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Original Article

Intensive Oral Hygiene Interventions during Therapy of Acute Leukemia May Result in Detrimental Outcomes: A Randomized Clinical Trial

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Abstract

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Objectives There are no standard guidelines on oro-dental care during induction therapy of acute leukemia (AL). This study aimed to assess the effect of intensive oral hygiene practice on oral mucositis, infection, and disease outcomes compared to standard clinical practice.

Materials and Methods Newly diagnosed patients with AL were randomized to receive either standard oral hygiene protocol (group A, $n = 92$) or comprehensive oral hygiene protocol (group B, $n = 91$). In group A, the oral hygiene indexes were measured by the dentist at baseline and at the end of treatment. In group B, weekly monitoring of oral hygiene indexes by the dentist and interventions in the form of oral cavity inspection, probing for gum health, and use of a soft toothbrush and education on oral hygiene practices were carried out.

Results The frequency of mucositis was higher in group B (60%) than in group A (40%; $p = 0.09$). There was no difference in the median Simplified Oral Hygiene Index (OHI-S; 0.5 vs. 0.6) and Silness and Loe plaque index (0.4 vs. 0.25) between the groups. The local (11 vs. 1%; $p = 0.005$) and systemic infection rate (82.2 vs. 65.2%; $p = 0.009$) were higher in group B than in group A.

Conclusion This study failed to show the superiority of a comprehensive oral hygiene protocol compared to standard protocol in reducing oral mucositis in patients receiving induction therapy for AL. We hypothesize that frequent intervention in the oral cavity may lead to the dissemination of infection.

Keywords

- oral hygiene
- intervention
- acute leukemia
- intensive oral hygiene
- Infection

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Introduction

Acute leukemia (AL) is a highly curable malignancy and, at the same time, is associated with life-threatening systemic infections during treatment.[1] Odontogenic infection can be a potential source for sepsis during severe myelosuppression postchemotherapy. Early and radical dental intervention may minimize the risk of oral and associated systemic complications. At the same time, there is a possibility of dissemination of infection due to frequent oral intervention in patients with immunosuppression. There are no standard practices for preventing, monitoring, and treating oral complications during induction therapy of leukemia. The effect of such comprehensive oral hygiene protocol on the infection rates and treatment outcomes in patients with leukemia has not been studied systematically in a randomized controlled study. The study aimed to assess the effect of comprehensive oral hygiene practice on oral mucositis, infection, and disease outcomes compared to standard practice in patients with AL on induction chemotherapy.

Patients and Methods

Study Design

This study was a randomized, open-label control trial. The primary objective of the study was to assess the effect of comprehensive oral hygiene practices on oral mucositis when compared to standard practice in patients with AL on induction chemotherapy. The secondary objectives of the study were to assess the effect of comprehensive oral hygiene protocol on local and systemic infections, induction outcomes, and survival compared to standard of care. This study was carried out in the medical oncology and dentistry departments from June 2016 to April 2019. The study protocol was approved by the institute's ethics committee (JIP/IEC/2016/28/931), and patients were included in the study after obtaining informed consent.

Randomization and Masking

Patients were randomly assigned to a 1:1 ratio to receive standard oral hygiene protocol (group A) or comprehensive oral hygiene protocol (group B). This was an open-label study. Randomization was done using a computer-generated fixed block size of four to receive standard oral hygiene protocol or comprehensive oral hygiene protocol. Allocation concealment was done using sequentially numbered, opaque sealed envelopes.

Procedures

The primary data for the study were collected using a standard proforma by the dietician on a weekly basis. Oral mucositis and chemotherapy complications were graded using the World Health Organization (WHO) score and National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03, respectively. Infections were classified as localized or systemic during the chemotherapy induction period.

Details of Chemotherapy and Antibiotic Protocol

Injection daunorubicin (60 mg/m^2) on day 1 (D1) to day 3 (D3) with injection cytarabine 100 mg/m^2 continuous infusion (CI) from D1 to D7 chemotherapy was used as induction chemotherapy in acute myelogenous leukemia patients.[1] Patients with acute lymphoblastic leukemia received one of the three protocols, namely, Multicenter protocol-841 (MCP - 841),[2] Berlin-Frankfurt Munster 95 protocol (BFM 95),[3] or German Multicenter ALL protocol 84 (GMALL 84).[4]

All dental examinations were carried out at the bedside by the dentist, and standard precautions for neutropenia and thrombocytopenia were followed. If platelet counts were less than 30,000/µL, probing was avoided. Instruments used for dental probing and hygiene measures were sterilized. Gentle rinsing of the mouth with chlorhexidine mouthwash was done prior to each dental examination. The dentist coordinated the follow-up with the oncology department to monitor for signs of infection. The oral hygiene status was assessed by the Simplified Oral Hygiene Index (OHI-S) score.[5]

Group A (Conventional Arm)

The dentist reviewed patients at the baseline and at the end of induction chemotherapy. During the induction treatment phase, referral to the dentist was done as and when the physician requested. The type and frequency of prophylactic mouthwashes were left to the discretion of the treating physician. The oncologist managed the treatment of oral mucositis and infections with antibiotics and analgesics.

Group B (Comprehensive Oral Hygiene Group)

The dentist monitored the patients on a weekly basis at bedside and interventions in the form of oral cavity inspection, probing for gum health, and use of a soft toothbrush with adequate aseptic precautions were carried out. The patients were educated on oral hygiene practices weekly by a dietician.

The pre- and postquestionnaire assessment of oral hygiene education was done on prior induction and induction completion. The questionnaire consisted of 16 questions that included oral care methods, and signs and management of oral complications.

The details of the intervention provided in the comprehensive oral hygiene group are described in ►**Supplementary Table S1** (available in the online version only). After completion of induction chemotherapy, patients were followed up for a minimum of 3 months.

The outcomes were measured at the end of induction therapy in group A and weekly in group B. The highest grade during this period was documented for analysis. If a patient progressed or died during the induction; the last documented grade was noted.

Outcomes

The primary outcome measure was the frequency of all-grade oral mucositis (WHO score) in each arm. The secondary outcomes were infection rates (local, systemic, and central venous), changes in the OHI-S, Silness and Loe plaque index scores, and induction outcome.

Induction outcome was measured by complete response defined as less than 5% blasts with absence of any extramedullary disease on the bone marrow performed at the end of induction.

Sample Size and Statistical Analysis

The sample size was based on the expected difference in the incidence of oral mucositis between the groups as 15% at a 5% level of significance and 80% power. The distribution of categorical data was expressed as frequency and percentages. The comparison of the variables between the groups was carried out using the chi-squared test or Fisher's exact test for the categorical data. All statistical analyses were carried out at a 5% significance level, and *p*-value less than 0.05 was considered significant.

Results

A total of 202 patients with AL were randomized during the study period from June 2016 to April 2019 into two groups, namely standard protocol and comprehensive protocol (►Fig. 1). A few patients in each arm were excluded for final analysis after randomization as they did not start therapy or due to unavailability of outcome data and acute promyelocytic leukemia. Patients included in the final analyses were 92 in group A and 91 in group B. The overview of patient enrolment, outcomes in terms of mucositis, systemic infections, induction outcomes, and vital stats are provided in ►Fig. 1.

Baseline Characteristics

The baseline clinical and demographic profiles in both groups were well matched. Children and adults constituted 30 and 70%, respectively, of the study population in both groups. Acute lymphoblastic leukemia and acute myeloid leukemia were represented equally in the study groups. Baseline central venous catheters were used in 45% of the patients in each group, most of them in acute myeloid patients. Baseline systemic infections were seen in 50% requiring antibiotic therapy. The nutritional assessment revealed that 38% of the patients in the study were malnourished.

The dentist assessed the baseline oral hygiene status in both groups before the start of chemotherapy. All the baseline oral hygiene parameters like dental caries, bacterial plaque, gum bleeding, candidiasis, gingival hypertrophy, and periodontal infections were equally distributed between

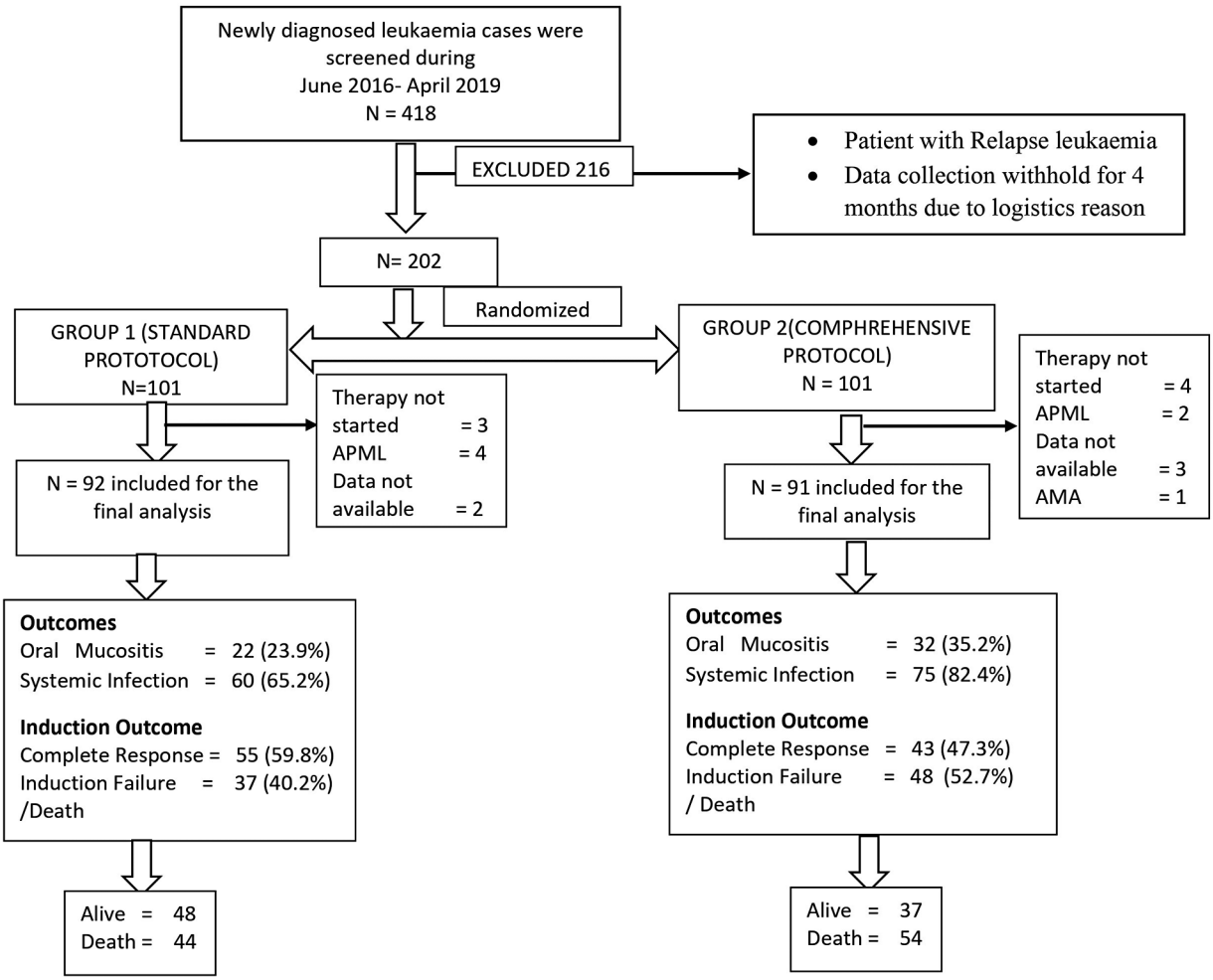

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT): standard oral hygiene group versus comprehensive protocol—randomized controlled trial (RCT). AMA, antimicrobial agent; APML, acute promyelocytic leukemia.

Table 1 Baseline clinical, oral hygiene, and demographic profile

Sl. no.	Characteristics	Group A ($N=92$)	Group B ($N=91$)
1	**Age**		
	<18 y ≥ 18 y	31 (33.7) 61 (66.3)	28 (30.8) 63 (69.2)
2	Sex M:F	1.79:1	1.68:1
3	**Diagnosis**		
	ALL AML	46 (50) 46 (50)	51 (56) 40 (44)
4	**Baseline systemic infection**		
	Yes No	45 (48.9) 47 (51.1)	48 (52.7) 43 (47.3)
5	**Baseline antibiotics**		
	Yes No	47 (51.1) 45 (48.9)	52 (57.1) 39 (42.9)
6	**Baseline catheter**		
	Yes No	41 (44.6) 51 (55.4)	43 (47.3) 48 (52.7)
7	**Baseline oral hygiene**		
	a. Dental caries	43 (46.7)	48 (52.7)
	b. Bacterial plaque	40 (43.5)	37 (40.7)
	c. Gum bleeding	12 (13)	19 (20.9)
	d. Periodontal infection	10 (10.9)	17 (18.7)
	e. Gingival hypertrophy	12 (13)	8 (8.8)
	f. Oral infection	4 (4.3)	4 (4.4)
	g. Mucositis	11 (12)	9 (9.9)
	h. OHI-S index (median with range)	0.8 (0.00–3.8)	0.8 (0–0.45)
	Good (0.0–1.2)	68 (73.9)	67 (73.6)
	Fair (1.3–3.0)	20 (21.7)	20 (22)
	Poor (3.0–6.0)	4 (4.3)	4 (4.4)
	i. Silness and Loe plaque index (median with range)	0.5 (0.0–2.50)	0.4 (0–3.2)
	Excellent (0)	19 (20.7)	14 (15.4)
	Good (0.1–0.9)	46 (50)	57 (62.6)
	Fair (1.0–1.9)	24 (26.1)	17 (18.7)
	Poor (2.0–3.0)	3 (3.3)	3 (3.3)

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; OHI-S, Simplified Oral Hygiene Index;

the two groups (►**Table 1**). Baseline mucositis (grade 1 or 2) was documented in 10% of the patients. The baseline mean OHI-S score and Silness and Loe plaque index were good in both groups. We noticed that the primary endpoint, the rate of oral mucositis, was numerically higher in group B (60%) than in group A (47%; $p=0.09$). The gastrointestinal complications, OHI-S index, Silness and Loe plaque index were similar between the two groups.

Postintervention at the End of Induction Therapy

The local complication rates were significantly higher in group A compared to group B after induction chemotherapy postintervention (1.1 vs. 11%; $p=0.005$). The systemic infection rates were significantly higher in the comprehensive group (82%) compared to the standard protocol (65%; $p=0.009$). The systemic infection type and site were similar between the groups. The catheter-related infections requiring removal did not differ between the groups. However, infection-related mortality was numerically higher in group B (18%) than in group A (30%). The complete remission rates were also numerically higher in the standard arm (60%) compared to the comprehensive group (48%; ►**Supplementary Table S2**, available in the online version only). The oral hygiene education provided by a nutritionist for patients in group B through didactic PowerPoint lectures and group activities was effective, as evidenced by significant post-test score improvement ($p=0.001$). The mouth wash frequency

adherence was better in the comprehensive group ($p = 0.004$; ►Supplementary Table S3, available in the online version only). On subgroup analysis, it was seen that patients with acute myeloid leukemia had better compliance to the use of mouthwash than patients with acute lymphoblastic leukemia. There was no significant change in the OHI-S and plaque index score during the weekly monitoring in the comprehensive group (►Supplementary Table S4, available in the online version only).

Survival Outcomes

The median duration of follow-up of the study group was 36 months (range: 31.4–40.6 months). The median event-free survival in groups A and B was 11 and 5 months, respectively ($p = 0.03$), as shown in ►Supplementary Figure S1 (available in the online version only). On univariate analysis, age ≥18 years, acute myeloid leukemia, comprehensive oral hygiene practice, oral mucositis, and systemic infections were significantly associated with poor event-free survival. On multivariate Cox proportional hazards, acute myeloid leukemia and oral mucositis were the only factors associated with poor survival (►Supplementary Table S5, available in the online version only).

Discussion

This study was designed to see if an intensive and comprehensive oral hygiene protocol was superior to a standard protocol. This is the first randomized control study looking at a comprehensive protocol that includes a standard prescribed oral preventive measure, weekly monitoring by the dentist, and regular oral hygiene education. There are no standard approved guidelines and reviews for the intensity of oral care and monitoring during leukemia induction therapy.[6–8] Chaveli López et al, in a review article, have described in detail the dental treatment before, during, and after chemotherapy, which has not been prospectively validated.[9] Our study revealed that comprehensive oral hygiene protocol was not superior to standard oral care in patients with AL in preventing mucositis, while the frequency of local complications and systemic infections was higher in the comprehensive protocol.

It is evident from the literature that preventive oral care compared to none during induction chemotherapy reduces the incidence of oral mucositis. The majority of the preventive oral hygiene studies have used a different oral formulation to reduce mucositis like chlorhexidine, bicarbonate, and honey in reducing oral mucositis in children with AL.[10] A cross-sectional study by Kapoor et al to assess the oral health status of children with leukemia showed that children with acute lymphoblastic leukemia undergoing treatment and following oral care protocol had a good OHI-S score and plaque index compared to healthy children.[5] It is important not only to document subjective assessment in terms of mucositis grade but also to have objective assessment using indices to evaluate oral hygiene. Our study showed that more than 70% of the patients had good oral hygiene defined by the indices at baseline in both groups.

In acute myeloid leukemia, the oral hygiene index is usually low due to gingival infiltration and hypertrophy with occasional bleeding.[11] The baseline oral hygiene in acute lymphoblastic leukemia and acute myeloid leukemia was comparable between the groups in our study, with nearly half of the patients having dental caries and bacterial plaque. Baseline mucositis was seen in 10% of the patients. The comprehensive group had numerically higher rates of periodontal infections (18 vs. 11%) but were not statistically significant. A study by Ponce-Torres et al showed that the incidence of periodontal infections in AL could be as high as 40% during induction therapy.[12] Periodontal infections increase the risk of local and systemic infections.

The primary endpoint for the study was oral mucositis, which was numerically higher in the comprehensive group than in the standard protocol group but did not reach statistical significance. The local and systemic infection rates were significantly higher in the comprehensive group. The catheter-related infections were similar in both groups.

The adherence to mouth wash was quite low between the two groups (41.7%) in the standard arm compared to the comprehensive group (66.7%), although it was higher in the comprehensive arm especially in the acute myeloid leukemia subset. The adherence data were collected for the mouth wash alone and not for the entire protocol. We cannot rule out whether the rate of mucositis or infection would have been lower if the overall adherence to mouth wash would have been higher in the comprehensive protocol. The effectiveness of oral hygiene education was confirmed with statistically significant improvement in posttest compared to the pretest evaluation. Mucositis and local and systemic infections were higher in the comprehensive protocol, which provides evidence that intensive oral care, frequent probing, and dental visits may be detrimental, and caution may be advised in the setting of leukemia. We hypothesize that frequent oral interventions like increased frequency of mouth wash may alter the oral flora resulting in dissemination of infection. Local oral diseases like periodontitis oral carries can occur due to microbial dysbiosis. The oral microbiome can alter the immune signals,[13] which may result in increased frequency of local and systemic infections in an already immunosuppressed patient. In patients with preexisting periodontal infections, probing for gum plaques may spread infection, especially in the neutropenic setting. A randomized controlled study on the prevention of oral mucositis in patients treated with high-dose chemotherapy and transplant using limited oral hygiene care and intensive oral hygiene care showed a reduced incidence of mucositis in the intensive group. The assessment of mucositis in that study was subjective. The incidence of documented septicemia was similar between the groups. The authors concluded that the superiority of intensive oral hygiene care was not clinically impressive as it did not reduce systemic infections.[14] The intensive oral hygiene care included initial treatment of dental lesions and toothbrushing compared to the low intense group, which excluded preventive dental treatment and gingival and toothbrushing. These patients had undergone dental procedures as part of the

pretransplant workup when the patients were neither on active treatment nor neutropenic. This contrasts with our patients who had minimal probing to assess the gingival health but were neutropenic and on active chemotherapy drugs, which may explain the increased systemic infections in our study. In a study by Toth et al, toothbrushes were used safely regardless of the blood counts in patients with hematological malignancies, but this had not been studied in a controlled setting. Our study recommended using a toothbrush in the comprehensive group, while the standard group used their finger to clean their tooth.[15,16] There is evidence that dental procedures such as tooth extraction, periodontal surgery, and root scaling increase the risk of systemic bacterial infections.[17] It is unclear whether procedures like gingival probing increase the risk of systemic infection.

The study did not show a difference in the occurrence of mucositis between the groups as the patients with the standard protocol were initially evaluated by the dentist, and all these patients followed minimal oral hygiene practices. Induction failure, which includes not achieving a complete response and death during induction, was numerically higher in the comprehensive protocol group. Event-free survival was significantly poor in the comprehensive protocol group, in patients with oral mucositis, and in patients with systemic infections. Patients with oral mucositis were independently associated with poor survival, which was confirmed on multivariate analysis. It is evident that oral care is necessary during leukemia induction to prevent oral mucositis; at the same time, we need to monitor and avoid dental procedures.

Strengths of the Study

To the best of our knowledge, this is the first randomized controlled study with a large sample size looking at the effect of comprehensive oral care in patients with leukemia. We used an objective method for scoring oral hygiene status using the OHI-S score and plaque index. The effectiveness of oral hygiene education was verified using pre- and posttest assessments.

Limitations

The secondary endpoints like local and systemic infections and induction outcomes were not adequately powered and are therefore exploratory, which must be confirmed. We cannot rule out contamination of the standard protocol group to oral hygiene education as both groups were admitted to the same hospital ward during the induction therapy. We did not stratify patients based on periodontitis, chemotherapy protocol, and type of leukemia during randomization.

Conclusion

This randomized controlled trial failed to show the superiority of a comprehensive oral hygiene protocol compared to the standard protocol in reducing oral mucositis in patients receiving induction therapy for AL. It is necessary to follow oral hygiene precautions to reduce oral mucositis; simultaneously, we need to be careful about the intensity of monitoring. Intensive oral care, including frequent dental visits, oral mouth wash, and interventions like probing, may be detrimental with increased local and systemic infections.

Authors' Contribution

B.D. made substantial contributions to the conception and design of the work, acquisition and interpretation of data for the work, drafting the work, and revising it critically for important intellectual content, and gave final approval of the version to be published. N.P.M. contributed to data acquisition and gave final approval of the version to be published. K.B. made substantial contributions to the conception and design of the work, acquisition of data, and revising the manuscript critically for important intellectual content, and gave final approval of the version to be published. S.K. made substantial contributions to the conception and design of the work, acquisition of data, and revising the manuscript critically for important intellectual content, and gave final approval of the version to be published. K.T.H.K. contributed to the analysis and interpretation of data for the work and gave final approval of the version to be published. M.A. contributed to data acquisition and gave final approval of the version to be published. N.D. contributed to data acquisition and gave final approval of the version to be published. P.G. contributed to revising the manuscript critically for important intellectual content and gave final approval of the version to be published. Y.N. contributed to the analysis and interpretation of data for the work, revising the manuscript critically, and drafting the work, and gave final approval of the version to be published.

All the authors agreed to be accountable for all aspects of the work and to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data and Code Availability

The datasets analyzed in this study are available with the corresponding author, which can be obtained on reasonable request. The datasets generated or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

This study was approved by the JIPMER Institute ethics committee (JIP/IEC/2016/28/931). All data used in this study were anonymized and coded before use. Written informed consent was obtained from each participant after explaining the purpose and procedure and their contribution in the study in their vernacular language.

Conflict of Interest

None declared.

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