reactions in Group NM, MS, PO were 7.2%, 3.7%, 17.5%, respectively. There was statistically significant difference in the rate of adverse reactions between the three groups (X^2=12.403, P=0.002). The results of the pairwise comparison show that the rate of adverse reactions of Group PO was higher than that of Group MS (P□0.05). It was worth noting that all the adverse reactions were improved after the drug was stopped. The results of adverse reactions were shown in Table 3.

Table 3 should appear at this location

The time for treatment to be effective

There was statistically significant difference in the time for treatment to be effective between the three groups (X^2=114.109, P□0.001). The treatment effect of 72% cases in Group NM reach III level and above within 1 month, while that of Group MS and PO was 18.7%, 11.7%. The results of the pairwise comparison show that the time for treatment to be effective of Group NM was shorter than that of Group MS, Group PO (P□0.05). The results of time for treatment to be effective were shown in Table 4.

Table 4 should appear at this location

Discussions

The current study reviewed the cases of infantile hemangioma that were admitted to the Department of Oral and Maxillofacial Surgery, School of Stomatology, China Medical University from January 2014 to October 2021. The total effective rate and cure rate was high, which showed that these treatments had obvious effect on infantile hemangioma. The result confirmed the previous studies[6, 9].

We explored the clinical application effects and adverse reactions of the three methods: introduction of timolol maleate with nano-microneedles (Group NM), application of timolol maleate (Group MS), and oral propranolol (Group PO). The results showed that Group NM and MS had a higher effective rate and cure rate, at the same time, the rate of adverse reactions was lower than oral propranolol, which were consistent with a Meta-analysis on the effect of timolol and oral use propranolol for the treatment of superficial infantile hemangioma, which showed that the overall effective rate of timolol group was significantly higher than that of propranolol group, and the incidence of systemic adverse reactions was significantly lower than that of propranolol group[14]. Timolol is a non-selective type II blocker, FDA approved for use in children with high intraocular pressure, open-angle glaucoma, adult hypertension, migraine, and post-myocardial infarction. Its action intensity is 8 times that of propranolol. Besides, we found a higher incidence of adverse reactions in infants with oral propranolol compared to timolol maleate. Oral propranolol is effective and effective in treating infantile hemangioma. However, there are a series of adverse reactions when using it. In addition, after oral administration of propranolol, the first-pass effect of liver is strong, the bioavailability is low, the individual difference is large, and it is easy to interact with other drugs, and the drug half-life is short, the blood concentration fluctuates greatly, which requires repeated administration[15-17].

What's more, the result suggested that delivery timolol maleate via nano-microneedles was most effective and safety. Some clinical studies have also found that the efficacy time and efficiency of topical drugs were significantly better than that of other parts in areas with thin corneous layer such as periorbital scalp and mucous membrane, suggesting that the key factor influencing the efficacy of topical drugs lies in skin permeability. The nano-microneedle is a new device that can promote the transdermal absorption of topical agents. It consists of 36 microneedles (250 μm in height) over an area of 5 × 5 mm. The needles are connected to a pen-like vibrator, which causes them to penetrate the skin with a frequency of 3000 times per minute. The diameter of each needle is only 80 nm, which is almost noninvasive. Utilizing this method, drug penetration can be increased by up to 10 or 20 times[11, 12, 18]. However, it should be noted

that the rate of “Local irritation from medication” of Group NM was higher than Group MS, which might be related to the application of nano-microneedles.

In Table 4, we could found the treatment effect of 72% cases in Group NM reach III level and above within1 month, while that of Group MS and C was 18.7%, 11.7%. Especially, there are 28 infants reach III level and above in 7 days.

Limitations

The limitation of the study was the need to review the cases in multi-center to improve the representativeness.

Conclusion

Our study revealed that introduction timolol maleate by nanometer microneedles is an efficacy and safety in infantile with superficial hemangioma. It has the highest effective rate and cure rate, lower incidence of adverse reactions, and shortest time for treatment to be effective.

Abbreviations

IH: Infantile hemangioma, BID: bis in die, SPSS: Statistical Package for Social Sciences, SD: Standard Deviation, NM: nanometer microneedle/ nano-microneedle, MS: medical swab, PO: per os.

Declarations

Ethics approval and consent to participate

The study proposal was approved by the Ethical Committee of School and Hospital of Stomatology, China Medical University (NO.K2020026), following the Declaration of Helsinki. Consent for publication

Availability of data and materials

The data supporting the findings of the proposed study are available from and managed by the Department of Medical Insurance and Records, which were used under license for the current study, and so are not publicly available.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no conflicts interests.

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There is no funding for this study

Authors' contributions

Jia Wang and Lulu Yuan were responsible for conception and design of this research. Xukai Wang gave directions to the study. Weiren Wang and Xujie Zhang played vital role in data collection and extraction. The first version of the manuscript was written by Lulu Yuan. All authors commented on previous versions of the manuscript. All authors viewed and approved the final manuscript.

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Tables

Table 1. Distributions of the three groups in categorical demographic and clinical variables (N=307)

	NM (n=97)	MS (n=107)	PO (n=103)	F/X^2	P
Age(days)	48.52±3.59	47.95±3.18	48.59±3.03	2.040[a]	0.132
Gender(n)					
male infants	45	49	50	0.174[b]	0.917
female infants	52	58	53		
Lesions					
head and face	62	78	71	1.912[b]	0.384
limbs and trunk	35	29	32		
Tumor area(cm^2)	7.60(5.65)	7.80(6.50)	8(6)	0.359[c]	0.836
Tumor thickness(mm)	0(1)	0(1)	0(1)	1.669[c]	0.434

a: *Analysis was performed with univariate analysis*

b: *Analysis was performed with x^2 test*

c: *Analysis was performed with nonparametric-test*

Table 2. The treatment outcomes, effective rate and cure rate in three groups (N=307)

	I	II	III	IV	The effective rate (n, %)	The cure rate (n, %)
NM (n=97)	2	5	16	74	90(92.8)	74(76.3)
MS (n=107)	7	13	26	61	87(81.3)	61(57.0)
PO (n=103)	3	8	27	65	92(89.3)	65(63.1)
x^2					6.589	8.613
P					0.037	0.013

Pairwise comparison show that the effective rate of Group NM was higher than that of Group MS (P□ 0.05), the cure rate of Group NM was higher than that of Group MS (P□0.05)

Table 3. The adverse reactions in three groups(N=307)

	vomiting	diarrhea	hypoglycemia	Low blood pressure	Low heart rate	Local irritation from medication	The rate of adverse reactions
NM (n=97)	0	0	0	0	0	7(7.2)	7(7.2)
MS (n=107)	0	0	0	0	0	4(3.7)	4(3.7)
PO (n=103)	2(1.9)	3(2.9)	5(4.9)	4(3.9)	4(3.9)	0	18(17.5)
x^2	12.403						
P	0.002						

Pairwise comparison show that the rate of adverse reactions of Group PO was higher than that of Group MS (P□0.05)

Table 4. The time for treatment to be effective (N=307)

	Within 7 days	Within 1 month	Within 1-2 months	Within 2-3 months	Within 4-6 months	Below the level III in 6 months
NM (n=97)	28	42	21	15	13	6
MS (n=107)	11	9	8	18	52	20
PO (n=103)	7	5	4	12	65	17
x^2	114.109					
P	0.000					

Pairwise comparison show that the time for treatment to be effective of Group NM was shorter than that of Group MS, Group PO (P□0.05)