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Role of intralesional bleomycin and intralesional triamcinolone therapy in residual haemangioma following propranolol

V. Pandey[1], P. Tiwari[2], S. P. Sharma[1], R. Kumar[1], O. P. Singh[3]

[1]Department of Paediatric Surgery, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India; [2]Department of Oral and Maxillofacial Surgery, Faculty of Dental Sciences, Institute of Medical Sciences, Banaras Hindu University, Varanasi, UP, India; [3]Department of Medicine, Institute of Medical Sciences, Banaras Hindu University Varanasi, UP, India

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Abstract. With the emergence of propranolol as the first choice of treatment for problematic infantile haemangioma at many centres, the number of patients with a partial or non-response to propranolol has also been growing. This study investigated the role of intralesional bleomycin and triamcinolone in patients with residual disease following propranolol therapy for infantile haemangioma. Sixty-seven patients with residual haemangioma were assigned randomly to receive either intralesional bleomycin (group A, $n = 36$) or intralesional triamcinolone (group B, $n = 31$). The response to treatment and adverse effects were assessed in both groups. All patients received at least four doses and a maximum of six doses of the assigned drug. In group A (mean follow-up 9.38 months), 47.2% had an excellent response and 44.4% a good response. In group B (mean follow-up 7.42 months), 25.8% had an excellent response and 48.4% a good response. There was no difference in overall response between the groups ($P = 0.074$). Among patients who were initially non-responders to propranolol, bleomycin showed a better response than triamcinolone ($P = 0.037$). This may be due to an overlap in the mechanism of action of propranolol and triamcinolone. Thus, intralesional bleomycin should be preferred in patients with no initial response to propranolol therapy, while bleomycin or triamcinolone can be used in patients with a partial response to propranolol therapy, as they have equal efficacy.

Key words: haemangioma; triamcinolone; bleomycin; intralesional therapy.

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Infantile haemangioma (IH) is the most common vascular tumour in children[1]. In contrast to other tumours, they can regress spontaneously after proliferation. However, in spite of spontaneous regression in many cases, they are a significant cause of morbidity in children because of complications such as ulceration, bleeding, itching, and scarring[1]. Currently

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available treatment modalities include systemic or intralesional corticosteroids, surgery, chemotherapeutic agents (bleomycin, vincristine, alpha-interferon), laser therapy, or a combination of these. Each option has some limitations due to adverse effects. Multiple studies have established the therapeutic role of propranolol in IH since the report of Leaute-Labreze et al. in 2008[2–4]. However, some patients are either partial responders or non-responders to this treatment and require additional therapeutic interventions following propranolol therapy.

Intralesional treatment options such as bleomycin and triamcinolone have shown excellent results in IH. Hence, the present study was performed to assess the role of intralesional bleomycin and triamcinolone in patients with a partial response or non-response to initial propranolol therapy.

Materials and methods

The study was conducted in the Department of Paediatric Surgery and Oral Surgery from June 2016 to May 2017 and was approved by the institutional ethics committee. Patients with problematic IH in the head and neck region, who were either non-responders or partial responders to previous propranolol treatment, were included in the study. Non-responders were defined as patients who had received propranolol at a dose of 2 mg/kg body weight in three divided doses for at least 3 months and who had regression of less than 25%. Partial responders werclinicale defined as those who had taken propranolol for at least 6 months and had a clinical response of between 25% and 50%.

All patients underwent baseline haemogram, blood sugar, and renal function tests. The patients were assigned randomly to treatment with either intralesional bleomycin (group A) or intralesional triamcinolone (group B) using a computer-generated random numbers table. Group A patients received intralesional bleomycin at a dose of 0.5 IU/kg (maximum of 15 IU in a single dose), repeated after 4 weeks on an outpatient basis. After each injection, the patients were observed for 24 hours for any adverse reactions. Group B patients received intralesional triamcinolone at a dose 2 mg/kg (maximum of 60 mg in a single dose), repeated after 4 weeks. Patients, who did not attend follow-up at $\geq$1 month after the completion of treatment were excluded from the study. Patients in both groups received at least four doses and a maximum of six doses of the assigned drug. All of the patients were serially photographed before the start of treatment and then at each monthly visit. The response was assessed clinically using these photographs, by two senior residents who were blinded to the group allocation. Each patient was categorized as an 'excellent responder' in the case of >50% regression of the lesion, 'partial responder' in the case of a 25–50% response, or 'non-responder' in the event of less than 25% regression of the lesion.

Data were coded and summarized using SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). The Student *t*-test/Mann–Whitney *U*-test was used to compare mean/median values in the quantitative data analysis, while the χ^2 test was used for qualitative data. A *P*-value <0.05 was taken as significant.

Results

A total of 74 patients were screened and assessed to determine eligibility for enrolment. Of these, 67 patients fulfilled the eligibility criteria and were included in the study. Nine patients were excluded. These patients either did not give consent for intralesional therapy or did not want any further treatment. Thirty-six patients were assigned to group A and 31 to group B. The mean age at initiation of therapy was 24.86 $\pm$ 3.109 months in group A and 27.87 $\pm$ 4.105 months in group B. The male to female ratio in group A was 1.4:1 and in group B was 1.8:1. The duration of previous treatment with propranolol was 4.86 $\pm$ 2.113 months in group A and 5.00 $\pm$ 1.983 months in group B. In group A, 44.4% of patients (16 out of 36) were previous non- responders to propranolol and 55.6% (20 out of 36) were partial responders. In group B, 41.9% of patients (13 out of 31) were non-responders and 58.1% (18 out of 31) were partial responders to previous propranolol therapy (Table 1).

Following treatment with intralesional bleomycin, 17 patients (47.2%) in group A showed an excellent response, 16 (44.4%) a partial response, and three (8.3%) did not respond. In group B patients, who received intralesional triamcinolone, eight (25.8%) were excellent responders, 15 (48.4%) were partial responders, and eight (25.8%) were non-responders. The overall response to treatment of the residual haemangioma did not differ between the bleomycin and triamcinolone groups ($P = 0.074$, Table 2).

The mean duration of follow-up after the completion of treatment was 9.38 $\pm$ 4.98 months in group A and 7.42 $\pm$ 3.34 months in group B. Overall, group A patients received 5.14 $\pm$ 0.72 doses of bleomycin, whereas group B patients received 5.67 $\pm$ 0.84 doses of triamcinolone. The mean duration of treatment in group A was 20.50 $\pm$ 3.00 weeks, and in group B it was 21.52 $\pm$ 3.56 weeks.

Overall, among the 67 patients with a partial response or no response to propranolol, 37.3% ($n = 25$) had excellent response (Figs 1 and 2) and 46.3% ($n = 31$) had a partial response (Figs 3 and 4) to intralesional therapy.

Two patients developed a superficial ulcer, one following the fourth dose and the other following the sixth dose of bleomycin. Both responded to conservative treatment and did not require any other intervention. Importantly, none of the patients treated with triamcinolone had a similar reaction.

Out of the 16 patients in group A who were initially non-responders to propranolol, eight (50.0%) had an excellent response. In group B, only one patient (7.7%) showed an excellent response among the 13 patients who were initially non-responders to propranolol. Overall, the response to bleomycin was better than the response to triamcinolone among patients who were initially non-responders to propranolol ($P = 0.037$) (Table 3).

Table 1. Initial response to propranolol therapy in the two groups.

Response to propranolol	Group A (Bleomycin)	Group B (Triamcinolone)	*P*-value
Partial response	20 (55.6%)	18 (58.1%)	0.086
No response	16 (44.4%)	13 (41.9%)	
Total	36	31	

Table 2. Overall response in groups A and B.

Response	Group A (Bleomycin)	Group B (Triamcinolone)	*P*-value
Excellent response	17 (47.2%)	8 (25.8%)	0.074
Good response	16 (44.4%)	15 (48.4%)	
No response	3 (8.3%)	8 (25.8%)	
Total	36	31	

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