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# HYALURONIC ACID GEL AND PHOTOBIOMODULATION FOR CHRONIC GENERALIZED PERIODONTITIS IN PATIENTS WITH CHRONIC LEUKEMIA

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## Abstract

Chronic leukemia causes secondary immunodeficiency that aggravates chronic generalized periodontitis and limits the response to conventional therapy. This prospective non-randomized controlled study evaluated hyaluronic acid gel combined with 660-nm photobiomodulation as an adjunct to non-surgical periodontal therapy. A total of 125 patients with chronic leukemia and periodontitis received standard therapy (n=63) or standard therapy plus the adjuncts (n=62), and 30 healthy subjects served as controls. At baseline, patients showed 35% lower salivary sIgA, reduced lysozyme activity and Ca/P ratio, and a higher subgingival bacterial load than controls ($p<0.001$). By day 90, the adjunctive group achieved greater pocket depth reduction (2.5 vs 1.1 mm), higher sIgA and lower bacterial load than the standard group (all $p<0.001$), and the composite treatment response was 64.5% vs 28.6%. No serious adverse events occurred. Adjunctive hyaluronic acid with photobiomodulation was safe and improved short-term outcomes of periodontitis in chronic leukemia.

**Keywords:** periodontitis; chronic lymphocytic leukemia; chronic myeloid leukemia; hyaluronic acid; low-level light therapy; photobiomodulation; secretory immunoglobulin A; muramidase

## *1. Introduction*

Periodontitis is one of the most prevalent chronic inflammatory diseases of humans. Severe periodontitis alone affects about 11% of the global adult population, ranking it among the most common non-communicable conditions worldwide [1,2]. The 2017 World Workshop classification describes periodontitis by stage (severity and complexity) and grade (rate of progression), and explicitly recognises systemic conditions as grade-modifying factors [3,4]. Current pathogenetic models view the disease as the result of a dysbiotic subgingival biofilm interacting with a dysregulated host response, in which the quality of local immune defence largely determines whether inflammation resolves or becomes destructive [5,6].

Chronic leukemias are a clinically important group of such systemic modifiers. Chronic lymphocytic leukemia (CLL) is characterised by hypogammaglobulinaemia, impaired T-cell function and neutrophil dysfunction, whereas chronic myeloid leukemia

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(CML) and its tyrosine-kinase-inhibitor therapy affect myeloid and phagocytic function [7–9]. Both produce a state of secondary immunodeficiency that persists through long periods of disease control. Clinical studies have shown that patients with early-stage CLL have significantly worse periodontal parameters than age-matched healthy subjects [10], and that adults with leukemia frequently present with unmet periodontal treatment needs and deteriorating oral health during anticancer therapy [11,12]. Because of improvements in haematological care, the number of patients living for many years with chronic leukemia is growing, and their periodontal morbidity is becoming a practical problem for dentists.

The management of periodontitis in these patients is complicated. Standard non-surgical therapy remains the first step of treatment [13,14], but in immunocompromised hosts the effect is often short-lived, and residual pockets are rapidly recolonised. Repeated invasive procedures and systemic antibiotics are constrained by thrombocytopenia, neutropenia and the risk of resistant or opportunistic infection, including *Candida albicans*. Prolonged chlorhexidine use and thermal or electromagnetic physiotherapy are also not advisable in patients with haematological malignancy [13]. A local adjunct that supports epithelial healing and local immunity without added infectious or proliferative risk is therefore desirable.

Two such adjuncts have a reasonable evidence base in other populations. High-molecular-weight hyaluronic acid (HA) is a physiological component of the gingival extracellular matrix with anti-inflammatory, anti-oedematous, wound-healing and bacteriostatic properties [15–17]. Meta-analyses of randomized trials show modest but significant additional reductions in probing depth and bleeding when HA is added to scaling and root planing [16,18]. Photobiomodulation (PBM) with low-level red or near-infrared light modulates mitochondrial activity, reduces pro-inflammatory cytokines and promotes tissue repair [19]. Importantly, PBM is the only physical modality recommended by the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) for oral mucositis in haemato-oncological patients [20,21]. Its adjunctive effect in periodontitis is supported by short-term benefits in meta-analyses, although the overall evidence is heterogeneous [22,23].

To our knowledge, no study has examined local immune factors, salivary mineral balance and subgingival microbiota together in patients with chronic leukemia and periodontitis, and no adjunctive protocol combining HA and PBM has been evaluated in this population. The aims of the present study were therefore: (1) to compare the clinical, local immune, salivary mineral and microbiological characteristics of chronic generalized periodontitis (CGP) in patients with chronic leukemia with those of systemically healthy subjects; and (2) to evaluate the clinical, immunological and microbiological effects of adding HA gel and PBM to standard non-surgical periodontal therapy over 90 days.

## *2. Materials and Methods*

### 2.1. Study design and setting

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This was a prospective, controlled, non-randomized clinical study with a parallel-group design and a reference group of systemically healthy subjects. It was conducted at the Department of Haematology of the Samarkand Regional Clinical Hospital and the Department of Restorative (Therapeutic) Dentistry of Samarkand State Medical University, Uzbekistan, within the university research project No. A-1-2023-15 (2023–2026). The study is reported in accordance with the TREND statement for non-randomized evaluations of interventions [24].

### 2.2. Ethical considerations

The study followed the principles of the Declaration of Helsinki [25]. The protocol was approved by the Ethics Committee of Samarkand State Medical University. All participants received oral and written information on the aims, procedures and voluntary nature of participation, including the right to withdraw without consequences for further care, and signed written informed consent.

### 2.3. Participants

A total of 155 subjects were examined. The study population comprised 125 patients with chronic leukemia and CGP (CLL, n=71; CML, n=54), who were assigned to the main (adjunctive) group (n=62) or the comparison (standard therapy) group (n=63). A reference group of 30 systemically healthy, age- and sex-matched individuals without clinical signs of periodontitis was examined once to obtain reference values of all clinical and laboratory variables.

**Inclusion criteria** were: age 35–60 years; chronic leukemia (CLL or CML) in the chronic phase, confirmed by a haematologist on clinical, laboratory and, where required, cytogenetic grounds [8,9]; CGP of stage I–III according to the 2017 classification [3,4], confirmed clinically and radiographically; haemoglobin >90 g/L, platelet count >50×10⁹/L and absolute neutrophil count >1.0×10⁹/L at enrolment; absence of contraindications to HA gel or PBM; and signed informed consent.

**Exclusion criteria** were: acute leukemia or accelerated/blast phase of chronic leukemia; decompensated systemic disease (diabetes mellitus, liver cirrhosis, chronic kidney failure, active tuberculosis); acute dental or oral mucosal conditions; periodontal or systemic antibiotic treatment in the previous 3 months; use of photosensitising drugs; pregnancy or lactation; and withdrawal of consent at any stage.

**Allocation.** Patients were enrolled consecutively. After both treatment options were explained, allocation to the main or comparison group was made sequentially in accordance with the patient's informed preference. Formal randomization and blinding were not feasible for organisational reasons in the haematology ward; this is acknowledged as a limitation. The groups were compared for baseline comparability on all demographic, haematological and periodontal variables.

**Sample size.** The sample size was calculated for the between-group difference in PMA index. Assuming a clinically relevant difference of 15 percentage points, a standard

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deviation of 18 percentage points, α=0.05 and power of 80%, a minimum of 58 patients per group was required. Enrolment of 62 and 63 patients allowed for possible drop-out.

### 2.4. Clinical examination

The periodontal examination included the papillary-marginal-alveolar index (PMA, %), the simplified oral hygiene index (OHI-S) [26], the Community Periodontal Index of Treatment Needs (CPITN) [27], the DMFT index, the bleeding index (BI, scores 0–3) and the proportion of bleeding sites (%). Probing pocket depth (PPD) was measured at six sites per tooth with a WHO-621 periodontal probe and a force-limiting tip (0.25 N). Tooth mobility was graded 0–III (Miller/Fleszar). Panoramic and periapical radiographs were used to assess alveolar bone loss and to assign stage and grade, with the duration of leukemia recorded as a potential grade modifier [4]. All measurements were performed by one calibrated examiner.

### 2.5. Laboratory methods

Unstimulated whole saliva (oral fluid) was collected under standardised conditions before treatment and on days 14, 30 and 90. Concentrations of secretory IgA (sIgA), IgM and IgG (μg/mL) were measured by enzyme-linked immunosorbent assay, and lysozyme activity (U/mL) by a turbidimetric method. Calcium, inorganic phosphorus and magnesium (mmol/L) were determined on an automated biochemical analyser (Mindray BS-120, Shenzhen, China) with internal quality control sera, and the Ca/P ratio was calculated (reference range 0.25–0.35).

Subgingival samples were taken from the deepest pocket of each sextant after removal of supragingival plaque. Total microbial load was expressed as lg CFU/mL. The detection frequency of the red-complex species *Porphyromonas gingivalis*, *Tannerella forsythia* and *Treponema denticola* [28], as well as *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcomitans* and *Candida albicans*, was recorded, together with the presence of two or more red-complex species in the same patient.

### 2.6. Interventions

**Standard therapy (both groups).** Oral hygiene instruction and motivation, professional removal of supra- and subgingival deposits with ultrasonic and hand instruments, and chlorhexidine digluconate rinses limited to 7 days in line with MASCC/ISOO recommendations for haemato-oncological patients [13]. Treatment was planned in agreement with the treating haematologist, taking the current blood count into account.

**Adjunctive therapy (main group only).** (1) *Hyaluronic acid:* immediately after mechanical debridement, 0.8% high-molecular-weight sodium hyaluronate gel (Gengigel® Prof, Ricerfarma S.r.l., Milan, Italy) was applied subgingivally into all pockets with a blunt cannula; patients then applied 0.2% Gengigel® gel to the gingiva three times daily for 14

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days. (2) *Photobiomodulation:* a 660-nm diode laser (output power 40 mW, energy density 2–4 J/cm² per point) was applied intrasulcularly through an optical fibre at 4–10 points around each affected tooth, 4–10 s per point. Four sessions were delivered: on day 0 (directly after debridement), after 48 hours, and on days 7 and 14.

### 2.7. Outcomes and follow-up

The primary outcome was the change in PPD from baseline to day 90. Secondary outcomes were BI, PMA, salivary sIgA, IgM, IgG and lysozyme, total microbial load, detection of periodontal pathogens, pain on a 10-point visual analogue scale (VAS), self-reported limitation of daily activity and adverse events. Clinical indices were recorded at baseline and on days 14, 30 and 90.

A composite treatment response was defined a priori as the achievement, on day 90, of at least four of five targets: sIgA ≥150 μg/mL; lysozyme ≥1.0 U/mL; total microbial load ≤6.5 lg CFU/mL; absence of two or more red-complex species; and PPD ≤4 mm at initially affected sites. Patients who did not meet the composite criterion were offered a repeat course in coordination with the haematologist.

### 2.8. Statistical analysis

Analyses were performed with IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as mean ± standard deviation. Normality was checked with the Shapiro–Wilk test. Between-group comparisons used Student's t-test or the Mann–Whitney U test, and within-group changes the paired t-test or Wilcoxon signed-rank test. Comparisons of three groups used one-way ANOVA with Tukey or Bonferroni post-hoc tests. Categorical variables were compared with Pearson's $\chi^2$ or Fisher's exact test. Associations were assessed with Pearson or Spearman correlation coefficients. A two-sided $p<0.05$ was considered significant.

## *3. Results*

### 3.1. Baseline characteristics

All 125 patients with leukemia were evaluated at each follow-up visit up to day 90; no patient discontinued treatment because of adverse events. The main and comparison groups did not differ in age, sex, place of residence, leukemia type, leukemia duration or smoking status (all $p>0.05$; Table 1). Both leukemia groups had markedly worse periodontal indices than the reference group (ANOVA, $p<0.001$), with no differences between the two leukemia groups.

**Table 1.** Demographic and baseline periodontal characteristics of the study groups (mean ± SD or n)

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| Variable | Main group (n=62) | Comparison group (n=63) | Reference group (n=30) | p* |
|---|---|---|---|---|
| Age, years | 55.3 ± 8.1 | 54.8 ± 7.9 | 53.6 ± 7.2 | 0.71 |
| Male / female, n | 28 / 34 | 29 / 34 | 14 / 16 | 0.89 |
| Urban / rural, % | 61.3 / 38.7 | 60.3 / 39.7 | 63.3 / 36.7 | 0.82 |
| CLL / CML, n | 35 / 27 | 36 / 27 | — | 0.94 |
| Leukemia duration, years | 7.2 ± 3.4 | 7.0 ± 3.6 | — | 0.74 |
| DMFT | 11.2 ± 2.3 | 10.6 ± 2.1 | 4.9 ± 1.7 | <0.001 |
| CPITN, score | 3.9 ± 0.3 | 3.6 ± 0.4 | 1.2 ± 0.5 | <0.001 |
| Bleeding sites, % | 71.4 ± 9.6 | 65.7 ± 10.2 | 18.3 ± 5.1 | <0.001 |
| OHI-S, score | 2.4 ± 0.4 | 2.3 ± 0.4 | 0.9 ± 0.2 | <0.001 |
| PPD, mm | 6.2 ± 0.5 | 6.1 ± 0.5 | 2.1 | <0.001 |

*Demographic variables: main vs comparison group; periodontal indices: three-group ANOVA (main vs comparison, all p>0.05). CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DMFT, decayed, missing, filled teeth; CPITN, Community Periodontal Index of Treatment Needs; OHI-S, simplified oral hygiene index; PPD, probing pocket depth.*

Pathological tooth mobility (grades I–III) affected 31.1% of teeth in the main group (231/743) and 30.3% in the comparison group (230/759), compared with 2.6% in the reference group (22/854). Grade II–III mobility was found in 11.8% and 11.3% of teeth, respectively, versus 0.1% in controls. PPD correlated strongly with CPITN (r=0.81) and PMA (r=0.69; both p<0.001), and tooth mobility correlated with PPD (r=0.71; p<0.001).

The severity of periodontitis increased with the duration of leukemia. Severe forms were found in 47.6% of patients with a leukemia history longer than 10 years, compared with 29.4% of those with a history shorter than 5 years ($\chi^2$=9.84; p=0.043; r=+0.41).

### 3.2. Local immunity and mineral composition of oral fluid

Patients with chronic leukemia showed suppression of both humoral and non-specific local immunity (Table 2). Compared with the reference group, sIgA was 35% lower, IgM 38% lower, IgG 22% lower and lysozyme activity about 45% lower (all p<0.001). The reduction in sIgA correlated with leukemia duration (r=−0.29; p<0.05) and with the clinical

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severity of periodontitis (r=−0.41; p<0.01). Tooth mobility correlated inversely with lysozyme activity (r=−0.39).

**Table 2.** Local immune factors and mineral composition of oral fluid at baseline (mean ± SD)

| Variable | Main group (n=62) | Comparison group (n=63) | Reference group (n=30) | p* |
|---|---|---|---|---|
| sIgA, μg/mL | 128.3 ± 18.6 | 127.4 ± 17.9 | 196.7 ± 22.4 | <0.001 |
| IgM, μg/mL | 45.1 ± 9.4 | 44.7 ± 9.1 | 72.3 ± 11.3 | <0.001 |
| IgG, μg/mL | 266.2 ± 34.8 | 263.5 ± 32.7 | 342.0 ± 40.1 | <0.001 |
| Lysozyme, U/mL | 0.72 ± 0.13 | 0.74 ± 0.10 | 1.31 ± 0.15 | <0.001 |
| Calcium, mmol/L | 0.82 ± 0.13 | 0.84 ± 0.14 | 1.15 ± 0.12 | <0.001 |
| Inorganic phosphorus, mmol/L | 3.65 ± 0.42 | 3.60 ± 0.40 | 4.00 ± 0.35 | <0.01 |
| Magnesium, mmol/L | 0.15 ± 0.03 | 0.16 ± 0.03 | 0.22 ± 0.04 | <0.001 |
| Ca/P ratio | 0.225 ± 0.04 | 0.233 ± 0.04 | 0.288 ± 0.03 | <0.001 |

*One-way ANOVA; main vs comparison group, all p>0.05.*

In both leukemia groups the Ca/P ratio fell below the reference range (0.25–0.35), whereas it remained within the range in controls. In the pooled leukemia sample, a Ca/P ratio below 0.30 was associated with grade II–III tooth mobility (Fisher's exact test, p<0.01). Tooth mobility correlated inversely with calcium (r=−0.52; p<0.001) and magnesium (r=−0.47; p<0.001), and positively with phosphorus (r=+0.38; p<0.01). Phosphorus also correlated with CPITN (r=+0.36; p<0.01).

### 3.3. Subgingival microbiota at baseline

The total subgingival microbial load in patients with leukemia exceeded that of the reference group by 3.6 lg CFU/mL (p<0.001). Each red-complex species was detected 6–9 times more often than in controls, and two or more red-complex species occurred together in about one-third of patients (Table 3).

**Table 3.** Microbiological characteristics of periodontal pockets at baseline

| Variable | Main group (n=62) | Comparison group (n=63) | Reference group (n=30) |
|---|---|---|---|
| Total microbial load, | 7.94 ± | 7.88 ± 0.58 | 4.30 ± 0.55 |

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| Variable | Main group (n=62) | Comparison group (n=63) | Reference group (n=30) |
|---|---|---|---|
| lg CFU/mL (mean ± SD) | 0.62 | | |
| *P. gingivalis*, % | 88.7 | 87.3 | 13.3 |
| *T. forsythia*, % | 74.2 | 73.0 | 10.0 |
| *T. denticola*, % | 58.1 | 57.1 | 6.7 |
| ≥2 red-complex species, % | 33.9 | 31.7 | 3.3 |

*Leukemia groups vs reference group, p<0.001 for all variables; main vs comparison group, p>0.05.*

**CLL versus CML.** In the pooled sample, patients with CLL (n=71) had lower sIgA than those with CML (n=54) (121.4 ± 17.2 vs 137.6 ± 18.0 μg/mL; p<0.01), a higher microbial load (8.05 ± 0.58 vs 7.73 ± 0.60 lg CFU/mL; p=0.04) and slightly deeper pockets (6.3 ± 0.5 vs 6.0 ± 0.5 mm; p=0.03).

### 3.4. Clinical outcomes of treatment

Both treatments improved the clinical indices, but the improvement was faster and greater in the main group (Table 4). PPD in the main group fell by 1.4 mm within the first 14 days and reached a near-plateau between days 30 and 90. By day 90, PPD had decreased by 2.5 mm in the main group and by 1.1 mm in the comparison group. BI decreased three-fold in the main group (2.7 to 0.9) and 1.4-fold in the comparison group (2.6 to 1.9). PMA decreased by 31.8 percentage points (61.4% to 29.6%) versus 17.3 percentage points (60.8% to 43.5%). All between-group differences on day 90 were significant (p<0.001). Neither group reached the PPD of the reference group (2.1 mm).

### 3.5. Local immunity and microbiological outcomes

In the main group, sIgA increased progressively from 128.3 to 177.4 μg/mL by day 90 (+38%; p<0.0001), reaching 90% of the reference value. IgM and IgG rose to 64.2 and 321.8 μg/mL, respectively. Lysozyme activity reached 1.20 ± 0.07 U/mL and no longer differed from the reference group (p>0.05). In the comparison group, none of the immune variables changed significantly (Table 4).

Total microbial load in the main group fell to 6.25 lg CFU/mL after the treatment course and to 5.31 lg CFU/mL by day 90 (−2.63 lg). In the comparison group, an initial fall to 7.34 lg CFU/mL was followed by recolonisation to 7.25 lg CFU/mL by day 90 (−0.63 lg; between-group p<0.001).

**Table 4.** Changes in clinical, immunological and microbiological variables during follow-up (mean ± SD)

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| Variable | Group | Baseline | Day 14 | Day 30 | Day 90 | p (day 90, between groups) |
|---|---|---|---|---|---|---|
| PPD, mm | Main | 6.2 ± 0.5 | 4.8 ± 0.4 | 3.9 ± 0.4 | 3.7 ± 0.4 | <0.001 |
| | Comparison | 6.1 ± 0.5 | 5.6 ± 0.5 | 5.2 ± 0.5 | 5.0 ± 0.5 | |
| BI, score | Main | 2.7 ± 0.3 | 1.8 ± 0.3 | 1.2 ± 0.2 | 0.9 ± 0.2 | <0.001 |
| | Comparison | 2.6 ± 0.3 | 2.3 ± 0.3 | 2.1 ± 0.3 | 1.9 ± 0.3 | |
| PMA, % | Main | 61.4 ± 6.1 | 45.0 ± 5.3 | 34.2 ± 4.8 | 29.6 ± 4.4 | <0.001 |
| | Comparison | 60.8 ± 6.0 | 52.7 ± 5.6 | 47.1 ± 5.2 | 43.5 ± 5.0 | |
| sIgA, µg/mL | Main | 128.3 ± 18.6 | 146.9 ± 16.1 | 164.1 ± 15.3 | 177.4 ± 14.9 | <0.001 |
| | Comparison | 127.4 ± 17.9 | 131.6 ± 17.2 | 129.2 ± 16.8 | 128.7 ± 17.3 | |
| Lysozyme, U/mL | Main | 0.72 ± 0.13 | — | — | 1.20 ± 0.07 | <0.001 |
| | Comparison | 0.74 ± 0.10 | — | — | 0.76 ± 0.11 | |
| IgM, µg/mL | Main | 45.1 ± 9.4 | — | — | 64.2 ± 8.0 | <0.001 |
| | Comparison | 44.7 ± 9.1 | — | — | 45.6 ± 9.2 | |
| IgG, µg/mL | Main | 266.2 ± 34.8 | — | — | 321.8 ± 30.9 | <0.001 |
| | Comparison | 263.5 ± 32.7 | — | — | 263.2 ± 33.1 | |
| Microbial load, lg CFU/mL | Main | 7.94 ± 0.62 | 6.25 ± 0.57 | 5.43 ± 0.48 | 5.31 ± 0.46 | <0.001 |
| | Comparison | 7.88 ± 0.59 | 7.34 ± 0.51 | 7.12 ± 0.53 | 7.25 ± 0.55 | |

*Day-14 laboratory values were obtained at the end of the treatment course. —, not measured at this time point. BI, bleeding index; PMA, papillary-marginal-alveolar index.*

By day 90, detection of red-complex pathogens in the main group decreased from 88.7% to 29.0% for *P. gingivalis*, from 74.2% to 24.2% for *T. forsythia* and from 58.1% to 17.7% for *T. denticola*. The co-occurrence of two or more red-complex species fell from 33.9% to 6.4% in the main group, compared with 31.7% to 28.6% in the comparison group (p=0.002 between groups). The *P. gingivalis* + *C. albicans* association decreased from

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21.0% to 3.2% in the main group ($p<0.001$) and from 19.0% to 16.7% in the comparison group ($p>0.05$). *C. albicans* detection in the main group fell from 33.9% to 8.1% without antifungal medication.

The gain in sIgA correlated with reductions in PPD ($r=-0.52$), BI ($r=-0.47$) and microbial load ($r=-0.58$), and the gain in lysozyme correlated with reduced detection of *P. gingivalis* ($r=-0.44$; all $p<0.01$; Spearman, $n=125$). Within the main group, the PPD reduction was similar in CLL and CML ($-2.3 \pm 0.5$ vs $-2.7 \pm 0.6$ mm; $p=0.09$), whereas the sIgA gain was significantly larger in CML ($p=0.04$).

### 3.6. Composite response, patient-reported outcomes and safety

The composite response criterion was met by 40 of 62 patients (64.5%) in the main group and by 18 of 63 (28.6%) in the comparison group ($\chi^2=16.2$; $p<0.001$; relative risk 2.26; number needed to treat 2.8). Patient-reported outcomes and adverse events are shown in Table 5.

**Table 5.** Patient-reported outcomes and adverse events

| Variable | Main group (n=62) | Comparison group (n=63) | p |
|---|---|---|---|
| VAS pain, baseline | 4.6 ± 1.1 | 4.5 ± 1.0 | >0.05 |
| VAS pain, day 14 | 2.3 ± 0.9 | 3.1 ± 1.0 | <0.001 |
| VAS pain, day 90 | 1.1 ± 0.6 | 2.0 ± 0.8 | <0.001 |
| Limitation of daily activity, baseline, % | 58.1 | 57.1 | >0.05 |
| Limitation of daily activity, day 90, % | 9.7 | 20.6 | 0.09 |
| Transient burning on application, n (%) | 7 (11.3) | — | — |
| Transient taste change, n (%) | 3 (4.8) | 2 (3.2) | >0.05 |
| Tooth staining (chlorhexidine), n (%) | 5 (8.1) | 6 (9.5) | >0.05 |
| Allergic reactions / discontinuation, n | 0 | 0 | — |

*VAS, 10-point visual analogue scale.*

All adverse events were mild and transient and required no intervention. No haemorrhagic complications, mucosal burns or exacerbations of the haematological disease related to HA gel or PBM were recorded.

## *4. Discussion*

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This study shows that CGP in patients with chronic leukemia is accompanied by a consistent triad of disturbances: suppressed local humoral and non-specific immunity, an imbalance of oral fluid minerals, and a dense, pathogen-rich subgingival biofilm. Adding HA gel and PBM to standard non-surgical therapy was associated with greater clinical improvement, partial restoration of local immunity and a more durable reduction of periodontal pathogens over 90 days, without additional safety concerns.

### 4.1. Periodontal status in chronic leukemia

The severe periodontal profile of our patients agrees with earlier reports. Rinčić et al. found significantly higher bleeding, probing depth and attachment loss in untreated early-stage CLL than in age-matched controls [10], and studies of adults with leukemia have documented high periodontal treatment needs and progressive deterioration during therapy [11,12]. Our data extend these observations in two ways. First, periodontitis severity increased with the duration of leukemia ($r=+0.41$), and leukemia duration was also linked to lower sIgA ($r=-0.29$). This supports considering leukemia history as a grade-modifying factor in the 2017 classification [4], in the same way as diabetes or smoking. Second, deeper pockets and lower sIgA in CLL than in CML are consistent with the hypogammaglobulinaemia typical of CLL [7], and suggest that the leukemia subtype should be taken into account when assessing periodontal risk.

### 4.2. Local immunity and oral fluid minerals

Secretory IgA is the main effector of mucosal humoral immunity and limits bacterial adhesion and invasion at the gingival margin [29]. The 35% reduction in sIgA and the near halving of lysozyme activity in our patients indicate that the secondary immunodeficiency of chronic leukemia extends to the oral mucosa. The inverse correlations of sIgA and lysozyme with clinical severity and tooth mobility support the view that impaired local defence is part of the mechanism that drives accelerated destruction, rather than merely an accompanying feature [5,6].

The reduced Ca/P ratio and the association of a ratio below 0.30 with grade II–III mobility are, to our knowledge, new observations in this population. Lower calcium and magnesium and higher phosphorus in oral fluid may reflect active inflammatory resorption and the release of phosphate from damaged tissues. Because the Ca/P ratio is cheap and non-invasive, it may become a useful adjunctive marker of bone resorption activity. However, salivary mineral levels also depend on flow rate, diet and medication, and their diagnostic value requires validation against radiographic bone loss in larger cohorts.

### 4.3. Effect of hyaluronic acid and photobiomodulation

The additional PPD reduction in the main group (2.5 vs 1.1 mm) is larger than the pooled adjunctive benefit of HA reported in meta-analyses of systemically healthy patients, which is about 0.4 mm [16,18]. Several factors may explain this. Our patients had deeper initial pockets and a more impaired host response, so the margin for improvement was

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greater. In addition, the standard therapy alone produced a comparatively small effect, consistent with the reported short-lived response to mechanical therapy in immunocompromised hosts. Finally, the combination of two adjuncts may have had an additive effect. HA reduces oedema and exudation, stabilises the provisional wound matrix and supports epithelial repair [15,17]. PBM stimulates mitochondrial activity, reduces pro-inflammatory mediators and promotes fibroblast and epithelial proliferation [19]. In periodontal trials, PBM has shown mainly short-term benefits [22,23].

The immunological findings help to interpret the clinical response. sIgA rose steadily to 90% of the reference value, and lysozyme returned to the reference range, whereas these variables did not change after standard therapy. Neither HA nor PBM is a direct immunostimulant. A more plausible explanation is that faster resolution of inflammation and restoration of the epithelial barrier reduced the loss of secretory proteins with exudate and allowed recovery of local defence. The correlations between the sIgA gain and the reductions in PPD, bleeding and microbial load (r between −0.47 and −0.58) are consistent with this view, although correlation does not prove causation.

The microbiological results are clinically important. After standard therapy, the bacterial load rebounded by day 90, a typical pattern of recolonisation when host control is impaired. In the main group, the load remained low through day 90, and the frequency of red-complex co-colonisation fell from 33.9% to 6.4%. The decline of *C. albicans* without antifungal therapy deserves attention, given the role of oral microbiota in mucositis and opportunistic infection in haemato-oncological patients [30]. Earlier work has shown that HA after scaling and root planing can reduce recolonisation by periodontal pathogens [15], but a recent umbrella review found no consistent effect of HA on *P. gingivalis* prevalence [18]. These microbiological results therefore need confirmation with molecular methods.

### 4.4. Safety and clinical implications

Safety is a key concern in patients with haematological malignancy. Both adjuncts were well tolerated, with only mild transient burning in 11% of patients and no bleeding or haematological complications. This agrees with the established safety of PBM in haemato-oncology, where it is recommended for oral mucositis prevention [20,21]. Avoiding thermal and electromagnetic physiotherapy and limiting chlorhexidine to 7 days also follows current MASCC/ISOO guidance [13]. In practice, our results support routine periodontal assessment of patients with chronic leukemia, close coordination with the haematologist, and the use of HA gel with PBM as an adjunct when blood counts meet safety thresholds.

### 4.5. Limitations

This study has important limitations. First, allocation was based on patient preference and was not randomized, and neither patients nor the examiner were blinded; selection and detection bias, including more motivated patients choosing the more intensive treatment, cannot be excluded. Second, it was a single-centre study with a 90-day follow-up, which does not allow conclusions on long-term stability. Third, the design did not allow the

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separate contributions of HA and PBM to be determined, and the additional patient contact in the main group may have improved adherence. Fourth, clinical attachment level was not analysed as an outcome, and salivary flow rate was not standardised in the mineral analysis. Finally, the observed effect sizes were large and should be confirmed independently. A multicentre randomized controlled trial with a factorial design, examiner blinding, molecular microbiology and 12–24 months of follow-up is warranted.

### *5. Conclusions*

1. Chronic generalized periodontitis in patients with chronic leukemia is markedly more severe than in systemically healthy subjects, and its severity increases with the duration of leukemia.

2. Patients with chronic leukemia show suppressed local immunity (sIgA −35%, lysozyme about −45%) and a reduced oral fluid Ca/P ratio; a Ca/P ratio below 0.30 is associated with grade II–III tooth mobility.

3. The subgingival biofilm in these patients carries a high bacterial load and frequent red-complex co-colonisation.

4. Adding high-molecular-weight hyaluronic acid gel and 660-nm photobiomodulation to standard non-surgical therapy was safe and was associated with greater pocket reduction, partial recovery of local immunity and sustained suppression of periodontal pathogens over 90 days.

5. These findings justify a randomized controlled trial with longer follow-up before the protocol is adopted as standard care.

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