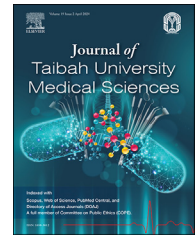




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Original Article

## Cephalometric analysis of patients with beta thalassemia receiving fetal hemoglobin induction therapy



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### المخلص

**أهداف البحث:** تهدف الدراسة إلى تقييم ما إذا كان العلاج التعريفي للهيموجلوبين الجنيني قادراً على تقييد أو حتى عكس التغيرات العظمية الرأسية المرتبطة لدى مرضى الثلاسيميا بيتا.

**طريقة البحث:** لقد كانت دراسة رصدية مقارنة. تم تقسيم ما مجموعه 90 مشاركاً بالتساوي إلى 3 مجموعات، مجموعة السيطرة ومجموعتي مرضى الثلاسيميا الكبرى الذين يخضعون لعمليات نقل الدم (مجموعة ثلاسيميا بيتا وأولئك الذين يتلقون العلاج التعريفي مع نقل الدم). بالإضافة إلى التاريخ والفحص، خضع جميع هؤلاء المرضى للتقييم الفوتوغرافي والتقييم الشعاعي باستخدام مخطط الرأس الجانبي. تم استخدام أنوفا أحادي الاتجاه متبوعاً باختبار توكي اللاحق لتحديد الاختلافات بين المجموعات الثلاث.

**النتائج:** اختلف العلاج التعريفي مع مجموعة نقل الدم بشكل كبير من حيث جميع الصور الفوتوغرافية وجدول الجمجمة وأغلبية المعلمات الرأسية مثل زوايا الوجه وارتفاعات الوجه الوسطى والسفلى والزوايا بين القواطع (ع = 0.036) من مجموعة الثلاسيميا بيتا حيث كانت القيم المتوسطة للعلاج التعريفي إلى جانب مجموعة نقل الدم مماثلة تقريباً لتلك الخاصة بالمجموعة الضابطة. بالإضافة إلى ذلك، كانت بعض قياسات الأسنان والأنسجة الرخوة أيضاً فرقا كبيراً بين المجموعات الثلاث. بالنسبة لغالبية هذه المعلمات، أظهر متوسط الفرق قيماً أعلى لمجموعة بيتا ثلاسيميا.

**الاستنتاجات:** يبدو أن العلاج التعريفي قد أدى إلى تحسين زوايا الوجه والارتفاعات والزوايا بين القواطع بينما لوحظ نمط الهيكل العظمي من الدرجة الثانية في مجموعة نقل الدم فقط. تشير هذه النتائج إلى أن العلاج بتعريف الهيموجلوبين الجنيني ربما يكون قد قيد بعض التغيرات في قياسات الرأس لدى مرضى الثلاسيميا بيتا.

**الكلمات المفتاحية:** بيتا ثلاسيميا؛ نقل الدم؛ العلاج التعريفي؛ قياس الرأس؛ تحليل قياسات الرأس

### Abstract

**Objective:** We aimed to determine the effects of fetal hemoglobin induction therapy in restricting or even reversing the cephalometric changes associated with beta thalassemia.

**Materials and methods:** In this comparative observational study, 90 participants were equally divided into three groups: a control group; patients with thalassemia major receiving blood transfusion (BT group); and patients receiving induction therapy (i.e., hydroxyl urea (5–10 mg/kg/day) or as much as 20 mg/kg/day) and thalidomide (2–10 mg/kg/day) along with blood transfusion (IT group). All patients underwent history taking and examination, photographic assessment, and radiographic evaluation with a lateral cephalogram. One-way ANOVA followed by post-hoc Tukey test was used to determine differences among groups.

**Results:** The IT group differed significantly from the BT group in all photographic and skull table parameters, and most cephalometric parameters, such as facial angle ( $p \leq 0.001$ ), middle and lower facial heights ( $p \leq 0.001$ ),

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and inter-incisal angle ( $p = 0.036$ ); the mean values in the IT group were similar to those in the control group. In addition, dental and soft tissue measurements significantly differed among groups. For most parameters, the mean difference indicated higher values in the BT group.

**Conclusion:** Induction therapy appeared to improve the facial angles, heights, and inter-incisal angles, whereas a class II skeletal pattern was observed in the transfusion only group. These findings suggest that fetal hemoglobin induction therapy might have restricted some of the cephalometric changes in patients with beta thalassemia.

**Keywords:** Beta thalassemia; Blood transfusion; Cephalometric analysis; Cephalometry; Induction therapy

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## Introduction

Beta thalassemia comprises a group of congenital illnesses with diminished red blood cell hemoglobin. The three main types are thalassemia major, intermedia, and minor. In thalassemia major, regular blood transfusion and suitable iron chelation prolong the life expectancy of affected individuals.<sup>1</sup> While there are various treatment options for beta thalassemia major, developing countries like Pakistan encounter obstacles such as limited access to convenient healthcare, ensuring safe blood transfusions and resistance to iron chelation therapy. Management of beta thalassemia major is difficult because of severe complications including hypercoagulability, iron overload, pericarditis, psychological problems, hepatocellular carcinoma, and osteoporosis.<sup>2,3</sup> Classical therapies for beta thalassemia major include red blood cell transfusion, iron chelation therapy to remove transfusion related iron overload in the body, hydroxyurea therapy, and erythropoietin administration.<sup>3,4</sup>

Craniofacial abnormalities in patients with beta thalassemia include bony changes resulting from ineffective erythropoiesis, along with the development of bone-expanding erythroid masses, bi-maxillary protrusions, and occlusal abnormalities. Widening of the diploic space in the skull results in thinning of the inner table and complete resorption of the outer table forming prominent trabeculae, thus resulting in a typical “hair on end” appearance. Dental and facial abnormalities include saddle nose, opened bite, and prominent malar bones. In addition, poor spacing of teeth because of skeletal modifications may cause upper lip retraction, thus forming a “chipmunk-like” face.<sup>5–7</sup>

Among the numerous management options available to treat thalassemia, one treatment involving the induction of fetal hemoglobin instead of abnormal hemoglobin is fetal hemoglobin induction therapy. In this therapy, hydroxyurea and thalidomide are administered along with blood

transfusion to decrease the abnormal hemoglobin chains by replacing them with fetal hemoglobin. Thalidomide induction considerably increases fetal hemoglobin (HbF) but the precise mechanism remains unknown. The effects may be attributable to the suppression of NF- $\kappa$ B induction caused by some inflammatory cytokines.<sup>8</sup> Hydroxyurea, in contrast, increases the formation of HbF and decreases the intracellular levels of sickle hemoglobin, thus leading to the polymerization of deoxygenated sickle hemoglobin.<sup>9</sup> Hydroxyurea is given at a dose of 5–10 mg/kg/day or as much as 20 mg/kg/day,<sup>10</sup> whereas thalidomide is given along with hydroxyurea at a dose of 2–10 mg/kg.<sup>11</sup> Both drugs are used primarily for sickle cell anemia; however, HbF induction therapy has also been used for patients with beta thalassemia major.

Both hydroxyurea and thalidomide have been used as part of fetal hemoglobin induction therapy, because they both increase HbF, thereby decreasing ineffective erythropoiesis and the load on the bone marrow, and preventing marrow expansion. However, whether these effects also reverse the bone marrow expansion and craniofacial abnormalities in patients remains unknown. No recent comprehensive study has emphasized the significance of hydroxyurea and thalidomide treatment in thalassemia major. Thus, the aim of this study was to determine whether fetal hemoglobin induction therapy might reverse cephalometric changes and bone marrow expansion in patients with beta thalassemia major.

## Materials and Methods

This observational study was performed at the Khyber Medical University's Institute of Basic Medical Sciences in Peshawar, Pakistan. Patients 4–12 years of age with thalassemia were recruited from the Fatimid Foundation and Hayatabad Medical Complex, and cephalometry was performed at Rehman Medical College after permission was granted by the respective institutional ethical committees. A total of 90 participants were recruited through non-probability consecutive sampling over 6 months. The groups were as follows:

- **Control group** comprising 30 age-matched healthy individuals with no history of facial surgery and craniofacial anomalies, who visited for any orthodontic purpose such as I-malocclusion.
- **Blood transfusion (BT) group** comprising 30 patients 4–12 years of age with beta thalassemia major who had received at least two blood transfusions in the previous 12 months.
- **Induction therapy (IT) group** comprising 30 patients receiving fetal hemoglobin induction therapy comprising blood transfusion + hydroxyurea + thalidomide for at least 12 months before the study.

Patients with beta thalassemia major with a history of dental or orthodontic treatment, major orthodontic deformity, or craniofacial abnormality, whether acquired or congenital, were excluded from the study. Control

participants were recruited from Rehman Medical Institute, whereas the BT and IT groups were recruited from the Fatimid Foundation. All patients with thalassemia received a transfusion regimen (Hb levels = 6–10 g/dL) and an iron chelating agent (desferrioxamine, 35–50 mg/kg) to manage iron overload, as well as folic acid supplements, whereas those undergoing induction therapy received hydroxyl urea (5–10 mg/kg/day or as much as 20 mg/kg/day) and thalidomide (2–10 mg/kg/day). Patient history and examination findings were recorded on an information form. Later, patient photographs were taken with a camera with  $4032 \times 3024$  pixel resolution for facial measurements, and a lateral cephalogram was also obtained.

#### Photographic analysis

For photographic analysis, the face was divided into three horizontal compartments: upper (from hairline to base of the nose), middle (from soft tissue bridge of the nose to oral commissure), and lower (from oral commissure to the chin). The face was further divided into horizontal planes i.e., forehead height, nasal height, height of the upperlip and mandibular height [Figure 1](#). These measurements were analyzed in ImageJ software version 1.52a.

#### Cephalometric analysis

For determining cephalometric parameters, lateral cephalograms were obtained for each patient from the side of the face, with very precise positioning. Patients with beta thalassemia major were asked to close their teeth in centric occlusion with the lips relaxed. Furthermore, a range of skeletal parameters (The angle between sella/nasion plane and the nasion/A plane (SNA), Sella-Nasion B-point (SNB), ANB (SNA-SNB), Pog to NB (from point Pog to Line NB), occlusal to Sella Nasion (SN), SN to Gnathion (GoGn), lower anterior facial height, wits, mandibular plane, facial plane, angle of convexity, and A–B plane angle) were computed with the cephalometric analysis program Viewbox 4. In addition, dental measurements (upper incisor to NA, upper incisor to NA in mm, lower incisor to NB, lower incisor to NB in mm, inter-incisal angle, lower incisor to GoGn, overjet, and overbite), as well as soft tissue measurements (upper lip to E plan, lower lip to E plan, and H angle) were recorded.

#### Data analysis

Data analyses were performed in SPSS V22. For quantitative data, mean and standard deviation were determined, whereas categorical variables were expressed as proportions. One-way ANOVA was performed to compare mean differences among the three groups, and was followed by a post hoc Tukey test for paired analysis to determine which groups differed in the parameters studied. A  $p$  value  $\leq 0.05$  was considered significant with a 95 % confidence interval.

## Results

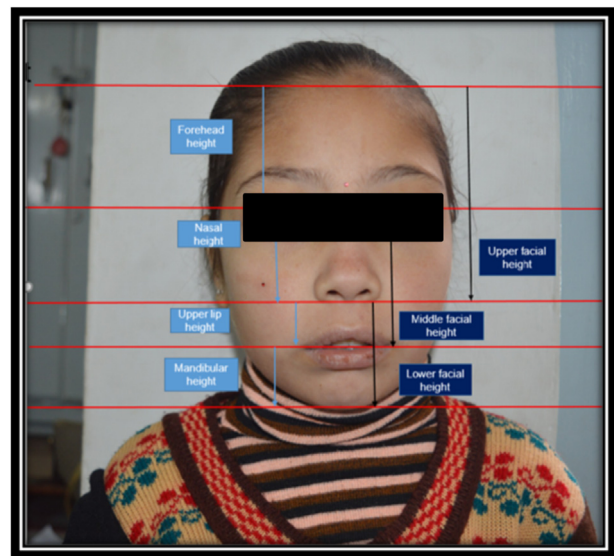
### Demographics, history, and physical examination findings

A total of 46 (51.11 %) boys and 44 girls (48.88 %) were included. The three groups did not differ significantly in age ( $p = 0.146$ ) or height ( $p = 0.252$ ); however, a significant difference was observed in weight among groups ( $p \leq 0.05$ ). In post hoc analysis, a statistically significant difference was observed between the BT and each of the other two groups ( $p = 0.001$ ).

On physical examination, although no significant difference was observed among groups in head circumference ( $p = 0.078$ ), approximately 56 % of the participants in the BT group had a head circumference  $>50$  cm. Furthermore, we observed no hearing and vision problems, or any associated temporomandibular joint pain or clicking on movement. The remaining findings are shown in [Table 1](#).

#### Photographic analysis

The three groups differed significantly in all photographic parameters. The mean values in the BT group were highest, and followed by those in the IT and the control group ([Table 2](#)). In post hoc analysis, all three groups differed significantly in all parameters ( $p = 0.001$ ), except for the upper face, forehead, and nasal height, in which the BT and IT groups did not differ significantly ([Table 2](#)).



**Figure 1:** Photographic parameters, with the face divided into three horizontal compartments: upper (from hairline to base of the nose), middle (from soft tissue bridge of the nose to oral commissure), and lower (from oral commissure to the chin) (right). The face was further divided into horizontal planes, i.e., forehead height, nasal height, height of upper lip, and mandibular height (left).

**Table 1: Transfusion history, physical, and dental examination findings of the study participants (n = 90).**

Variables	Control group	<sup>a</sup> BT group	<sup>b</sup> IT group
<b>Blood transfusion frequency</b>			
Once per month	0	8 (26.7 %)	7 (23.3 %)
Two times per month	0	16 (53.3)	1 (3.3 %)
Three times per month	0	6 (20 %)	0
None	30 (100 %)	0	22 (73.3)
<b>Iron chelation</b>			
Yes	0	18 (60 %)	4 (13.3 %)
No	30 (100 %)	12 (40 %)	26 (86.6 %)
<b>Physical examination</b>			
Head circumference	52.41 ± 8.04	49.98 ± 4.11	48.76 ± 6.02
Number of teeth	19.30 ± 3.26	24.07 ± 2.86	22.67 ± 2.51
<b>Cavities</b>			
Yes	0 (0)	19 (63.3 %)	8 (26.7 %)
No	30 (100 %)	11 (36.7 %)	22 (73.3 %)
<b>Tooth crowding</b>			
Yes	0	19 (63.3 %)	3 (10 %)
No	30 (100 %)	11 (36.7 %)	27 (90 %)

<sup>a</sup> BT = blood transfusion group.

<sup>b</sup> IT = induction therapy group.

**Table 2: Photographic analysis of the study groups (n = 90). Values are means and standard deviations.**

Parameters	Control group	BT group	IT group	Post hoc Tukey test		
				CG vs BT	BT vs IT	IT vs CG
Upper face height	35.27 ± 2.18	44.21 ± 6.87	41.60 ± 5.56	0.001 <sup>a</sup>	0.248	0.001 <sup>a</sup>
Middle face height	16.86 ± 1.08	24.47 ± 4.06	21.73 ± 3.03	0.001 <sup>a</sup>	0.001 <sup>a</sup>	0.001 <sup>a</sup>
Lower face height	13.45 ± 1.03	21.04 ± 5.17	16.88 ± 4.24	0.001 <sup>a</sup>	0.001 <sup>a</sup>	0.001 <sup>a</sup>
Forehead height	21.14 ± 2.22	26.97 ± 5.67	24.97 ± 3.71	0.001 <sup>a</sup>	0.248	0.001 <sup>a</sup>
Nasal height	12.81 ± 0.67	16.07 ± 2.71	14.72 ± 1.54	0.001 <sup>a</sup>	0.057	0.001 <sup>a</sup>
Upper lip height	5.30 ± 0.49	8.94 ± 2.02	7.41 ± 1.83	0.001 <sup>a</sup>	0.001 <sup>a</sup>	0.001 <sup>a</sup>
Mandibular height	7.76 ± 0.95	12.01 ± 3.47	9.40 ± 2.73	0.001 <sup>a</sup>	0.001 <sup>a</sup>	0.001 <sup>a</sup>

CG = control group, BT = blood transfusion group, IT = induction therapy group, NS = not significant.

<sup>a</sup> The mean difference was considered significant at the  $p \leq 0.05$  level.

### Cephalometric analysis

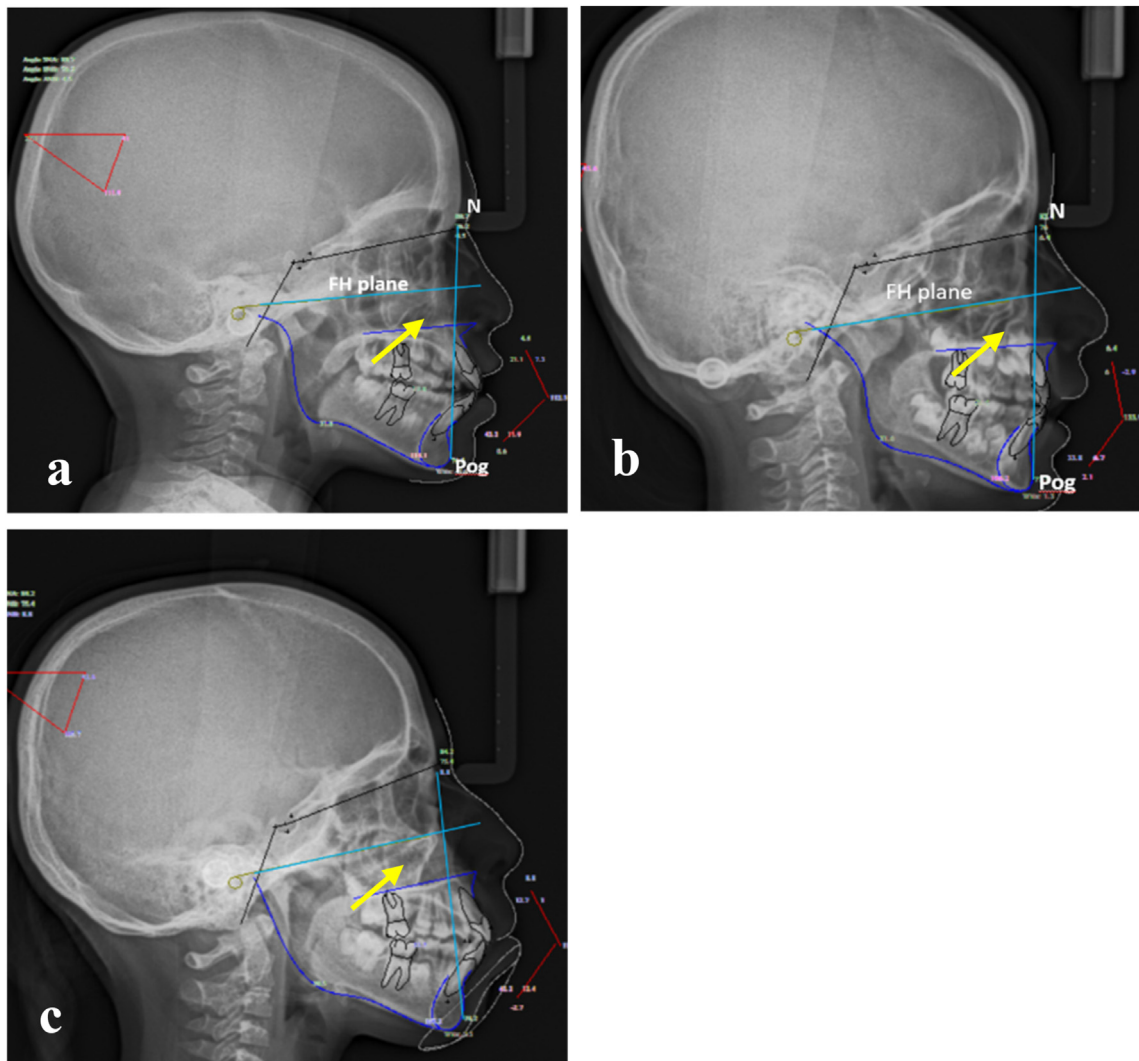
Skeletal measurements in all three groups differed significantly in ANB ( $p = .008$ ), Pog to NB ( $p < .001$ ), maxilla-mandibular difference ( $p < .001$ ), lower anterior facial height ( $p = .005$ ), facial angle ( $p < .001$ ), and angle of convexity ( $p < .001$ ). The mean difference in ANB angle was greatest in the IT group, which was followed by the BT group and the control group. Furthermore, the mean differences in the lower anterior facial height, and the facial angle, were highest in the BT group, which was followed by the IT group and the control group (Figure 2). However, the mean angle of convexity was greatest in the IT group, which was followed by the BT group and the control group. The other remaining parameters showed no considerable differences among groups. The mean ± SD,  $p$  values, and post hoc values are reported in Table 3.

### Dental soft tissue and skull table measurements

The following dental measurements in all three groups differed significantly: lower incisor to NB (mm) ( $p = .007$ ), inter-incisal angle ( $p < .001$ ), and overbite ( $p < .001$ ). The mean ± SD,  $p$  values, and post hoc values are indicated in Table 4.

Soft tissue measurements in all three groups differed significantly in only the upper lip to E plane ( $p = 0.003$ ). The mean difference in mean upper lip to E plane value was largest in the control group, which was followed by the BT group and the control group. The remaining parameters did not significantly differ among groups. The mean ± SD,  $p$  values, and post hoc values are indicated in Table 4.

Skull table measurements (outer table, inner table, and diploe) differed significantly among groups. The mean



**Figure 2:** Comparison of facial angle among groups. a. BT group b. Control group c. IT group. No significant difference in facial angle was observed between the control and induction therapy groups. The yellow arrows indicate facial angles.

**Table 3: Skeletal measurements of the participants (n = 90). Values are means and standard deviations.**

Parameters	Control group	BT group	IT group			
				CG vs BT	BT vs IT	IT vs CG
ANB	3.89 ± 3.27	5.95 ± 3.70	6.52 ± 3.10	0.065	0.800	<b>0.006<sup>a</sup></b>
Pog to NB	1.99 ± 1.50	-0.98 ± 2.79	0.02 ± 2.48	0.001 <sup>a</sup>	0.318	0.002 <sup>a</sup>
Maxillo-mandibular difference	22.44 ± 5.66	19.34 ± 5.28	16.32 ± 5.13	0.082	0.072	0.001 <sup>a</sup>
Lower anterior facial height	72.21 ± 4.86	75.98 ± 5.98	71.70 ± 5.09	0.026 <sup>a</sup>	0.012 <sup>a</sup>	0.916
Facial angle	82.05 ± 3.48	84.71 ± 3.29	80.85 ± 3.70	0.010 <sup>a</sup>	0.001 <sup>a</sup>	0.407
Angle of convexity	2.92 ± 3.83	6.38 ± 4.08	6.48 ± 3.54	0.004 <sup>a</sup>	0.994	0.001 <sup>a</sup>
SNA	80.65 ± 6.10	83.78 ± 5.31	83.33 ± 5.15	NS	NS	NS
SNB	76.77 ± 4.24	77.82 ± 3.82	76.84 ± 4.12	NS	NS	NS
SNPg	77.74 ± 4.21	77.30 ± 3.98	76.86 ± 4.20	NS	NS	NS
Wits	0.29 ± 3.96	1.14 ± 3.92	2.54 ± 3.46	NS	NS	NS
Occlusal to SN	18.46 ± 4.73	16.49 ± 7.02	17.82 ± 4.74	NS	NS	NS
SN to GoGn	31.89 ± 4.63	32.83 ± 6.40	29.05 ± 7.39	NS	NS	NS
Mandibular plan	29.27 ± 3.93	27.22 ± 5.58	28.04 ± 5.02	NS	NS	NS
A-B plan	-6.92 ± 4.31	-7.55 ± 5.02	-7.32 ± 5.60	NS	NS	NS

CG = control group, BT = blood transfusion group, IT = induction therapy group, NS = not significant.

<sup>a</sup> The mean difference was considered significant at the  $p \leq 0.05$  level, following post Hoc analysis.

**Table 4: Dental, soft tissue, and skull table measurements of the participants (n = 90). Values are mean and standard deviations.**

	Control group	BT group	IT group	Post hoc Tukey test		
				CG vs BT	BT vs IT	IT vs CG
<b>Dental parameters</b>						
Lower incisor to NB	4.91 ± 3.06	6.08 ± 3.42	5.87 ± 3.595	0.007 <sup>a</sup>	0.763	0.027 <sup>a</sup>
Inter-incisal angle	132.2 ± 11.8	120.2 ± 34.4	124.52 ± 25.	0.009 <sup>a</sup>	0.036 <sup>a</sup>	0.327
Overbite	0.48 ± 4.07	0.19 ± 3.27	1.01 ± 2.20	0.064	0.031 <sup>a</sup>	0.990
Upper incisor to NA	15.38 ± 7.8	15.11 ± 9.07	15.46 ± 7.9	NS	NS	NS
Upper incisor to NA	1.95 ± 3.52	2.22 ± 4.80	1.76 ± 4.33	NS	NS	NS
Lower incisor to NB	27.41 ± 7.8	27.56 ± 10.7	28.65 ± 9.29	NS	NS	NS
Lower incisor to GoGn	98.97 ± 7.2	92.83 ± 26.6	98.67 ± 19.6	NS	NS	NS
Overjet	3.92 ± 4.008	3.98 ± 2.384	3.50 ± 2.302	NS	NS	NS
<b>Soft tissue parameters</b>						
Upper lip to E plane	0.18 ± 3.15	0.40 ± 3.27	0.04 ± 2.34	0.006 <sup>a</sup>	0.975	0.007 <sup>a</sup>
Lower lip to E plane	0.58 ± 2.35	0.82 ± 2.13	0.87 ± 2.19	NS	NS	NS
H angle	17.19 ± 5.68	18.11 ± 6.90	16.55 ± 7.12	NS	NS	NS
<b>Skull table measurement</b>						
Inner table	2.37 ± 0.68	1.95 ± 0.81	1.96 ± 0.65	0.000 <sup>a</sup>	0.026 <sup>a</sup>	0.000 <sup>a</sup>
Outer table	2.31 ± 0.60	1.90 ± 0.56	1.97 ± 0.46	0.000 <sup>a</sup>	0.908	0.000 <sup>a</sup>
Diploe	4.33 ± 2.46	5.93 ± 2.68	6.52 ± 4.67	0.000 <sup>a</sup>	0.441	0.004 <sup>a</sup>

BT = blood transfusion group, IT = induction therapy group, NS = not significant.

<sup>a</sup> The mean difference was considered significant at the  $p \leq 0.05$  level. CG = control group.

differences in the inner table and the outer table were greatest in the control group, which was followed by the IT group and the BT group. Furthermore, the mean difference in the diploe was largest in the IT group, which was followed by the BT group and the control group. The mean ± SD,  $p$  values, and post hoc values are indicated in Table 4.

## Discussion

In patients with thalassemia, little is known regarding cephalometric features and the feasibility of orthodontic treatment. This study was designed to determine cephalometric, soft tissue, and dental changes in patients with beta thalassemia undergoing blood transfusion with or without fetal hemoglobin induction therapy. The findings indicated that most skeletal, dental, and soft tissue parameters differed among groups; however, few differences in physical examination findings were observed among groups.

Because the inclusion criteria were restricted to certain ages, the mean age showed no considerable difference among groups, in contrast to a study conducted in Malaysia in which patients with thalassemia were compared with healthy individuals with an age range of 5–18 years.<sup>12</sup> In addition, the mean height did not substantially differ among the three groups, thereby suggesting that both transfusion and induction therapy did not appear to affect vertical growth, whereas patient weight significantly differed among groups. Induction therapy appeared to have a positive effect on the weight of patients with beta thalassemia. In another study, the participants' weight was found to be below the 5th percentile of the weight in the control group, probably as a result of the disease itself, owing to inadequate physical activity and poor nutrition.<sup>13</sup>

In physical examinations, although the mean head circumference was highest in the control group, which was followed by the BT and IT group, the differences were not significant. These findings suggested that, despite a risk of

frontal bossing in patients receiving blood transfusion, no difference in head circumference measurements was observed. This finding may be attributable to either the relatively small sample size or the limited age range among our study participants. However, another study has reported a significantly greater head circumference in the thalassemia group than the control group.<sup>14</sup> No individuals in our study had hearing or vision problems, or temporomandibular joint pain or any clicking on movement of this joint, in contrast to observations during the chronic stages of sickle cell disease, in which hearing loss affects 45 % of patients, probably because of the use of deferasirox as a chelating agent.<sup>15</sup> We observed a significant difference in the number of teeth and tooth crowding among groups; however, the findings in the BT and IT groups did not differ significantly. Our findings indicated a significant difference in tooth number between control and BT group participants, as well as control and IT group participants. Examination revealed cavities and delayed emergence of milk teeth in the BT and IT groups. The results of our study are consistent with those of another study on children 3–15 years of age, which has established a significant association between oral health and thalassemia in young individuals.<sup>16</sup>

In the photographic analysis, all measurements were significantly greater in the BT and IT groups than the control group. The photographic parameters were clearer in the BT group than the IT and control groups. This finding was consistent with the greater overall bony growth in the BT group, owing to excessive extra medullary hematopoiesis.<sup>17,18</sup> Furthermore, the photographic parameter measurements in the IT group, although different from those of the control group, showed a smaller mean difference than observed in the BT group, thereby suggesting that induction therapy might have decreased extra-medullary hematopoiesis by increasing hemoglobin production, as suggested in the literature.<sup>19</sup> Interestingly, post hoc analysis revealed that the IT

and BT groups did not differ significantly in upper face, nasal, and forehead heights, possibly because of the relatively small sample size or the duration of therapy in the IT group. A prior study has reported shorter upper facial height and lower facial height in patients with thalassemia receiving blood transfusion than control participants, thus suggesting a differential delay in the development of the facial skeleton in individuals with thalassemia.<sup>20</sup>

All three groups differed significantly in some skeletal measurement parameters. Post hoc analysis revealed that the Pog to NB, maxilla-mandibular difference, and angle of convexity significantly differed among all groups. The ANB angle did not differ between the control and BT groups, whereas the lower anterior facial height and facial angle in the IT group were similar to those in the control group, thus suggesting that induction therapy might have improved these two parameters. Comparison of the remaining parameters indicated no significant differences among the three groups, possibly because the small sample size might have concealed minor differences. Patients with beta thalassemia major have considerable intermaxillary discrepancies, evaluated according to the ANB angle, as well as short cranial bases and small mandibles, thus resulting in a class II skeletal appearance.<sup>21</sup> In another study, individuals with thalassemia have been found to have a greater angle from the maxillary plane to the mandibular plane than controls, in agreement with the results of our study.<sup>22</sup> Similarly, we observed a decreased ratio of posterior to anterior height of the face and a considerably shorter ramus length, mandibular body, and posterior face height. Furthermore, all three groups considerably differed in lower incisor to NB (mm), inter-incisal angle, and overbite. In terms of dental measurements, similarly to findings in studies performed in Kuwait, KSA, Morocco, and Yemen.<sup>23,24</sup> In another study, a diminished inter-incisal angle has been reported to result in proclined incisors in patients with beta thalassemia receiving only blood transfusions, in agreement with our findings, thus resulting in protrusion of the maxillary incisors.<sup>25</sup> Furthermore the inter-incisal angle in the IT and control groups did not significantly differ in post hoc analysis. This finding further suggested that induction therapy might affect the overall alignment of the teeth, thus resulting in an inter-incisal angle within the same range as that in the control group.

In soft tissue measurements, only the upper lip to E plane differed significantly across the three groups; interestingly, in post hoc analysis, the BT and IT groups did not appear to differ significantly. These findings suggested that the bony changes observed in the skeletal measurements were not evident in soft tissue analysis, possibly because of observer bias or the relatively small sample size in both groups. One study has reported extra protrusive lower and upper lips in a sample of the Omani population comprising 150 individuals.<sup>26</sup> Finally, similar patterns were observed in changes pertaining to the inner and outer table of the skull. All three groups differed significantly in skull table measurements. However, the differences were not significant between the BT and IT groups. The diploe was largest in the IT group, which was followed by BT and the control groups. This difference was again not significant between the BT and IT groups. These findings suggested that the skull table measurements might not substantially vary among patients receiving induction therapy.

Like most scientific research, our study had limitations that might affect the interpretation of our research findings. The study project was constrained by a limited sample size, but this aspect was partially mitigated by the low frequency at which patients undergo fetal hemoglobin induction therapy, which would have made enrolling a larger sample within the given timeframe impractical. All measurements were conducted manually by a single observer using semi-automated software, which might have subjected the findings to observer bias. Fully automatic software would have resulted in more precise readings. In addition, having multiple observers or computation of intra-rater reliability would have avoided observer biases. Follow-up studies should be performed to determine the long-term changes in individuals receiving induction therapy. Our study was also limited to patients receiving hydroxyurea and thalidomide as induction therapy.

## Conclusion

Our findings indicated significant differences among BT groups, revealing distinct characteristics such as a class II skeletal pattern, shortened cranial base length, a small mandible, and increased anterior and decreased posterior vertical dimensions, thus leading to severe facial deformities. Notably, induction therapy had positive effects on the facial angle, lower anterior facial height, and inter-incisal angle in treated patients. These findings suggest a potential limitation of cephalometric changes with fetal hemoglobin induction therapy. However, gaining conclusive evidence regarding the therapy's ability to reverse these changes and assess long-term benefits or adverse effects would require further investigation through extended studies. These insights are crucial for orthodontists and oral-maxillofacial surgeons, by offering valuable guidance in addressing deformities and refining treatments to achieve optimal esthetic and functional outcomes in affected individuals.

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## Conflict of interest

The authors have no conflict of interest to declare.

## Ethical approval

The ethical approval of this study was obtained from the Ethical Review Committee of Khyber Medical University, Peshawar, Pakistan, under the code DIR/KMU-EB/CA/000704.

## Authors contributions

The following authors contributed to the manuscript, in accordance with ICJME guidelines, as follows: **AA** performed data collection and analysis, and drafted the manuscript. **NB**

performed conception and design of the research, supervised the data collection and analysis, drafted the manuscript, and approved the final version. **YMY** performed conception and design of the research, and supervised the data collection. **SS** performed research design and data analysis, and approved the final version of the manuscript. **SHH** performed data analysis and approved the final version of the manuscript. **SRH** performed data analysis and approved the final version of the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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