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# How to use bleomycin A5 for infantile maxillofacial haemangiomas: Clinical evaluation of 82 consecutive cases

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ABSTRACT

*Objective:* Bleomycin A5 has been reported effective for infantile haemangioma (IH), but the usage and complications were described a little. We have used bleomycin A5 to treat maxillofacial IHs for 15 years. This paper describes the procedures to use bleomycin A5 and avoid its complications based on our clinical practices.

*Methods:* Bleomycin A5 (8 mg, powder) was mixed with 2% lidocaine (3 ml) and dexamethasone (1 ml, 5 mg), the mixture concentration is 2 mg/ml (bleomycin A5). The drug was given by multiple intralesional injections, with the dosage calculated according to the age of the patient and size of the lesion. Cautions were paid to the drug dosage and concentration, as well as the depth of injection. The patients were also given oral prednisone (2–5 mg/kg every other day) during proliferating stage.

*Results:* After treatment with bleomycin A5 in appropriate quantity and concentration, injecting depth, all haemangiomas involuted completely, with smaller lesions showing better recovery of skin colour and less scar formation, and no serious side effects happened.

*Conclusion:* Bleomycin A5 is an effective treatment for IHs. Oral prednisone is necessary for patients at proliferating stage.



## 1. Introduction

Infantile haemangiomas (IHs), the most common tumours of infancy, are benign vascular proliferations composed of densely packed capillaries, with endothelial cells and pericytes expanding in a lobular pattern. In contrast to vascular malformations, IHs are usually absent or inconspicuous at birth, and are instead characterized by a remarkably rapid postnatal proliferation and a slow spontaneous involution. Despite their ability to involute, it is difficult to assess the prognosis of some lesions. Even small haemangiomas can, at certain sites, have major aesthetic consequences. Larger lesions can progress to cause maxillofacial deformity, and lead to complications such as bleeding, ulceration, and obstruction. For these reasons, some clinicians (Muir et al., 2004; Omidvari et al., 2005; Pienaar et al., 2006) advise early intervention in IHs. Conservative therapies include pharmacotherapy, laser therapy, and regular consultation with the treating physician.

Bleomycin (BLM, also known as blenoxane) was first isolated as a $Cu^{2+}$-containing glycooligopeptide antibiotic from the culture medium of *Streptomyces verticullus*. It was soon found to be an anticancer agent, acting in the S phase of the cell cycle to cleave DNA strands and thereby obstruct cell proliferation, and has since become one of the most widely used cancer drugs (Shastri et al., 1971; Marek and Ostrowski, 1986; Ming, 2003). Recently, bleomycin A5 was found to be effective in treating haemangioma (Muir et al., 2004; Omidvari et al., 2005; Pienaar et al., 2006). Pienaar et al. used, as the sole agent, a locally injected dose of 0.3–0.6 mg/kg bleomycin. In 73% of patients, the haemangioma responded with a greater than 75% reduction in size. Other investigators have achieved similar results, suggesting that bleomycin A5 might be a viable new treatment for this disease.

Although these papers have provided clinical evidence that bleomycin A5 is effective for IH, little was described on how to use bleomycin A5 and prevent its side effects. Over the past 15 years, we have used bleomycin A5 as a sclerosing agent to treat IH. We found that bleomycin A5 has some side effects which are related to the quantity, concentration, injecting position, depth and times. In addition, bleomycin A5 cannot prevent IH from growing in the proliferative stage and, oral prednisone is necessary in this circumstance. We review our clinical experiences over the last 9 years in the present study.

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## 2. Materials and methods

### 2.1. Patients

We reviewed a total of 82 cases of IH treated with bleomycin A5 at the Peking University Hospital of Stomatology between 1997 and 2005. The patients (34 males and 48 females) presented within their first year of life, with the majority under 4 months of age (Fig. 1). The haemangiomas were generally less than 6 cm in diameter (Fig. 2).

### 2.2. Diagnostic criteria

IH was diagnosed on the basis of the patient's age, the appearance and extent of the lesion, and the appearance of the lesion on ultrasonography, magnetic resonance imaging (MRI), or colour Doppler. Care was taken to distinguish haemangiomas from vascular malformations. All haemangiomas were located on the head, face, or neck.

### 2.3. Application of bleomycin A5

The sclerosing mixture consisted of 3 ml 2% lidocaine, 8 mg bleomycin A5 (powder) and 5 mg dexamethasone (1 ml). The concentration was diluted to 1 mg bleomycin A5 in every 2–3 ml of solution for less than 5-month old children and special sites (eyelid and mucosa).

To minimize bleeding, the mixture was injected using a five-gauge needle at multiple sites adjacent to the lesion, in a radial pattern, until the surface of the tumours became a little pale. The dosage was calculated according to the age of the patient, size of the lesion and growth phases. If the haemangioma is too big and needs larger dose of drug, the total dose must be less than 0.3 mg/kg, and the concentration can be further diluted to 1 mg/4 ml to produce more solution for treating most of the lesion at the same time.

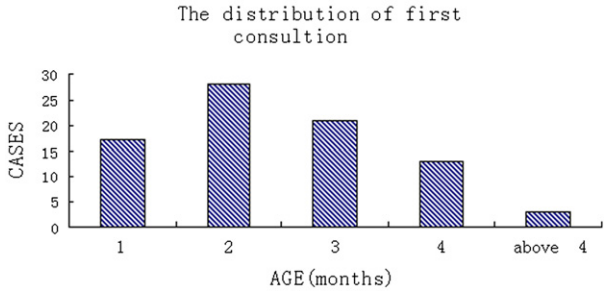


**Fig. 1.** Age of first consultation.

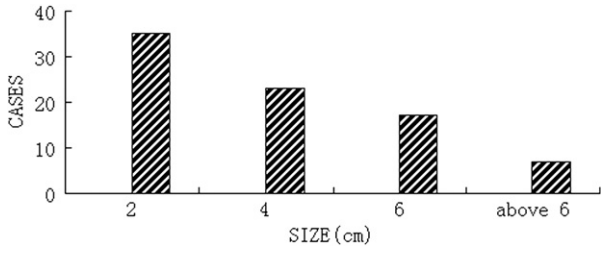


**Fig. 2.** Distribution of haemangioma size.

Generally, lesions less than 2 cm in diameter were given less than 1 mg bleomycin A5 per dose, and a total of five treatments were generally sufficient. Larger haemangiomas were given a dose of 3 mg bleomycin per injection before the age of 1 year. The interval between injections was 2–4 weeks with a total of no more than seven times in one therapeutic period. Subsequent treatment periods started 3 months later if further treatment was necessary. The total dose of bleomycin A5 for children was below 40 mg per treatment period.

The amount of bleomycin A5 is usually less than 0.5 mg when the baby is less than 3 months, the amount less than 1.5 mg before 6 months, less than 2 mg before 1-year old, less than 2.5 mg before 2 years old (the dosage according to age and lesion's size in Table 1).

Prednisone was prescribed at 2–5 mg/kg for 1 month or more in patients less than 7 months old. Children more than 7 months old were not usually given prednisone. If the lesion was greater than 4 cm in diameter, another course of prednisone treatment was needed.

### 2.4. Evaluation of bleomycin A5 treatment results

The size and blood flow of each haemangioma were evaluated using colour ultrasonography every 2 months. Changes in colour and scar formation were also evaluated every 2 months. The degree of satisfaction of family members was assessed according to the appearance of the patient at the completion of treatment.

## 3. Results

Treatment effectiveness was rated on a three-point scale (Table 2). Scale I means the lesions involuted completely, with restoration of normal function, and the colour of the skin and mucosa returned to normal. Scale II means the lesions involuted completely, but either a scar formed or the colour did not return completely to normal. Scale III means the lesions involuted only partially.

As summarized in Table 1, all haemangiomas involuted completely after treatment with bleomycin A5. However, haemangiomas greater than 2 cm in diameter tended to heal with more scar formation and a less satisfactory return to normal skin colour. Parental satisfaction with the results was highest when haemangiomas were less than 6 cm. but the degree of dissatisfaction was higher with a haemangioma more than 6 cm in diameter.

### 3.1. Size/colour and blood flow changes

The lesion usually begins to decrease after the third treatment, the height of lesion first decreases with colour fading, then the diameter decreases after the fourth to fifth injection and blood flow declines, but the blood flow signal disappears earlier than colour (usually after 5–6 injections in those whose diameter is less than 4 cm).

Examples of typical cases are shown in Figs. 3–5.

Complications included oedema, ulceration, gastrointestinal side effects, and others (Table 3). Oedema tended to appear

**Table 1**
Dosage according to lesion's size and patient's age.

| | Lesion size (diameter, cm) | | | Age (month) | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0–2 | 2–4 | 4–6 | >6 | <3 | <6 | <12 | <24 |
| Amount (mg) | 1 | 2 | 3 | >3 | 0.5 | 1.5 | 2 | 2.5 |

**Table 2**
Results of bleomycin A5 treatment for IHs.

| Size (cm) | 0–2 | | | 2–4 | | | 4–6 | | | Above 6 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Degrees | I | II | III | I | II | III | I | II | III | I | II | III |
| Cases | 21 | 14 | 0 | 8 | 15 | 0 | 5 | 12 | 0 | 0 | 7 | 0 |
| Percentage (%) | 60 | 40 | | 34.8 | 65.2 | | 28.8 | 71.2 | | | 100 | |
| Satisfaction (%) | | 88.6 | | | 82.6 | | | 88.2 | | | 57.1 | |

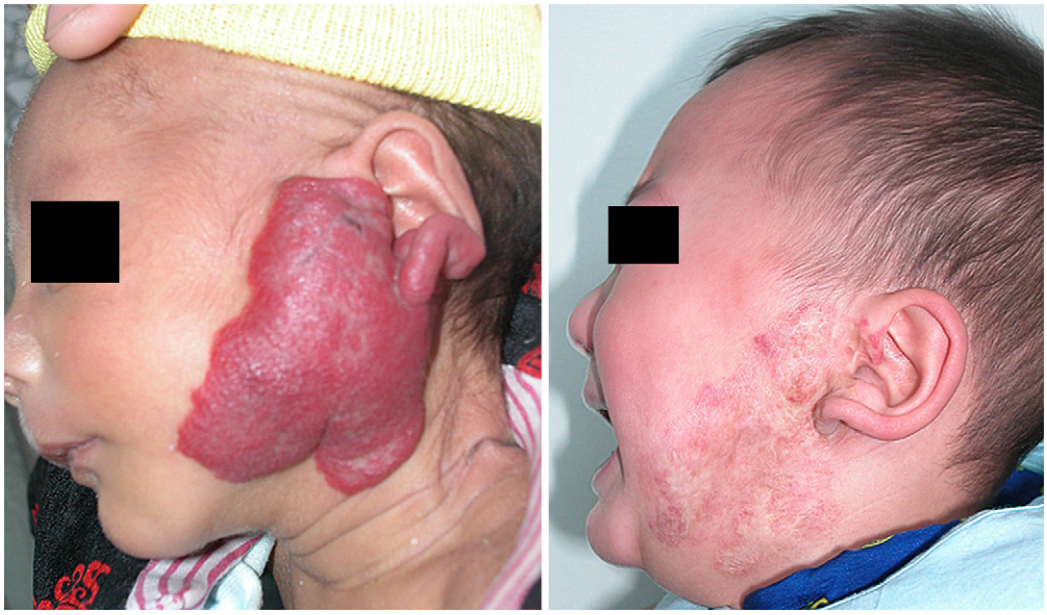

**Fig. 3.** This boy presented at 40 days of age with a haemangioma in the left parotid area. bleomycin A5 was given once every 4 weeks for a total of seven treatments. The haemangioma had completely involuted 1 year later. The overall response was Scale II.

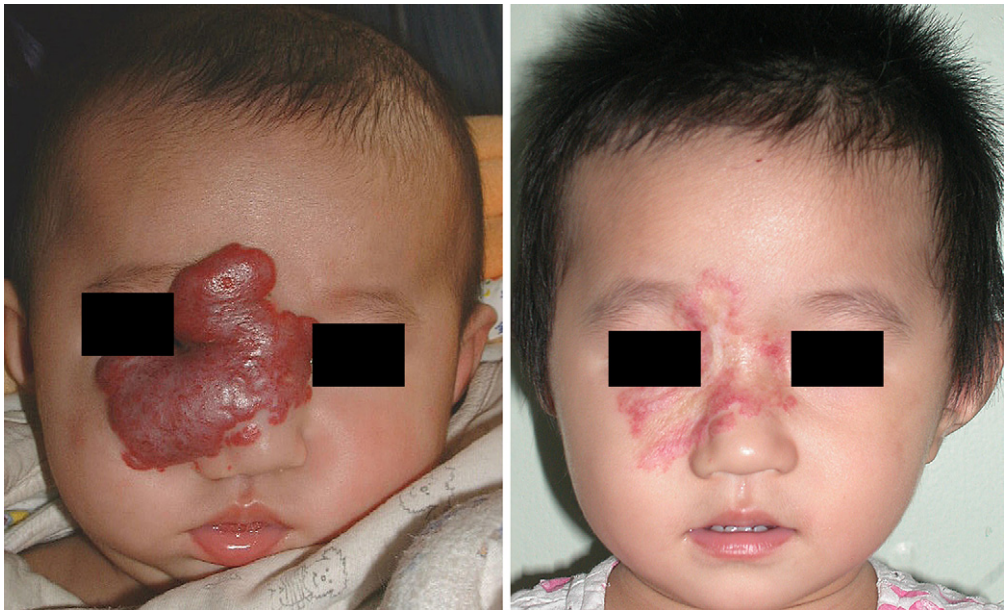

**Fig. 4.** This girl had a haemangioma at the centre of her face that involved the nose, right eyelid, and bilateral medial canthi. The haemangioma involuted 1 year and 5 months after bleomycin treatment. The overall response was Scale II.

approximately 4 h after injection and reached a peak 2 days later, disappearing after approximately 7 days (the longest being 15 days). Ulceration was apparent on the surface of haemangiomas after treatment, but generally healed and disappeared over a 15-day-period, with little scar formation. Gastrointestinal side effects included nausea and lack of appetite, usually occurring the day after treatment and disappearing by the third day.

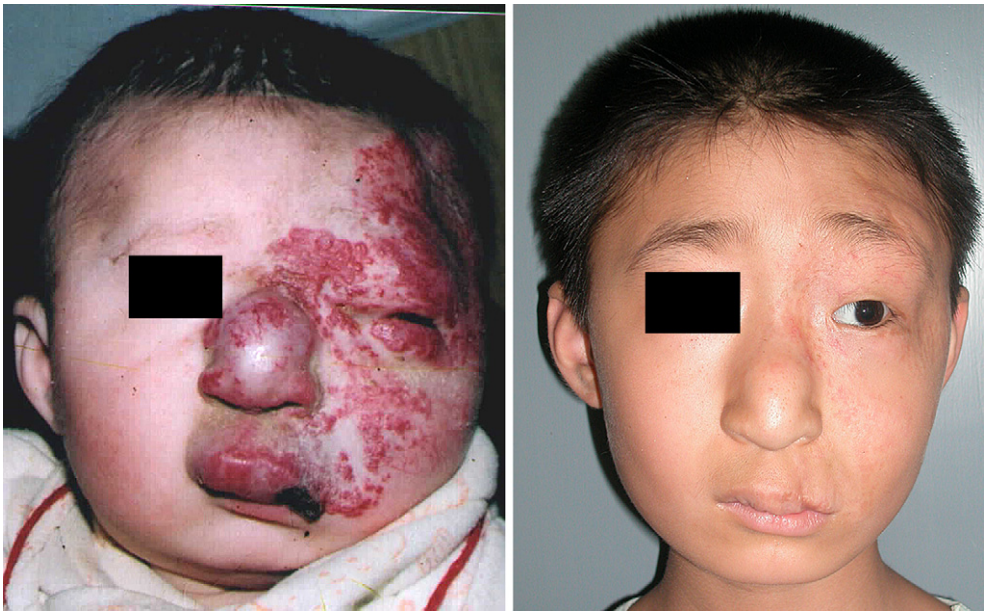

**Fig. 5.** A large haemangioma was present on the left face, involving the eyelid, nose, and upper lip. Bleomycin A5 was given once a month for 7 months. Four months later, treatment was resumed again. The total treatment period was 2 years and 4 months. Three years later, the haemangioma had completely involuted, with few scars, the overall response was Scale I.

**Table 3**
Complications of treatment.

| Complications | Oedema | Gastrointestinal | Ulceration | Pneumonic fibrosis | Others |
|---|---|---|---|---|---|
| Cases | 82 | 5 | 6 | 0 | 0 |

## 4. Discussion

IHs tend to be small lesions that can involute spontaneously. Unfortunately, some IHs not only fail to involute, but progress further, sometimes inducing deformity that interferes with organ function. No ideal method yet exists to predict the prognosis of IH. Whether or not these lesions should be treated remains controversial, but our clinical experience leads us to suggest that IH should be treated at an early stage to prevent further proliferation and complications.

Well-established treatments for IH include intralesional or systemic corticosteroids, interferon-α, laser therapy, cryotherapy, and surgical excision (Jensen et al., 1990; Khalid and John, 2000; Hohenleutner et al., 2001; Poetke et al., 2004; Vesnaver and Dovsak, 2006, 2009).

We observed that haemangiomas generally proliferated rapidly over the first 7 months of life, with the highest growth rates observed in the third and sixth months. Although bleomycin A5 effectively inhibited haemangioma proliferation, side effects limited the maximum dose of any single treatment, potentially leading to insufficient treatment of lesions greater than approximately 4 cm in diameter. We observed that the rapid proliferation of a few haemangiomas treated was not immediately controlled after bleomycin injection. In these cases, we used prednisone as adjuvant therapy. Although this regimen differs from that recommended by other authors (Muir et al., 2004; Omidvari et al., 2005; Pienaar et al., 2006), we were able to cure every IH we treated at our hospital.

We have achieved encouraging results by targeting angiogenesis in the haemangioma, using bleomycin A5 as a sclerosing agent, combined with oral prednisone in some cases. When should the drug be given? A small dose is enough to cure the disease in the small, early lesion. We therefore suggest that the drug is given as the lesion emerges. A 0.1–0.2 mg bleomycin A5 usually is enough for lesion in 0.5 cm diameter. The lesion will disappear after taking treatment for two or three times.

### 4.1. Dosage and concentration

The lesion size and the weight and age of the patient should be taken into account when bleomycin A5 is given. Only the defined amount was prescribed, prednisone was given orally and triamcinolone intralesionally if the lesion was too big.

The concentration is usually 0.5 mg/ml. High concentrations may lead to ulceration, especially in the area of lip/mucosa and eyelid, and scar may result.

### 4.2. Interval

The drug was given at an interval of 2–4 weeks under the age of 8 months. Two rapid growing stages of haemangioma are at 3 and 6 months, close observation and prescription are necessary during these periods. After 8 months, the review interval may be extended to 2 months because the haemangioma is usually entering the involutary stage.

### 4.3. Side effect and prevention

#### 4.3.1. Swelling

The irritating effect leads to the tissue swelling, and usually disappears 5–7 days later. No special treatment is needed.

#### 4.3.2. Ulceration

Ulceration often happens in children (under 3 months) and special sites. High concentration/large dosage and superficial injection are the main reasons.

*4.3.3. Gastrointernal reaction*

Nausea and vomiting are common, often happening in the second or third day after drug administration, lasting for 1–2 days. No special treatment is needed. Contaminants and large dosage are the main reasons.

*4.3.4. Fever*

Some patients may have fever, usually below 37.5°C. No special treatment is needed.

*4.3.5. Shock*

Large dosage and allergic to drug are the main reasons. The dosage must be controlled strictly. Very few children can be allergic to bleomycin A5, but they must stay in hospital for 1 h to be observed after treatment.

*4.3.6. Pneumonic fibrosis*

We had no cases of pneumonic fibrosis in using bleomycin A5, but care must be taken to discontinue injection after eight treatments. Treatment may continue after an interval of 2 months. Dexamethasone was given synchronously. Chest X-ray is necessary for patients after six treatment sessions.

Bleomycin A5 is believed to act on IHs by reducing the proliferation of vascular endothelial cells. The onset of involution is usually heralded by a change in colour, from bright red to purple or grey, which usually appears after several treatments. We found that lesions less than 2 cm in diameter could usually be effectively treated with five injections and a total amount of bleomycin A5 of less than 10 mg. However, when the diameter exceeded 4 cm, as many as eight injections and a total amount of more than 16 mg bleomycin were required. We observed that the therapeutic effect was correlated positively with the dosage of bleomycin A5 given, and inversely with the lesion size. Oedema and, less frequently, ulceration were the most common complications. However, serious side effects were rarely observed, presumably due to the lower dosage used in this treatment compared to chemotherapy.

## 5. Conclusion

We have evaluated the effectiveness of bleomycin A5 in 82 cases of IH, and found that all haemangiomas responded by involuting completely, with better recovery of skin colour and less scar formation when the lesion size was small. Our results suggest that IHs can be effectively treated with bleomycin A5 injection. Attention to the methods and details we describe should help to avoid side effects and complications.

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