Clinical Profile of Paediatric Hemangiomas, Response to Oral Propranolol, and Comparison of Intralesional Bleomycin and Triamcinolone in Propranolol Non Responders at a Tertiary Care Center in North India

Gulab Dhar Yadav, Shraddha Verma, Ashish Varshney, Adiveeth Deb

Background: A paradigm shift has occurred regarding the treatment of cutaneous hemangiomas over the last few years, from an open surgical approach to a conservative or minimally invasive approach. There are various treatment modalities described, and response to them is variable and unpredictable. This study was conducted to study the clinical profile of children with uncomplicated cutaneous hemangiomas, their response to oral propranolol, and compare intralesional bleomycin and intralesional triamcinolone among nonresponders to propranolol.

Materials and Methods: A trial was conducted among 158 children <12 years with cutaneous hemangiomas from January 2019 to October 2020 in Kanpur, Uttar Pradesh. Based on the response to propranolol, partial/nonresponders were later assigned randomly to either receive intralesional bleomycin ($n = 30$) or intralesional triamcinolone ($n = 29$). Response to treatment and complications were assessed in two groups. All children were followed up for 6 months.

Results: Of 158 children, complete response to propranolol was found in 99 (62.7% [95% confidence interval (CI): 54.6%–70.1%]) children. Partial and no response was found in 33 (20.9% [95% CI: 15.0%–28.2%]) and 26 (95% CI: 16.5% [11.2%–23.4%]) children, respectively. In the bleomycin group, 66.7%, 23.3%, and 10.0% of patients showed excellent, good, and poor response, respectively, and in the triamcinolone group, 27.6%, 24.1%, and 48.3% showed excellent, good, and poor response, respectively ($P = 0.002$). However, there was no significant difference between them in terms of complications.

Conclusion: Intralesional bleomycin was found to be a better drug in terms of response compared to triamcinolone. There are no significant differences in complications between them. Further studies are needed to further evaluate the combined efficacy of bleomycin with triamcinolone and other treatment modalities.

Keywords: Cutaneous hemangioma, intralesional bleomycin, intralesional triamcinolone, propranolol

INTRODUCTION

Vascular anomalies are congenital lesions of abnormal vascular development. They are classified as vascular tumors and malformations, by the International Society for the Study of Vascular Anomalies in 1996. Infantile hemangioma (IH) is the most common vascular anomaly, occurring in 1-2% of infants. IHs are characterized by rapid proliferation during the first year of life followed by involution, which usually begins by 18 months. However, some IHs may have prolonged involution or persistent growth.

Methods:

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Conclusion: Intralesional bleomycin was found to be a better drug in terms of response compared to triamcinolone. There are no significant differences in complications between them. Further studies are needed to further evaluate the combined efficacy of bleomycin with triamcinolone and other treatment modalities.

Keywords: Cutaneous hemangioma, intralesional bleomycin, intralesional triamcinolone, propranolol

Address for correspondence: Dr. Adiveeth Deb, Department of General Surgery, GSVM Medical College, Kanpur, Uttar Pradesh, India. E-mail: adiveeth@gmail.com
most common vascular tumor in children, characterized by pathologic endothelial cell proliferation.[2] The prevalence of IH is 1.1%–2.6% in term neonates, globally, and 0.1%–0.28% in India.[3]

In contrast to other tumors, they can regress spontaneously after proliferation. Historically, hemangiomas were managed with close observation over their lifecycle.[4] 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, and hence, around 40% of children require further intervention.[2]

The currently available treatment modalities include systemic or intralesional corticosteroids, chemotherapeutic agents (bleomycin, vincristine, and alpha-interferon), laser therapy, surgery, or a combination of these. Each option has some limitations due to adverse effects.[5-8]

A paradigm shift has occurred regarding the treatment of hemangiomas over the past few years. The therapeutic role of propranolol as the first line of treatment in IH has been established by various studies, since its inception in 2008.[9-11] However, some patients are either partial responders or nonresponders to this treatment and require additional therapeutic interventions following propranolol therapy.

Some intralesional therapies for IH include corticosteroids, cyclophosphamide, bleomycin, and interferon. There have been various studies suggesting beneficial effects of intralesional therapy of corticosteroids and bleomycin in IHs.[12-15] However, studies comparing the intralesional treatment of corticosteroids and bleomycin are lacking, particularly in this part of the country. Hence, this study was conducted to study the clinical profile of children with uncomplicated cutaneous hemangioma and to compare the efficacy of intralesional bleomycin and intralesional triamcinolone among the nonresponders to propranolol therapy, in terms of size reduction and adverse effects.

**Materials and Methods**

A nonrandomized controlled trial was conducted in the Department of General Surgery of LLR and Associated Hospitals, GSVM Medical College, Kanpur, from January 2019 to October 2020 among the children aged 0–12 years with cutaneous hemangioma. The study was conducted after obtaining approval from the Institute Ethics Committee and consent from the participants. All children aged 0–12 years with uncomplicated cutaneous hemangiomas presenting to the outpatient department or admitted in the Department of General Surgery were included in the study. Children with infected hemangiomas, hemangiomas of the solid organs, contraindication to oral propranolol (bronchial asthma, cardiac anomalies, and diabetes mellitus), and who had taken any previous treatment for the same lesion (oral/intralesional) were excluded from the study.

Data were collected using a proforma which consisted of the sociodemographic characteristics, natal history, and the clinical history (size, site, and color of the lesion at the time of the presentation). All patients were then given oral propranolol at a dose of 2 mg/kg body weight in two divided doses for 3–6 months. Response was assessed after every month in terms of regression in size of the lesion (maximum diameter).

A proper history, clinical examination, and baseline investigations were carried out for all patients before initiation of propranolol therapy to look for any preexisting contraindications. Although the diagnosis of hemangioma was mostly clinical, ultrasonography with color Doppler was done in cases with diagnostic uncertainty.

Based on the clinical response to oral propranolol, children were divided into three groups:

- **Responders**: More than 50% regression in size of the lesion after treatment
- **Partial responders**: 25%–50% regression in size of the lesion after 6 months of treatment
- **Nonresponders**: <25% regression in size of the lesion after 3 months of treatment.

Only partial responders and nonresponders were taken up for intralesional therapy. Partial responders and nonresponders were allotted either to Group A or Group B through simple random sampling.

- **Group A**: Children received intralesional bleomycin at a dose of 0.5 IU/kg (maximum of 15 IU in a single dose), repeated after 3–6 weeks on an outpatient basis. After each injection, children were observed for 24 h for any adverse reactions.
- **Group B**: Children received intralesional triamcinolone at a dose of 2 mg/kg (maximum of 60 mg in a single dose), repeated after 3–6 weeks on an outpatient basis.

Patients were followed up at 1, 3, and 6 months after the initiation of intralesional therapy. A thorough history was taken and a proper examination was done to look for any adverse effects of therapy. The maximum diameter of the lesion was noted at every follow-up.

Adequate treatment was given for any adverse effects if developed. The next dose of the intralesional drug (bleomycin/triamcinolone) was also administered at follow-up.

At the end of 6 months of intralesional therapy, regression in size of the lesion was noted and compared to the size at the initiation of treatment. Based on the percentage regression in size, the response was divided into three groups:
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• Excellent response: More than 75% regression in the size of lesion
• Good response: 25%–75% regression in the size of lesion
• Poor or no response: <25% regression in the size of lesion.

Adverse effects following intralesional therapy were also tabulated and compared in both the groups. The efficacy of bleomycin and triamcinolone was then compared in terms of clinical response and incidence of adverse effects after intralesional therapy.

**Statistical analysis**

Data were collected, tabulated, and analysed using the Statistical Package for the Social Sciences (SPSS®; SPSS Inc., IBM Corp., Armonk, NY, USA), version 21.0, on an IBM compatible computer. Categorical variables such as gender and site of lesion were expressed as frequency and percentages. Continuous variables such as age and size of the lesion were presented as mean (standard deviation). The response rate and complications were expressed as percentages with a 95% confidence interval. Chi-square test was used to compare the baseline characteristics and the response rate between the two intervention groups. Independent samples t-test was used to compare the size of the lesion before the intervention between the groups. *P* <0.05 was considered statistically significant.

**RESULTS AND OBSERVATIONS**

Out of 167 children with cutaneous hemangioma, 158 children were eligible for oral propranolol and were included in the study [Figure 1]. The mean age of the children was 38 (8.4) months and the male-to-female ratio was 1:1.3. About 68.4% of children were term babies and at the time of enrolment around 74% of children had head-and-neck lesions. The mean size of the lesion was found to be 4 (2.9) cm with 61.0% of children presenting with a size of 2–5 cm. Cutaneous disfigurement was reported more among patients (76.6%) [Table 1].

Complete response to propranolol was found in 99 (62.7% [95% confidence interval CI: 54.6%–70.1%]) children. Partial and nonresponse was found in 33 (95% CI: 20.9% [15.0%–28.2%]) and 26 (95% CI: 16.5% [11.2%–23.4%]) children, respectively.[Table 2] For further evaluation, total partial and nonrespondents to propranolol were divided into two groups. Comparison of baseline characteristics between the two groups is shown in Table 3. The two groups were comparable in terms of age, gender, natal history, site of the lesion, and the size of the lesion before the start of therapy. The mean dose of bleomycin was 3.1 (0.4) IU and the mean dose of triamcinolone was 3.8 (1.8) mg and the difference was found to be statistically significant (*P* = 0.039) mg. The mean duration of treatment among Group A was found to be 20.5 (3.0) weeks and in Group B was 21.5 (3.6) weeks but was not significant statistically (*P* = 0.238).

Among 30 children in Group A, 66.7%, 23.3%, 10.0% of Group A patients showed excellent, good, and poor response, respectively following the intervention [Supplementary Figures 2,3,6,7,11,12,13]. Similarly, among 29 children in Group B, 27.6%, 24.1%, and 48.3% showed excellent, good, and poor response, respectively [Supplementary Figures 1,4,8,9,10]. Excellent response was found to be significantly higher among the children who received bleomycin when compared to the children who received triamcinolone (*P* = 0.002) [Table 4].

### Table 1: Sociodemographic characteristics of children with cutaneous hemangioma on propranolol therapy in general surgery (n=158)

| Characteristics       | Frequency, n (%) |
|-----------------------|------------------|
| Age groups (years)    |                  |
| <1                    | 61 (38.6)        |
| 1-3                   | 32 (20.3)        |
| 4-5                   | 30 (18.9)        |
| 6-8                   | 21 (13.3)        |
| 9-12                  | 14 (8.9)         |
| Gender                |                  |
| Female                | 89 (56.3)        |
| Male                  | 69 (43.7)        |
| Natal history         |                  |
| Preterm               | 32 (20.3)        |
| Term                  | 108 (68.4)       |
| Postterm              | 18 (11.4)        |
| Site of lesion        |                  |
| Head and neck         | 116 (73.4)       |
| Extremities           | 15 (9.5)         |
| Trunk                 | 27 (17.1)        |
| Presenting complaints |                  |
| Cosmetic disfigurement| 121 (76.6)       |
| Feeding problems      | 8 (5.1)          |
| Visual disturbances   | 24 (15.1)        |
| Nasal obstruction     | 5 (3.2)          |
| Size of lesion (cm)   |                  |
| <2                    | 21 (13.3)        |
| 2-5                   | 96 (61.8)        |
| >5                    | 41 (25.9)        |

### Table 2: Response to propranolol among children with cutaneous hemangioma on propranolol therapy in general surgery (n=158)

| Response      | Frequency (n) | Percentage (95% CI) |
|---------------|---------------|---------------------|
| Respondents   | 99            | 62.7 (54.6-70.1)    |
| Partial       | 33            | 20.9 (15.0-28.2)    |
| Nonrespondents| 26            | 16.5 (11.2-23.4)    |

CI: Confidence interval
In regard to complications following treatment, there was no significant difference in complication rates between the two groups (40.0% vs. 44.8%; \( P = 0.710 \)). Hyperpigmentation (23.2%) was the common complication among the children who received bleomycin and redness (27.6%) was the common complication among the children in triamcinolone group [Table 5].

**DISCUSSION**

IH is one of the causes of great pain and apprehension for most parents and it is one of the frequent problems of childhood encountered in clinical practice. Nevertheless, the chronic course of the disease and the associated complications add to the problem. Various treatment modalities are available and it depends on the type, location, and size of the lesions, the patient’s status, and the complications following treatment. In addition, the response to the different treatment modalities is variable and unpredictable. Hence, it becomes imperative to study the best available management options in terms of response to treatment and lesser complications.

Our study found that the mean age of the children was 38 ± 8.4 months with 38.6% of the children being infants. Our results are in line with a study by Leung et al.\[^{16}\] which stated that hemangiomas often appear in the first few weeks of life as areas of pallor, followed by telangiectatic or faint red patches. They then grow rapidly in the first 3–6 months of life. Rapid growth during the neonatal period (birth to 4 week) is the historical hallmark of IHs.

The occurrence was more common among the females with male-to-female ratio of 1:1.3. Prospective studies in the United States and Europe have shown that infants who develop IHs are more likely to be females (female-male-ratio of 1.4:1–3:1).\[^{17-20}\] A retrospective study from India had also found a female predominance of 2.3:1, which is in line with our study findings. The detailed cause of the female preponderance is not yet understood. However, several studies have suggested that estrogen (E2) can attribute to the female preponderance and the E2 signaling is important in angiogenesis.\[^{21}\] Previous reports had shown that the level of E2 in healthy children was significantly lower than that in IH patients, and estrogen receptors could be found in the hemangioma tissue.\[^{22,23}\]

Various studies have shown that propranolol is an effective first-line treatment for IH with minimal side effects with response rates ranging from 60% to 80%.\[^{7,8}\] With the increase in the number of children being treated with propranolol, the number of partial responders and nonresponders has also been growing. Our study found that complete response to propranolol was found in 99 (62.7% [95% CI: 54.6%–70.1%]) children. Partial and nonresponse was found in 33 (20.9% [95% CI: 13.4–32.1%]) children.

| Complications | Frequency (n) | Percentage |
|---------------|--------------|------------|
| Group A (bleomycin) | 12 | 40.0 (23.2-59.2) |
| Hyperpigmentation | 7 | 23.3 |
| Hypopigmentation | 1 | 3.3 |
| Hypertrophic scar | 2 | 6.7 |
| Superficial ulcer | 2 | 6.7 |
| Group B (triamcinolone) | 13 | 44.8 (26.9-64.0) |
| Redness | 8 | 27.6 |
| Lipatrophy | 2 | 6.9 |
| Hypertrichosis | 1 | 3.4 |
| Sterile abscess | 2 | 6.9 |

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**Table 3: Baseline characteristics of children with cutaneous hemangioma (partial/nonresponders to propranolol) between the intervention groups (n=59)**

| Characteristics          | Intervention arm | \( P \) |
|--------------------------|------------------|--------|
|                          | Group A \((n=30), n (%)\) | Group B \((n=29), n (%)\) |
| Age (years)              |                  |        |
| <1                       | 3 (10.0)         | 4 (13.8)| 0.455 |
| 1-3                      | 3 (10.0)         | 1 (3.5) |        |
| 4-5                      | 7 (23.3)         | 8 (27.6) |        |
| 6-8                      | 5 (16.7)         | 9 (31.0) |        |
| 9-12                     | 12 (40.0)        | 7 (24.1) |        |
| Gender                   |                  |        |
| Male                     | 15 (50.0)        | 20 (69.0) | 0.138 |
| Female                   | 15 (50.0)        | 9 (31.0) |        |
| Natal history            |                  |        |
| Preterm                  | 11 (36.7)        | 5 (17.2) | 0.208 |
| Term                     | 17 (56.6)        | 20 (69.0) |        |
| Postterm                 | 2 (6.7)          | 4 (13.8) |        |
| Site of lesion           |                  |        |
| Head and neck            | 19 (63.3)        | 15 (51.7) | 0.564 |
| Extremities              | 6 (20.0)         | 6 (20.7) |        |
| Trunk                    | 5 (16.7)         | 8 (27.6) |        |
| Size before start of therapy, mean±SD | 3.2±1.3 | 2.8±1.4 | 0.273 |

**Table 4: Response to intervention between the groups \((n=59)\)**

| Response          | Intervention arm | \( P \) |
|-------------------|------------------|--------|
|                   | Group A \((n=30), n (%)\) | Group B \((n=29), n (%)\) |
| Excellent         | 20 (66.7)        | 8 (27.6) | 0.002 |
| Good              | 7 (23.3)         | 7 (24.1) |        |
| Poor              | 3 (10.0)         | 14 (48.3) |        |
| Dose of the drug, mean±SD (IU/mg) | 3.1±0.4 | 3.8±1.8 | 0.039 |
| Duration of treatment, mean±SD (weeks) | 20.5±3.0 | 21.5±3.6 | 0.238 |

**Table 5: Complications between the intervention groups following therapy**

| Complications         | Frequency (n) | Percentage |
|-----------------------|--------------|------------|
| Group A (bleomycin)   | 12 | 40.0 (23.2-59.2) |
| Hyperpigmentation     | 7 | 23.3 |
| Hypopigmentation      | 1 | 3.3 |
| Hypertrophic scar     | 2 | 6.7 |
| Superficial ulcer     | 2 | 6.7 |
| Group B (triamcinolone) | 13 | 44.8 (26.9-64.0) |
| Redness               | 8 | 27.6 |
| Lipatrophy            | 2 | 6.9 |
| Hypertrichosis        | 1 | 3.4 |
| Sterile abscess       | 2 | 6.9 |
15.0%–28.2%) and 26 (95% CI: 16.5% [11.2%-23.4%]) children, respectively. It is also noteworthy to mention that the study by Betlloch-Mas et al.\cite{24} showed a similar response to propranolol (70%) as did our study findings. Even more, the response to propranolol was almost 100% in a study conducted by Leaute-Labreze et al.\cite{25} One another interesting finding in our study is that 39.4% of the responders were <1 year of age, and 42.3% of the nonresponders to propranolol were in the age group of 8–12 years. Thus, it can be stated that response to oral propranolol decreased with increasing age of initiation of treatment. Studies state that propranolol is effective during the proliferative phase of growth with vasoconstriction, inhibition of angiogenesis, and induction of apoptosis as the possible mechanisms. Hence when it is started at the proliferative phase, it inhibits the growth of the lesion and promotes the regression. It may be that the children who did not benefit from the therapy had passed this proliferative stage.\cite{25}

With regard to response to treatment among the partial/nonresponders to propranolol, it was found that the excellent response was significantly higher among the children in the bleomycin group when compared to the triamcinolone group. Even on subgroup analysis, among the partial responders and the nonresponders, the response rate was significantly higher among the bleomycin group. Various studies had established the efficacy of intralesional bleomycin in hemangioma. A study by Piennar et al. had reported a response of more than 75% in about 65% of their cases.\cite{26} Similarly, an excellent response to bleomycin with minimal adverse reactions has been reported by other authors.\cite{27,28}

Bleomycin acts by exerting a nonspecific inflammatory reaction through a local sclerosing effect on the endothelial cells. A study by Pandey et al. had reported the same response rate for bleomyicn where 47.2% had an excellent response and 44.4% had a good response to treatment with bleomycin.\cite{29} Not surprisingly, the mean dose of the drug was also significantly higher for the children in triamcinolone group. Even though bleomycin was found to be more effective in terms of response among the two drugs, the safety profile was equal among both the drugs. Even triamcinolone was better in terms of response in our study. Gangopadhyay et al. reported an overall response rate of 88.6% with the administration of intralesional triamcinolone, and no side effects occurred.\cite{30} Similarly, other authors have reported excellent results of intralesional triamcinolone with minimal adverse effects.\cite{31,32}

**Conclusion**

Intralesional bleomycin has a better response among children with partial/no response to oral propranolol when compared to intralesional triamcinolone. It is also important to note that there could be an overlap in the mechanism of action of triamcinolone and propranolol when compared to bleomycin because it is found that those who are nonresponders to propranolol had poor responses to triamcinolone. Hence, bleomycin could be used to provide additional benefits to patients on propranolol. However, further studies are needed to prove the mechanism and thus siding in the effective management of the children with IH.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/them consent for his/her/them images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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**Supplementary Figure**

**Supplementary Figure 1:** A 11-year-old male with hemangioma over left angle of mouth. The patient was a non-responder to oral propranolol. But then, showed good response to intralesional triamcinolone.

**Supplementary Figure 2:** A 3-month-old female with hemangioma over scalp. The patient was a non-responder to oral propranolol. But then, showed good response to intralesional bleomycin. However, the patient developed a scar at the site of lesion.

**Supplementary Figure 3:** Group A patient with forehead lesion; showing a good response to intralesional bleomycin: (a) before treatment; (b) after treatment.

**Supplementary Figure 4:** Group B patient with lesion over upper lip; showing a good response to intralesional triamcinolone: (a) before treatment; (b) after treatment.

**Supplementary Figure 5:** 4-month-old male with haemangioma over right side of neck. Patient was a non-responder to oral propranolol. But then, showed good response to intralesional bleomycin.

**Supplementary Figure 6:** Group A patient with an lesion over left ear; showing excellent response to intralesional bleomycin: (a) before treatment; (b) after treatment.

**Supplementary Figure 7:** 9-year-old female with haemangioma over right side of forehead. Patient was a non-responder to oral propranolol. But then, showed excellent response to intralesional bleomycin.

**Supplementary Figure 8:** 2.5-year-old female with haemangioma over left forearm. Patient was a non-responder to oral propranolol. But then, showed good response to intralesional triamcinolone.
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Supplementary Figure 9: Group B patient with right post auricular lesion; showed an excellent response to intralesional triamcinolone: (a) before treatment; (b) after treatment.

Supplementary Figure 10: 2 year old female with haemangioma over dorsum of nose. Patient was a partial responder to oral propranolol. But then, showed excellent response to intralesional triamcinolone.

Supplementary Figure 11: 1.5 year old male with haemangioma over left cheek. Patient showed partial response to oral propranolol and then showed excellent response to intralesional bleomycin. However, patient developed hyperpigmentation after disappearance of lesion.

Supplementary Figure 12: 12 year old female with haemangioma over upper lip and left angle of mouth. Patient was a non responder to oral propranolol. But then, showed excellent response to intralesional bleomycin.

Supplementary Figure 13: 11 year male patient with haemangiomas over left angle of mouth which responded only partially to oral propranolol. Patient then showed a good response to intralesional bleomycin.