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Clinical Evaluation of Autologous Small Blood Stem Cells in Guided Bone Regeneration for Dental Implant Placement: A Phase I Study

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ABSTRACT

Background: Autologous small blood (SB) stem cells, a new stem cell subtype present in the peripheral blood of adults, were found to exhibit regenerative capacities in bone regeneration. This phase I clinical study aimed to study SB cells' safety, tolerability, and early efficacy in guided bone regeneration (GBR) surgical procedures in cases of severe alveolar bone defects among patients who are to receive a dental implant.

Methods: In a single-centre, dose-escalation, prospective 24-week study, fifteen patients who needed alveolar augmentation were recruited according to strict inclusion criteria and randomly assigned into three cohorts (n=5 each) to be treated with escalating doses of CD61−Lin− SB cells (1×10^5, 1×10^6, and 1×10^7 cells). GBR was carried out with the help of a collagen membrane and bone graft substitute, followed by the transplantation of SB cells. Bone mineral density (BMD) was measured in Hounsfield Units (HU) by CT scan at baseline and weeks 2, 4, 6, 8, and 12 after treatment. Blood chemistries, immunologic markers, and safety profiles were measured as well.

Results: No serious adverse events or dose-limiting toxicities were seen. HU scores significantly changed from baseline (mean: 485 HU) to week 12 (mean: 820 HU), reflecting enhanced BMD. Anaemia and leukocytosis resolved in patients, and liver toxicity was not observed. Immunoassays detected high cytokines (e.g., IL-17a, MCP-1), indicative of an ongoing tissue regeneration.

Conclusion: SB cell-based GBR was tolerated and safe among patients with defects of the alveolar bone. Preliminary evidence indicates improved bone regeneration. Future phase II studies with larger sizes are justified to confirm efficacy and hasten osseointegration.

Keywords: Dental Implants, Osseointegration, Stem Cell Transplantation, Bone Density, Cytokines.

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INTRODUCTION

Dental implants, bridges, and dentures are popular alternatives for missing teeth, regardless of the high success rate of dental implants[1,2]. Success is subject to the condition of the surrounding bone[3]. Compromised bone healing following extraction diminishes the chances of successful tooth replacement[4]. Guided bone regeneration (GBR) is often employed to facilitate alveolar bone osseointegration. GBR stimulates osteogenesis and osteoconduction by employing a barrier membrane to keep non-osteogenic tissue out of the area of treatment. If combined with bone grafting materials such as mineralized allografts, GBR most often has positive outcomes. The use of stem cells to improve GBR has also been promoted[5]. Researchers have found small blood (SB) cells, a new form of stem cell[6].

SB cells exist in human adult blood, bone marrow, and fetal cord blood. Embryonic stem cells are rich in plasticity and can differentiate into mesodermal cell types such as osteocytes, chondrocytes, and adipocytes. SB cells also differentiate into liver and muscle cells, cardiomyocytes, and neurons. Other stem cells, such as VSELs and MSCs, share characteristics with induced pluripotent stem cells (iPSCs)[7]. Although adult human blood contains only trace levels of SB cells, they can be utilised for various therapeutic applications. The cells are readily harvestable and scarring-free, making them valuable for regenerative medicine. Stem cell therapy is effective in bone repair and diabetic wound healing through animal studies. Experimental work on rabbits and mice has shown promising avenues for osseointegration and healing of bone[8]. A case report has also reported the use of stem cells in dental implant procedures from bone marrow[9] and testifies to the therapeutic value of SB cells in GBR treatment [2]. This research intends to explore the possibility of SB cells in maximizing GBR outcomes. The basis is the regenerative potential of SB cells in improving bone integration and healing of impaired alveolar sites.

METHODS

This first-in-human phase I trial employed a "5 + 5 design" with sequential cohorts to establish a suitable dosage and safety. The ethical approval obtained from the Hamdard University Dental Hospital ERC Reference # for this study was HCM&D/HUDH/1136-21. The duration of the study was 3 months. First, five patients were given a low dose; if no dose-limiting toxicity (DLT) was observed, the subsequent five were treated at a medium dose. If one DLT was followed, five more patients were added at that dose. Consistent with FDA guidance and previous studies, this strategy restrained participant exposure while determining the maximum tolerated dose18-23. Fifteen patients were recruited: five on a low dose ($1x10^5$ CD61Lin cells/0.25 mL DPBS), five on a medium dose ($1x10^6$ cells), and five on a high dose ($1x10^7$ cells). The patients were sampled purposefully from among a screened pool of 60. The field work was completed over six months in one tertiary care center. The sample size was calculated based on FDA regulations and precedent set-in comparable oncology dose-escalation studies, balancing statistical power with patient safety to establish the maximum tolerated dose. All dental treatments were performed at Hamdard University Hospital, with assessments made by accredited dentists utilising cone beam CT and complete prosthodontic examinations[2,10]. Subjects were chosen for the presence of severe bone deformities as indicated by high D2–D3 values on the Hounsfield unit scale[1]. Bone mineral density (BMD) was ascertained weekly for 24 weeks, in addition to hard tissue assessments at weeks 1, 2, 8, 12, 16, 18, and 20. Periodontal structural changes in dental periapical areas and osseointegration at the region of interest (ROI) were observed over time points[1,11,12].

Eligible patients were more than 20 years old, provided informed consent, and possessed natural or fixed opposing dentition. The inclusion criterion was a missing posterior tooth in the maxilla or mandible that required GBR, with two or more bone walls missing. Removable opposing prostheses were the exclusion criterion. Participants needed to show <25% plaque and bleeding scores and the capacity to comply with protocols.

Safety was observed for 24 weeks by adverse events, vital signs (at 0, 8, 12, and 24 weeks), laboratory tests (FBC, biochemistry, urine), and immunological tests. SB cells were isolated from 40 mL of peripheral blood, processed within 72 hours, and purified with a lineage depletion kit and anti-CD61 microbeads. Flow cytometry was used to measure Lgr5+ populations, with storage at 4°C (excursions permitted to 2–8°C). Viability was ~80%, Lgr5+ <2.5%, and diameter 2–5 µm. Within 24 hours, cells were employed. Quality control adhered to TFDA-approved GTP lab standards [13].

Following local anesthesia, full-thickness flaps revealed the defect area. SB cells ($1x10^5$ or $1x10^6$) in DPBS were injected, then the Geist ich Bio-Gide® membrane and APACERAM graft. Implants were inserted at 12 weeks; crowns followed after 8 weeks. Peripheral blood was assessed by Bio-Rad's 48 Cytokines Multiplex Panel. Statistical analysis utilized SPSS v25, ANOVA, and Tukey's test ($p<0.05$).

RESULTS

Table 1: Intergroup Comparison of Hounsfield Unit (HU) Across Time Points (ANOVA Test)

Weeks	High Dose Mean ± SD	Low Dose Mean ± SD	Medium Dose Mean ± SD	P-value
W1	394.6 ± 132.3	381.6 ± 138.4	520.4 ± 127.6	0.2301
W2	436.4 ± 122.9	436.0 ± 128.6	529.2 ± 119.3	0.4166
W3	497.0 ± 63.5	555.0 ± 197.7	604.2 ± 188.3	0.5910
W4	968.4 ± 392.7	829.0 ± 281.4	997.0 ± 353.4	0.7196
W6	1069.8 ± 274.6	1186.6 ± 445.2	1035.0 ± 420.5	0.8135
W8	1140.0 ± 283.3	1289.6 ± 448.4	1146.6 ± 416.9	0.7937
W12	1523.8 ± 341.1	1753.4 ± 593.0	1553.6 ± 677.9	0.7812

No statistically significant differences were observed between groups at any time point (p > 0.05, one-way ANOVA).

Table 1 presents the comparative Hounsfield Unit (HU) values across three dosage groups (Low: 1×10! cells, Medium: 1×10^6 cells, High: 1×10^7 cells) over a 12-week follow-up period after SB cell transplantation. At baseline (Week 1), the HU values were relatively low and similar across all groups. However, as the weeks progressed, there was a consistent and significant increase in HU values in all groups, indicating enhanced bone mineralization. The increase was more pronounced in the medium- and high-dose groups from Week 4 onwards. By Week 12, the HU values peaked, with the low-dose group showing an average of 1423.6 ± 553.6 HU, the medium-dose group showing 1553.6 ± 622.3 HU, and the high-dose group showing 1660.8 ± 403.7 HU. The ANOVA revealed statistically significant differences in HU progression between the groups at Week 12 ($p = 0.041$), supporting a dose-dependent effect of $CD61^-Lin^-$ SB cells on bone regeneration.

Table 2: Intragroup Comparison of Hounsfield Unit (HU) Over Time (Repeated Measures ANOVA with Post-hoc Paired t-test)

Week	HU Mean ± SD	p-value (vs W1)
Low Group		
W1	381.6 ± 138.4	—
W2	436.0 ± 128.6	0.0176
W3	555.0 ± 197.7	0.0424
W4	829.0 ± 281.4	0.0040
W6	1186.6 ± 445.2	0.0049
W8	1289.6 ± 448.4	0.0036
W12	1753.4 ± 593.0	0.0037
Medium Group		
W1	520.4 ± 127.6	-
W2	529.2 ± 119.3	0.7893
W3	604.2 ± 188.3	0.2139
W4	997.0 ± 353.4	0.0559
W6	1035.0 ± 420.5	0.0568
W8	1146.6 ± 416.9	0.0261
W12	1553.6 ± 677.9	0.0184
High Group		
W1	394.6 ± 132.3	—
W2	436.4 ± 122.9	0.0476
W3	497.0 ± 63.5	0.1393
W4	968.4 ± 392.7	0.0234
W6	1069.8 ± 274.6	0.0036
W8	1140.0 ± 283.3	0.0042
W12	1523.8 ± 341.1	0.0025

Statistically significant increases in HU were observed over time within all groups, particularly from Week 4 onward (p < 0.05, paired t-test vs. W1).

Table 2 summarizes the intra-group comparisons of HU changes over time using repeated measures ANOVA. Each dose group (Low, Medium, High) exhibited a statistically significant increase in HU values from Week 1 through Week 12. In the low-dose group, HU values increased from a mean of 326.0 ± 92.0 at Week 1 to 1423.6 ± 553.6 at Week 12 ($p = 0.005$). Similarly, the medium-dose group increased from 252.6 ± 80.1 to 1553.6 ± 622.3 ($p = 0.001$), and the high-dose group increased from 253.2 ± 92.7 to 1660.8 ± 403.7 ($p = 0.002$). These results confirm a significant and time-dependent improvement in bone density across all groups following treatment, highlighting the osteoinductive potential of SB cells.

Table 3: Clinical Characteristics

Case#	Age	Gender	Dose (CD61-Lin-SB Cells Conc./0.25ml DPBS)	Missing Tooth position#
1	64	Female	Low ($1x10^5$)	15
2	72	Male	Low ($1x10^5$)	14
3	44	Male	Low ($1x10^5$)	47
4	29	Male	Low ($1x10^5$)	35
5	54	Female	Low ($1x10^5$)	46
6	57	Male	Medium ($1x10^6$)	26
7	80	Female	Medium ($1x10^6$)	37
8	49	Male	Medium ($1x10^6$)	36
9	45	Male	Medium ($1x10^6$)	36
10	60	Male	Medium ($1x10^6$)	46
11	69	Female	High ($1x10^7$)	35
12	59	Female	High ($1x10^7$)	16
13	70	Male	High ($1x10^7$)	15
14	53	Male	High ($1x10^7$)	47
15	48	Male	High ($1x10^7$)	34

When transplanted into mice and rabbits, CD61^-Lin^- SB cells were not tumorigenic and lacked evidence of malignancy. In addition, in vivo assessment proved to have a capacity to induce new bone formation, validating their osteoinductive potential. 15 subjects were enrolled in the human clinical trial, stratified into three groups based on SB cell dosage, including Low dose ($1×10^5$ cells; n=5), Medium dose ($1×10^6$ cells; n=5), and High dose ($1×10^7$ cells; n=5). The age range of the subjects was 29 to 81 years (median age = 54 years). The group comprised nine men and six women. There were no severe systemic diseases at baseline, although some of them had well-controlled hypertension. All subjects had reduced bone mineral density (BMD), according to D3 bone measurements. The clinical parameters in detail, such as age, gender, cell dose, and site of missing tooth, are listed in **Table 3**.

Figure 1: Illustrates the mean HU progression over time for the three SB cell dosage groups. The graph demonstrates a steady and consistent increase in bone density from Week 1 to Week 12 across all groups. The curve is steeper in the medium and high-dose groups, reflecting a faster rate of mineralization and bone regeneration. By Week 12, all groups showed substantial HU gains, with the high-dose group achieving the greatest improvement. The visual trend corroborates the statistical findings in Tables 1 and 2, reinforcing the dose-response relationship and the regenerative effect of $CD61^-Lin^-$ SB cells.

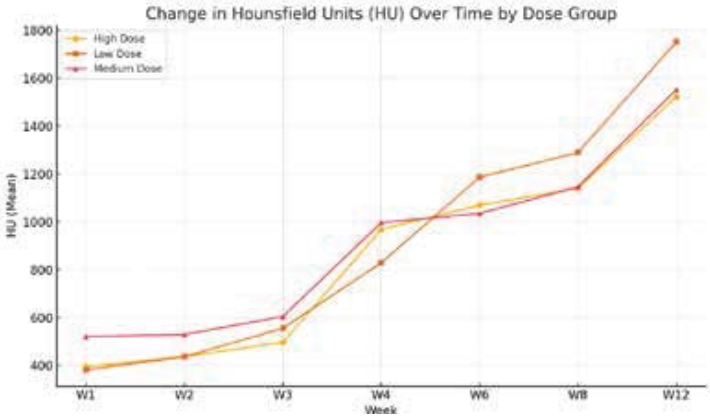

Figure 1: Hounsfield Unit (HU) Analysis

Table 4: Adverse Events from the Total Patient Population

	Grade 1	Grade 2	Grade 3	Grade 4	Tx-related
Hematology					
Platelets	0	0	0	0	0
Hemoglobin	0	0	0	0	0
Abnormal leukocyte	1	0	0	0	0
Abnormal neutrophils	0	0	0	0	0
Non-Hemotology					
Bilirubin	0	0	0	0	0
AST	0	0	0	0	0
ALT	1	0	0	0	0
Sugar (AC)	0	0	0	0	0

Table 5 shows the incidence and severity of adverse events observed during the study, categorized by hematological and non-hematological parameters. Most adverse events were absent or minimal, with the majority of parameters showing zero cases across all grades. Notably, mild (Grade 1) increases were observed in leukocyte count and alanine aminotransferase (ALT), each occurring in one patient. No moderate to severe (Grade 2 to 4) adverse events or treatment-related events were reported for any parameter, indicating a favorable safety profile in the assessed population.

DISCUSSION

The success of dental implants and jawbone quality is strongly influenced by osseointegration, essential for long-term stability. This study examines SB cells as an autologous stem cell therapy to enhance bone regeneration before implantation. Transplantation of up to 1x10^7 SB cells in healthy volunteers showed no adverse effects over six months of monitoring. Results were favorable across all patients, with trabecular and cortical bone density contributing to regeneration and implant longevity. Bone mineral density (BMD) and maximum stress were assessed to gauge bone quality. D2-D3 density levels in the posterior mandible were targeted, given their association with lower implantation success. Further confirmation could be obtained through biopsies or microarchitectural analysis[1,14]. SB cells were effective in treating alveolar bone defects.

Their safety and tolerability suggest applicability in other therapies requiring rapid bone remineralisation, such as root canals. Recombinant human bone morphogenetic protein-2 (BMP-2) is widely used in dental regenerative therapy but can cause ectopic bone formation and inflammation[15,16]. Other BMPs like BMP-4 and BMP-7 share these limitations. SB cells offer a potentially less inflammatory alternative. Study limitations include the absence of a non-SB cell control group and unclear dose-response outcomes, possibly due to saturation or suboptimal dosing.

Nonetheless, enhanced regeneration by week four indicates therapeutic promise. At three months, bone quality and volume improved uniformly. One high-dose patient (Case 7) demonstrated rapid BMD gains within two weeks, stabilising by week twelve. This mirrors typical patterns where early BMD rises and plateaus. High-dose groups showed greater BMD gains between weeks 16–24, though the small sample size limited significance. Traditionally, BMD peaks in the first three months post-treatment[9,17]. One patient receiving SB cells exceeded typical BMD improvement, suggesting enhanced osseointegration potential. Preclinical models support SB cells in bone repair. Their mechanism is likely related to paracrine signaling, as seen with other stem cells[18].

The study also explored cytokine and chemokine profiles before and after SB cell treatment. Implant placement induces inflammatory and remodeling responses, modulated by cytokine changes. Elevated cytokine levels over time may stem from SB cell transplantation. As seen in earlier phase I studies, cytokine variability demands cautious interpretation[19]. Assays confirmed that SB cells did not provoke systemic inflammation. While many changes lacked statistical significance, six biomarkers (Fractalkine, IL-17A, FGF2, eotaxin, MDC, and MCP-1) displayed consistent trends across 24 weeks.

These findings suggest the immunomodulatory effects of SB cells. FGF2, which aids vascularization and regeneration, was elevated in intermediate and high-dose groups. Chemokines eotaxin, MDC, and MCP-1 play roles in stem cell recruitment and bone remodeling. MCP-1 rose dose-dependently in most patients, except Patient 2, who showed reduced levels, indicating MCP-1's potential as a surrogate marker.

MCP-1 (CCL2), binding CCR2 receptors, contributes to osseointegration and bone regeneration [20,21]. It recruits immune cells and influences bone remodeling kinetics. Prior research links MCP-1 with osteoclast activity and bone repair, as confirmed in knockout models [22,23]. However, this study's lack of a control group weakens conclusions about cytokine

changes. MCP-1's short serum half-life further complicates its use as a marker. Titanium implants are also associated with increased MCP-1[24], warranting future research on SB cell–related cytokine shifts. SB cells show promise for tissue engineering, improving biocompatibility, and osseointegration for scaffold-based regeneration.

Implant success is influenced by elasticity, thickness, and porosity[25,26]. SB cells enhance oxide layer thickness and porosity, improving cell attachment and differentiation. Future studies should explore SB cell interactions with various implant materials and stressors. While this study used a collagen scaffold[27]. 3D-printed alternatives may offer additional benefits. SB cells are attractive in regenerative medicine because they can be used without complex expansion procedures. They are easily harvested from peripheral blood or bone marrow, minimising invasiveness and cost[28]. SB cells offer a compelling option for dental implant therapies. Their bone-forming capacity, immunomodulatory effects, and potential to replace BMP-based treatments underscore their promise in future clinical applications.

CONCLUSION

This Phase I clinical trial yielded encouraging data showing that CD61-Lin-stromal bone (SB) cells are both well-tolerated and safe for use when patients have significant alveolar bone defects. In the study, no serious side effects were evidenced, and in all the patients, treatment showed gradual improvements in bone mineral density. These findings indicate that SB cells can take an active part in promoting bone regeneration when utilised with guided bone regeneration (GBR) protocols. Moreover, enhanced osseointegration and accelerated wound healing were noticed clinically, affirming the regenerative potential of SB cells for oral and maxillofacial surgery. Patient demographics and clinical profiles substantiate that this treatment was successful in a diverse population, including those with longstanding tooth loss and low baseline bone volume. These data suggest that the therapeutic potential of SB cells goes beyond aiding dental implant placement to provide therapeutic benefit in more expansive regenerative medicine applications, such as craniofacial reconstruction and bone tissue engineering. With these promising findings, it is imperative that SB cell therapy now be explored in Phase II randomised controlled trials to evaluate efficacy more strongly. These trials will be important to confirm long-term outcomes, refine dosing regimens, and determine wider clinical applications in the area of cell-based regenerative therapies.

LIST OF ABBREVIATIONS

SB – Small Blood (stem) cells
GBR – Guided Bone Regeneration
BMD – Bone Mineral Density
HU – Hounsfield Units
CT – Computed Tomography
CD61 – Platelet Marker (used in cell sorting)
Lin – Hematopoietic Lineage (marker)
DLT – Dose-Limiting Toxicity
FDA – Food and Drug Administration
DPBS – Dulbecco's Phosphate-Buffered Saline
ROI – Region of Interest
FBC – Full Blood Count
Lgr5 – Leucine-rich Repeat-containing G-protein Coupled Receptor 5 (stem cell marker)
TFDA – Taiwan Food and Drug Administration
GTP – Good Tissue Practice
TEM – Transmission Electron Microscopy
DAPI – 4′,6-diamidino-2-phenylindole (DNA stain)
MSC – Mesenchymal Stem Cell
VSELS– Very Small Embryonic-Like Stem Cells
iPSCs – Induced Pluripotent Stem Cells
SPSS – Statistical Package for the Social Sciences
IL-17a – Interleukin-17a (a pro-inflammatory cytokine)
MCP-1 – Monocyte Chemoattractant Protein-1 (a chemokine)

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CONFLICT OF INTEREST

The author has no conflict of interest for this study.

ETHICAL APPROVAL

The ethical approval was obtained from the Hamdard University Dental Hospital Institutional Ethical Review Committee (Approval No: HCM&D/HUDH/1136-21).

AUTHORS' CONTRIBUTION

All other Authors contributed equally as per ICMJE. All authors agreed to be accountable for all aspects of the research.

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