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Pingyangmycin with triamcinolone acetonide effective for treatment of lymphatic malformations in the oral and maxillofacial region

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ABSTRACT

Objective: The aim of this study was to evaluate the therapeutic effects of intralesion injection of pingyangmycin in combination with triamcinolone acetonide or pingyangmycin alone on lymphatic malformations in oral and maxillofacial regions.

Methods: Twenty-nine cases with lymphatic malformations in the oral and maxillofacial region were divided into experimental and control groups. Thirteen patients in the experimental group underwent intralesion injections of pingyangmycin in combination with triamcinolone acetonide, and 16 patients of control group underwent intralesion injections of pingyangmycin alone. The effects of treatments were assessed by measuring lesion volume and facial deformity before and after treatment.

Results: Two years after the treatment, the volumes of macrocystic and microcystic lesions were 3.7% ± 0.3 and 4.2% ± 0.4 of pre-treatment volume in the experimental group, respectively, whereas the volumes of macrocystic and microcystic lesions in control group were 15.4% ± 1.3 and 24.1% ± 3.1, respectively. Facial appearance was satisfactory in all subjects in the experimental group, whereas facial asymmetry remained in varying degree in control group.

Conclusion: Intralesion injection of pingyangmycin with triamcinolone acetonide was more effective than pingyangmycin alone for treatment of lymphatic malformations in oral and maxillofacial regions.

1. Introduction

Lymphatic malformations are localized areas of abnormal development of the lymphatic system (Bloom et al., 2004). About 90% of cases in the oral and maxillofacial region occur when patients are under 2 years old and account for more than 75% of all lymphatic malformations (Zhou et al., 2011). Medical history and physical examination are generally sufficient to diagnose lymphatic malformations, however magnetic resonance imaging (MRI) and computed tomography (CT) can help to confirm the diagnosis and to differentiate the lesions from venous anomilies and also to determine the extent of the lesion (Watzinger et al., 1997; Tao et al., 2010). Lymphatic malformations can roughly be divided into the macrocystic, microcystic, or mixed lesions based on response to sclerotherapy (Smith et al., 1996).

Lymphatic malformations in the oral and maxillofacial region often lead to dysfunction and cosmetic disfigurement. Some patients may have trouble in breathing, eating, speaking, and lesions can even become life-threatening because of infections, trauma, hemorrhage, or the compression of the respiratory tract by the rapid enlargement of the pathological tissue (Hartl et al., 2000). There are several treatment options for lymphatic malformations documented in the literature, including laser therapy, sclerotherapy, surgical resection or a combination of these methods (Kobus et al., 1982; Watzinger et al., 1997; Zheng et al., 2005; Grimmer et al., 2006; Kang and Song, 2008; Bajaj et al., 2011). Sclerotherapy is currently recommended as one of the major treatments for the lesions (Zhou et al., 2011); sclerosing agents include bleomycin A5 and pingyangmycin, OK-432, etc. (Smith et al., 1996; Laranne et al., 2002; Alonso et al., 2005; Bai et al., 2009; Sainsbury et al., 2011). All these agents can be effective to some extent for treatment of lymphatic malformations. We have used pingyangmycin effectively to treat lymphatic malformations or hemangiomas in the oral and maxillofacial region for more than 20 years (Luo and Zhao, 2011), but with some problems puzzling us. For example, the lesions become harden after several intralesion injections so that the sclerosing agent can not diffuse smoothly in these areas due to sclerosis of the lesions; the clinical effects remain unsatisfactory in some cases. In addition, the side effects of

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pingyangmycin may be more harmful to the patients with long-term use. Therefore, the side effects of pingyangmycin need to be overcome during sclerotherapy. Furthermore, facial appearances of some patients remain asymmetric after sclerotherapy and may need plastic surgery to correct the facial asymmetry.

Triamcinolone acetonide is a long acting glucocorticoid, which not only inhibits collagen synthesis but also accelerates collagen degradation, in addition to its ability to repress inflammation (Niessen et al., 1999; Basadonna et al., 1999; Oh et al., 2007). Moreover, glucocorticoids also have inhibitory effects on the development of tumor lymphangiogenesis (Yano et al., 2006) or giant cell granuloma (Shirani et al., 2011; Rachmiel et al., 2012), implying that it may also inhibit the development of diseased lymphatic vessels. Corticosteroids can decrease the risk of bleomycin-induced lung fibrosis by reducing the dosage of bleomycin (Jensen et al., 1990). Whether triamcinolone acetonide could enhance the therapeutic effects of pingyangmycin on lymphatic malformations in oral and maxillofacial regions remained to be explored.

To overcome the problems already mentioned, we explored whether intralesion injections of pingyangmycin in combination with triamcinolone acetonide could have a better therapeutic effects than pingyangmycin alone for treatment of lymphatic malformations in the oral and maxillofacial region.

2. Materials and methods

2.1. Patients

From August, 2005 to October, 2009, 29 cases of lymphatic malformations in the oral and maxillofacial region were recruited in the Department of Oral & Maxillofacial Surgery, Peking University Stomatologic Hospital. The ages of the patients ranged from 20 days to 19 years. Diagnosis of lymphatic malformations was made on the basis of patient history, clinical examination, B-ultrasound, MRI, and paracentesis. Patients were randomly divided into experimental and control groups. An experimental group (13 patients with 7 males and 6 females, containing 3 cases after surgical resection) had intralesional injection with pingyangmycin in combination with triamcinolone acetonide, whereas a control group (16 patients with 10 males and 6 females, containing 3 cases after surgical resection) had intralesion injection with pingyangmycin alone.

2.2. Preinjection preparation

Chest X-ray, blood test and electrocardiogram (ECG) were performed to ensure a negative result before sclerotherapy.

2.3. Preparation of sclerosing agents

Pingyangmycin (8 mg) was dissolved in saline with 2% lidocaine hydrochloride (5 ml) and 1 ml of dexamethasone (5 mg). Triamcinolone acetonide (50 mg/5 ml) was mixed with 2% lidocaine hydrochloride (5 ml). The final concentration of pingyangmycin was 0.625 mg/ml.

2.4. Dosage

The dose of pingyangmycin was calculated according to the age and weight of the patient and the size of the lesion. The maximal dose for an adult patient was less than 8 mg per treatment, while the dose for children was less than 0.2 mg/kg body weight per treatment. The total dose of one treatment course consisted of 8 treatments with interval of 2–4 weeks was less than 40 mg for adult patients. The interval between treatment courses was often 2–3 months. All the patients were treated for 2 treatment courses.

2.5. Intralesion injection

Pingyangmycin was injected into the lesion using a 7-gauge needle in a fan-shaped direction. In the experimental group, triamcinolone acetonide was usually injected some time after the injection of pingyangmycin and especially into the hardened areas of pingyangmycin-induced fibrosis or inflammatory response. Later, pingyangmycin could be injected into the softened area again to destroy the remaining diseased lymphatic vessels. The total injection time for triamcinolone acetonide was about half of that of

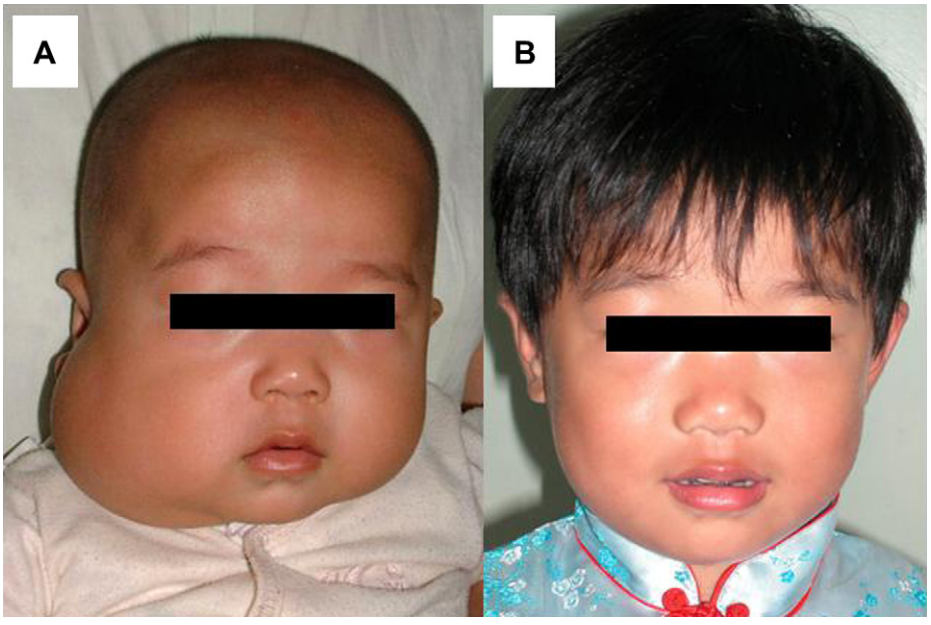

Fig. 1. Representative case of a 4-months boy with lymphatic malformations in the region of right face and neck. The patient was treated with pingyangmycin in combination with triamcinolone acetonide for 2 years. The facial appearance looks symmetric 5 years after treatment. A: Before treatment; B: after treatment.

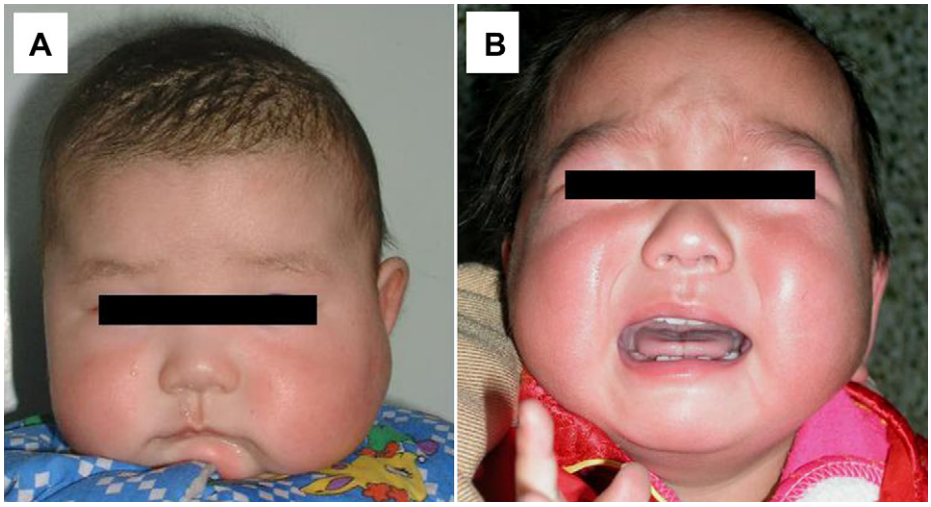

Fig. 2. Representative case of a 6-months boy with lymphatic malformations in the region of left face. The patient was treated with pingyangmycin in combination with triamcinolone acetonide. Facial appearance looks symmetric and shows no any sign of facial nerve injury 2 years after treatment. A: Before treatment; B: facial expression after treatment.

pingyangmycin. For macrocystic lesions the lymphatic fluid was aspirated prior to injection of pingyangmycin, while for microcystic lesions pingyangmycin was injected directly into the lesions.

2.6. Facial appearance estimation

All the patients had photos taken, lateral profile photos at oblique angle 15° and frontal photos at elevated angle 30° before treatment, after each treatment course and 2 years after treatment. As facial appearance is an important factor to contribute to person's self-confidence and social standing (Springer et al., 2012), facial appearance was estimated 2 years after the treatment by the patients themselves or the parents of the patients as either very satisfactory, satisfactory and non-satisfactory.

2.7. Measurement of lesion volume

MRI was taken for all the patients before treatment, after each treatment course and 2 years after treatment. The volumes of lesions were measured on the images of MRI and presented as percentage of pre-treatment volume.

3. Results

3.1. Improvement of facial appearance

Two years after the treatment, facial appearances of the patients in the experimental group were significantly improved and all graded as very satisfactory or satisfactory, better than that of the patients in the control group. There was no case showing any sign of facial nerve injury in either group during and after the treatment (Figs. 1–3).

3.2. Regression of lesion

The size of macrocystic and microcystic lesions in the experimental group and control group were both reduced significantly after treatment, with the regression of lesions in experimental

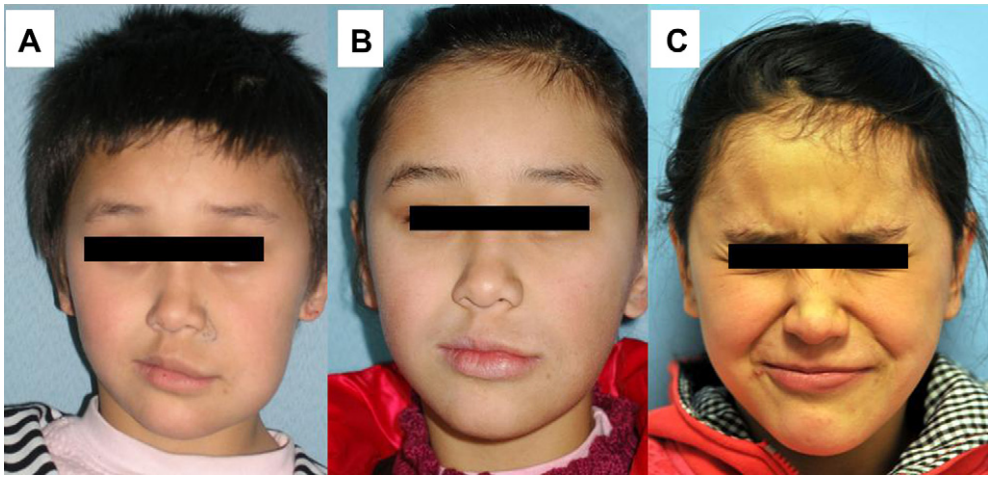

Fig. 3. Representative case of 9-years girl with lymphatic malformations in the region of left face with bilateral asymmetry after surgery. The patient was treated with pingyangmycin in combination with triamcinolone acetonide. Pingyangmycin was intralesionally injected monthly with the dose of 3 mg and a total of 15 months. Triamcinolone acetonide was intralesionally injected with the dose of 10 mg and interval of 2–3 months and a total of 8 times. Facial appearance was significantly improved without any sign of facial nerve injury 2 years after treatment. A: Before treatment; B: after treatment; C: facial expression after treatment.

group faster than that of control group. The volumes of lesions in experimental group were significantly smaller than that of control group at all time points (Table 1).

4. Discussion

In this study, we showed that intralesion injection of pingyangmycin in combination with triamcinolone acetonide or pingyangmycin alone could both effectively treat lymphatic malformations in the oral and maxillofacial region, however, pingyangmycin with triamcinolone acetonide showed better effects in involution of the lesions and improvement of facial appearance than that of pingyangmycin alone.

Enhancement of the therapeutic effects of pingyangmycin by triamcinolone acetonide on lymphatic malformations in oral and maxillofacial regions may be for the following reasons. First, triamcinolone acetonide may suppress the proliferation of both fibrous tissue and lymphatic endothelial cells in the lesions. Second, after injection into the hardened lesion, triamcinolone acetonide could especially reduce pingyangmycin-induced fibrosis or the inflammatory response to facilitate pingyangmycin to diffuse well in the harden lesion. Third, injection of triamcinolone acetonide into the hardened lesion, especially the areas with over-proliferated fibers, benefits the recovery of facial appearance as triamcinolone can promoter collagen degradation. In addition, another advantage of combination with triamcinolone acetonide is that triamcinolone acetonide may also help to prevent pulmonary fibrosis by decreasing the dose of pingyangmycin and the whole treatment time.

The traditional treatment of choice for lymphatic malformations has been surgical resection (Kang and Song, 2008; Bajaj et al., 2011), but the surgical procedure is often difficult due to the infiltrative nature of lymphatic malformations and their proximity to vital structures. In addition, the high postoperative complication rate, including wound infection and nerve injury, is a problem (Bloom et al., 2004). Emery and colleagues found an incidence of permanent postoperative nerve palsy of 33% in the cases of surgical extirpation (Emery et al., 1984). The cosmetic outcome after such radical surgery may be unacceptable, especially in children, because it is an essentially benign lesion. As an alternative to surgical extirpation, a multitude of sclerosing agents have been tried.

Pingyangmycin is a chemotherapeutic drug and belongs to the same family as bleomycin. Pingyangmycin has been used effectively for treatment of lymphatic malformations for several decades in China (Zheng et al., 2005; Bai et al., 2009). Pingyangmycin can induce cell death through breaking DNA double strands and inhibiting DNA synthesis (Tai et al., 1998). In the treatment of lymphatic malformations, pingyangmycin is believed to selectively destroy the lymphatic endothelial cells of the cystic wall, which is more sensitive to pingyangmycin than other cells. After pingyangmycin treatment, fibroblasts proliferate with increase of collagen fiber in the lumens and the cyst wall is thickened (Bai et al., 2009).

Although pingyangmycin is effective in treating lymphatic malformations, it has some side effects, such as hair loss, gastrointestinal reaction, skin pigmentation change, and severe effects such as pulmonary fibrosis or over dosage-caused instant shock. Therefore, attention should be paid in the treatment with pingyangmycin for lymphatic malformations. First, it is necessary to strictly restrict the dose of pingyangmycin and to examine the lungs of patients with X-ray after every treatment course. Second, concerning the infant patients, the interval time between treatment courses should be enough for the contraction of the lesions.

Table 1
Volumes of lesions after treatments (percentage of pre-treatment, mean ± SD)

Groups	Types of lesions	After 1st treatment course (%)	After 2nd treatment course (%)	2 Years (%)
Experimental group	Macrocystic	38.8 ± 6.6	18.3 ± 2.7	3.7 ± 0.3
	Microcystic	62.3 ± 5.9	35.2 ± 3.4	4.2 ± 0.4
Control group	Macrocystic	47.6 ± 5.3	26.7 ± 3.3	15.4 ± 1.3
	Microcystic	70.4 ± 8.7	51.9 ± 4.5	24.1 ± 3.1

5. Conclusions

Intralesion injection of pingyangmycin in combination with triamcinolone acetonide showed better effects than pingyangmycin alone for treatment of lymphatic malformations in the oral and maxillofacial region.

Conflict of interest

The authors declare no conflicts of interest.

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