

Comprehensive Oral Health Care to Reduce the Incidence of Severe Early Childhood Caries (s-ECC) in Urban China

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Objective: To explore the effectiveness of comprehensive oral health care to reduce the caries incidence for children with severe early childhood caries (s-ECC) in an urban area in China.

Methods: A total of 357 children aged 3 to 4 years old and diagnosed with s-ECC were recruited in this randomised controlled, single-blinded clinical trial for 1 year. Children of two different kindergarten classes were enrolled in this study and randomly divided into a test group (205 children) and a control group (152 children). The test group received comprehensive oral health care, which included: oral health examination, oral health education, topical fluoride application and dental treatment, and the children in the control group only received the oral health examination. The evaluation of the oral health questionnaire for parents was also performed. An evaluation was carried out at the time of recruitment and 1 year later to explore the effectiveness of the comprehensive oral health care model.

Results: The differences in decayed teeth (dt), decayed tooth surfaces (ds), filled teeth (ft), filled tooth surfaces (fs) and the ratio of $ft/(dt + ft)$ between the two groups were statistically significant ($P < 0.001$) at 1 year. The incidence of caries in the control group was higher than that of the test group ($P = 0.02$). The rate of awareness of oral health knowledge ($P = 0.01$) and the practice of good diet habits ($P = 0.02$) by parents in the test group were significantly higher than those in the control group.

Conclusion: The present study demonstrated that the comprehensive oral health care program reduces and prevents caries amongst children with s-ECC.

Key words: caries, child, comprehensive oral health care

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Dental caries is a common, complex and chronic disease resulting from an imbalance between risk factors and protective factors over time¹. Early childhood caries (ECC) is a very common and consequential chronic disease affecting young children². The prevalence of caries of primary teeth in China is high³.

The Third Chinese National Oral Health Survey in 2005 estimated that the prevalence of dental caries in a 5-year-old group was 66.0% and that the average decayed, missing and filled primary teeth (dmft) was 3.5 per child. The indices of decayed teeth (dt), decayed tooth surfaces (ds), filled teeth (ft), missing teeth (mt), filled tooth surfaces (fs), decayed, missing, and filled teeth (dmft), missing tooth surfaces (ms) and decayed, missing, and filled tooth surfaces (dmfs) were common indices to evaluate caries. The Significant Caries Index (SiC) of 5-year-old children was 8.333. In other words, the dmft of the most serious third of affected children was 8.33. Thus, a preventive and control program for dental caries in children should focus on high-risk children, those diagnosed with severe early childhood caries (s-ECC) and children below 5 years of age.

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The ECC has been defined by the American Academy of Pediatric Dentistry (AAPD) in 1999⁴. In children younger than 3 years of age, more than one of the decayed, missed or filled tooth surfaces due to caries in smooth surface is indicative of s-ECC. From ages 3 years old through to 5 years old, one or more cavitated, missed, or filled smooth surfaces due to caries in primary maxillary anterior teeth or dmfs ≥ 4 (age 3 years old), dmfs ≥ 5 (age 4 years old), or dmfs ≥ 6 (age 5 years old) surfaces was also regarded as s-ECC⁵. Severe early childhood caries progresses rapidly and is difficult to control⁵. Caries and its consequence affect oral and general health⁶.

The Third Chinese National Oral Health Survey in 2005 showed that only 20% of 5-year-old children brush their teeth twice a day and that 20% of 5-year-old children have not started brushing their teeth at all¹. The risk factors of caries are not only multiple, but also complex². Hence multiple preventive methods are required to control s-ECC. Clinical studies have shown the effectiveness of some preventive methods, such as oral health education^{5,7-11}, fluoride toothpaste^{12,13} etc. A few studies reported that oral health education for the parents could decrease the occurrence of s-ECC^{5,7-11}. Other studies explored the effect of fluoride toothpaste in caries prevention^{12,13}. Another study observed the effect of fluoride varnish in preventing early childhood caries¹⁴. So far, preventive strategies had focused mainly on one age group of children and consisted of a single preventive strategy at one time¹⁵⁻¹⁷. The objective of the present program is to develop a comprehensive oral health care model for s-ECC in kindergartens in urban areas of China, and to evaluate its effectiveness in reducing and preventing dental caries.

Materials and methods

Enrollment of participants

This program was a single-blinded clinical trial designed to test the effect of comprehensive oral health care for s-ECC. The patients were selected by the random cluster sampling method. Children of two different kindergarten classes were enrolled in this study and randomly divided into a test group (205 children) and a control group (152 children). The two kindergarten classes were matched in size, organisation and level. The oral health statuses of the two groups were also similar at baseline. Only children that met the eligibility criteria were included in this study.

The eligibility criteria of the samples were as follows: children aged 3 to 4 years old diagnosed with s-ECC enrolled in primary classes and middle classes of kindergartens in urban areas of Beijing. The parents of the enrolled children signed a consent form. The test group received comprehensive oral health care, which included: oral health examination, oral health education, topical fluoride application and dental treatment, and the control group only received oral health examination twice a year. When the study was finished, the children in the control group would receive our comprehensive oral health care, such as dental treatment and fluoride application, after their parents signed the consent form. The study was approved by the Peking University Institutional Review Board in Beijing (IRB00001052-10090).

Baseline evaluation

The baseline evaluation included an oral health examination and an evaluation of the oral questionnaire. Oral health examination was carried out using a plain mirror, Community Periodontal Index (CPI) probe and artificial light. The oral health examination evaluated dmfs. Four faculty members from the Department of Preventive Dentistry at the Peking University School and the Hospital of Stomatology conducted the oral health examination. Before the baseline investigation, these faculty members received training by an epidemiologist who attended the Third Chinese National Oral Health Survey. Through the standard consistency examination, the Kappa values for examiners were calculated. The inter-examiner Kappa value before the survey ranged from 0.82 to 0.91. During the survey, the standard assessment of consistency was performed, where the inter-examiner Kappa value ranged from 0.80 to 0.93, and the intra-examiner value ranged from 0.82 to 0.97.

With the collaboration of the doctors and teachers in the kindergartens, the questionnaires were distributed to the parents of the participants. The questionnaire was prepared by the author and then modified by taking advice from several specialists, who were responsible for the design of the questionnaires used in the Third Chinese National Oral Health Survey. Further modifications of the questionnaire were performed following a pre-test, and the final version was used in this project. The content of the questionnaire included questions evaluating the risk factors, sociodemographic data, diet habits and oral hygiene habits of children diagnosed with s-ECC, as well as questions evaluating the Knowledge, Attitude and Practice (KAP) of parents regarding oral health in their children. The

questionnaire which evaluated the awareness of oral health knowledge included four sub-questions, such as “the role of fluoride application to prevent caries was uncertain”, “pit and fissure sealant could prevent caries”, “brush teeth twice a day could prevent primary caries” and “oral health examination regularly could find oral health problems in time”. The questionnaire which evaluated the correct attitude for oral health care also included four sub-questions, such as “our tooth were instinctive and had little relationship with self-protection”, “oral health was very important to our life”, “mothers with bad teeth would affect their children’s teeth” and “primary teeth caries did not need treatment”. The questionnaires were multiple-choice questions. The answers of these questions included “agree”, “disagree” or “no answer”. Awareness rate of oral health knowledge and the correct rate of attitude for oral health care was the ratio of the number of the correct sub-questions:the number of the total sub-questions.

Comprehensive oral health care model for the test group

The comprehensive oral health care model for the test group included oral health examination, oral health education, topical fluoride application and dental treatment.

The oral health professionals delivered lessons and lectures to the teachers once a year and the standard Power Point (PPT) files would be given to the teachers for them to teach children. Physicians and kindergarten teachers would deliver the oral health education lessons for children about three to four times per year. If teachers had any questions about oral health care, the oral health professionals would provide professional help. Parents underwent oral health education lectures at least once a year, which was performed by oral health professionals. The education focused on the following topics: the relationship between oral health and systemic health; the importance of oral health for children; the skills of oral hygiene for children; how to help children brush their teeth; diet habits useful for oral health; and instructions regarding consuming sugar products.

Topical fluoride (1.23% fluoride) in the form of fluoride foam was given to the children aged between 3 to 5 years old. Fluoride foam was placed in a suitable tray and retained in the mouth for 4 min twice a year after oral health examination during the same period. This treatment was given by oral health professionals after obtaining consent from the parents. Another four faculty members from the Department of Preventive Dentistry at the Peking University School and Hospital

of Stomatology conducted the fluoride application. Before the fluoride application, these faculty members received training by experienced professionals.

Oral health examinations were performed by oral health professionals twice a year before fluoride application. The parents were then informed about the results of the oral health examination, including information regarding teeth that needed treatment. Dental treatment was performed only after obtaining their signed consent. Faculty members from the Department of Preventive Dentistry at Peking University School and the Hospital of Stomatology provided dental treatment for the children. The treatment included pit and fissure sealant, filling of caries and root canal therapy of primary teeth.

The comprehensive oral health care evaluation survey

One year after the baseline investigation, a survey was conducted to evaluate the effect of the comprehensive oral health care program. The content of the survey included the evaluation of the oral health status of the children via an oral health examination and the evaluation of the oral health knowledge level of parents via an evaluation of the oral health questionnaire.

Data analysis

The Statistical Product and Service Solutions 18.0 (SPSS, Illinois, USA) was used to analyse the data. The distribution of the gender and age among the test and the control groups was tested with the chi-square test. The difference between the caries indices of the control and the test groups at baseline and at 1 year was analysed with an independent t test. Paired t tests were used to compare the caries indices (dt, mt, ft, dmft and the ratio of the (dt + ft)/ft, ds, ms, fs and dmfs) of the children between the baseline and 1 year. Independent t tests were used to compare the continuous variables between the two groups, such as “the awareness rate of oral health knowledge” and “the correct rate of attitude for oral health care”. Cross-tabulation analysis was used to compare the categorical variables between the two groups, such as the diet and oral hygiene habits of children.

Results

General information

A total of 357 children aged from 3 to 4 years old diagnosed with s-ECC were subjected to baseline investiga-

Table 1 Comparison of the baseline characteristics of the test group and the control group.

	Control group		Test group		Total	
	N	Proportion (%)	N	Proportion (%)	N	Proportion (%)
Gender						
Boys	57	46.72	85	47.22	142	47.02
Girls	65	53.28	95	52.78	160	52.98
Total	122	100.00	180	100.00	302	100.00
Age group						
3 years old	44	36.07	77	42.78	121	40.07
4 years old	78	63.93	103	57.22	181	59.93
Total	122	100.00	180	100.00	302	100.00

Table 2 The oral health status of children at baseline.

	Control group		Test group		Independent t test	
	X	SD	X	SD	t	P
Dt	3.84	2.94	3.85	3.18	-0.02	0.987
Mt	0.02	0.13	0.01	0.07	0.93	0.353
Ft	0.75	1.98	0.48	1.08	1.53	0.127
Dmft	4.61	3.43	4.34	3.28	0.70	0.482
Ratio of the (dt+ft)/ft	0.11	0.26	0.12	0.26	-0.30	0.761
Decayed tooth surfaces						
Ds	7.94	7.37	7.71	7.25	0.28	0.782
Missing tooth surfaces						
Ms	0.05	0.46	0.02	0.30	0.62	0.538
Filled tooth surfaces						
Fs	1.25	3.61	1.02	2.35	0.69	0.489
Decayed, missing, and filled tooth surfaces						
Dmfs	9.25	8.16	8.74	7.62	0.55	0.586
Number of permanent teeth						
Number of permanent teeth	0.20	0.87	0.07	0.47	1.71	0.089
Number of primary teeth						
Number of primary teeth	19.83	0.58	19.90	0.42	-1.24	0.215

Dt: decayed teeth; Mt: missing teeth; Ft: filled teeth; Dmft: decayed, missing, and filled teeth; Ds: decayed tooth surfaces; Ms: missing tooth surfaces; Fs: filled tooth surfaces; Dmfs: decayed, missing, and filled tooth surfaces; SD: standard deviation.

tion. After 1 year, 302 (84.6%) participants completed the intervention and evaluation, while 55 (15.4%) were lost to follow up. In total, 302 children diagnosed with s-ECC were recruited, and their average age was 4.25 (standard deviation [SD] = 0.75) years. There were 142

boys (47%) and 160 girls (53%). The distribution of the gender and age among the test and the control groups was similar (Table 1). The average ages of the control group and the test group were 4.31 (SD = 0.61) years and 4.21 (SD = 0.83) years, respectively.

Table 3 The oral health status of children after 1 year.

	Control group		Test group		Independent t test		
	X	SD	X	SD	t	P	
Dt	3.61	3.17	2.22	2.90	3.93	0.000	***
Mt	0.04	0.24	0.00	0.00	2.32	0.021	*
Ft	1.33	2.43	2.63	2.72	-4.25	< 0.001	***
Dmft	4.98	3.80	4.84	3.47	0.31	0.757	
Ratio of the (dt+ft)/ft	0.21	0.32	0.56	0.41	-7.78	< 0.001	***
Ds	8.03	7.46	5.19	7.25	3.30	< 0.001	***
Ms	0.20	1.12	0.00	0.00	2.36	0.019	*
Fs	2.55	5.05	5.20	5.68	-4.16	< 0.001	***
Dmfs	10.78	9.31	10.39	8.35	0.37	0.708	

Dt: decayed teeth; Mt: missing teeth; Ft: filled teeth; Dmft: decayed, missing, and filled teeth; Ds: decayed tooth surfaces; Ms: missing tooth surfaces; Fs: filled tooth surfaces; Dmfs: decayed, missing, and filled tooth surfaces; SD: standard deviation.

*: $0.01 \leq P < 0.05$

** : $0.001 \leq P < 0.01$

***: $P < 0.001$

Oral health status of children

The caries indices in terms of dt, mt, ft, dmft, and the ratio of the (dt + ft)/ft, ds, ms, fs and dmfs, of the control and the test groups at baseline was not significantly different (Table 2).

In contrast, the caries indices were significantly different between the control group and the test group at the second evaluation 1 year later, including dt, mt, ft, the ratio of the (dt + ft)/ft, ds, ms and fs (all $P < 0.05$, Table 3). The incidence of primary caries in the control group and the test group were 43.4% and 31.7%, respectively, which was significantly different ($\chi^2 = 4.354$, $P = 0.02$).

The caries indices of the children were compared at baseline and at 1 year within each group using the paired t test. In the test group the dt, ft, dmft and the ratio of the (dt + ft)/ft, ds, fs and dmfs were significantly different ($P < 0.001$), between baseline and the second evaluation. In the control group the ft, the ratio of the (dt + ft)/ft, fs and dmfs values were significantly different ($P < 0.001$), between baseline and the second evaluation (Table 4).

KAP of the parents and the diet and oral hygiene habits of children

The following indices between the two groups were not significantly different at enrollment: the awareness rate of oral health knowledge and the correct rate of attitude to oral health care; the proportion of children with a correct diet habit; and whether parents helped or checked the results of toothbrushing.

At the 1 year evaluation, the awareness rate of oral health knowledge and the correct rate of attitude to oral health care in the test group had increased. The difference in the awareness rate of oral health knowledge between the control group and the test group was statistically significant ($t = -2.549$, $P = 0.012$) (Table 5). Similarly the difference in the proportion of correct diet habits between the control group and the test group was statistically significant ($\chi^2 = 4.373$, $P = 0.026$) (Table 6).

Table 4 The oral health status between baseline and the second evaluation.

	Baseline		Evaluation		Variation		Paired t test	
	Mean	SD	Mean	SD	Mean	SD	t	P
Control group								
Dt	3.84	2.94	3.61	3.17	-0.24	2.20	1.19	0.235
Mt	0.02	0.13	0.04	0.24	0.02	0.16	-1.75	0.083
Ft	0.75	1.98	1.33	2.43	0.57	1.47	-4.31	< 0.001 ***
Dmft	4.61	3.43	4.98	3.80	0.36	1.72	-2.32	0.022 *
Ratio of the (dt+ft)/ft	0.11	0.26	0.21	0.32	0.11	0.26	-4.04	< 0.001 ***
Ds	7.94	7.37	8.03	7.46	0.09	4.06	-0.25	0.807
Ms	0.05	0.46	0.20	1.12	0.15	0.81	-2.01	0.056
Fs	1.25	3.61	2.55	5.05	1.30	2.80	-5.12	< 0.001 ***
Dmfs	9.25	8.16	10.78	9.31	1.53	4.02	-4.21	< 0.001 ***
Test group								
Dt	3.85	3.18	2.22	2.90	-1.63	2.67	8.21	< 0.001 ***
Mt	0.01	0.07	0.00	0.00	-0.01	0.07	1.00	0.319
Ft	0.48	1.08	2.63	2.72	2.14	2.69	-10.71	< 0.001 ***
Dmft	4.34	3.28	4.84	3.47	0.51	1.51	-4.49	< 0.001 ***
Ratio of the (dt+ft)/ft	0.11	0.25	0.56	0.41	0.12	0.26	-13.35	< 0.001 ***
Ds	7.71	7.25	5.19	7.25	-2.51	5.32	6.33	< 0.001 ***
Ms	0.02	0.30	0.00	0.00	-0.02	0.30	1.00	0.319
Fs	1.02	2.35	5.20	5.68	4.18	5.49	-10.22	< 0.001 ***
Dmfs	8.74	7.62	10.39	8.35	1.65	2.92	-7.57	< 0.001 ***

Dt: decayed teeth; Mt: missing teeth; Ft: filled teeth; Dmft: decayed, missing, and filled teeth; Ds: decayed tooth surfaces; Ms: missing tooth surfaces; Fs: filled tooth surfaces; Dmfs: decayed, missing, and filled tooth surfaces; SD: standard deviation.
 *: 0.01 ≤ P < 0.05; **: 0.001 ≤ P < 0.01; ***: P < 0.001

Table 5 The KAP of parents at the second evaluation.

	Control group		Test group		Independent t test	
	X	SD	X	SD	t	P
Awareness rate of oral health knowledge	56.13%	0.25	65.63%	0.27	-2.549	0.012 *
Correct rate of attitude for oral health care	76.96%	0.20	79.69%	0.21	-0.935	0.351

SD: standard deviation

*: $0.01 \leq P < 0.05$

Table 6 Diet habits and oral hygiene habits of children at the second evaluation.

	Control group		Test group		Total	
	N	Proportion (%)	N	Proportion (%)	N	Proportion (%)
Proportion of correct diet habit						
No	52	61.9	36	45.6	88	54.0
Yes	32	38.1	43	54.4	75	46.0
Total	84	100.0	79	100.0	163	*100.0
Whether helped or checked the results of brush						
No	45	48.4	45	51.1	90	49.7
Yes	48	51.6	43	48.9	91	50.3
Total	93	100.0	88	100.0	181	100.0

*: $0.01 \leq P < 0.05$

Discussion

Findings from this study showed that comprehensive oral health care could reduce and prevent caries of children with s-ECC. In conjunction with oral health education, the oral health knowledge and the practice of good diet habits by parents were significantly improved.

s-ECC is a multifactorial disease that cannot be controlled effectively by a single preventive method and requires a comprehensive prevention strategy. The comprehensive oral health care model was used in this study for the test group and included oral health examination, oral health education, topical fluoride application and dental treatment. This model focused not only on the prevention of caries, but also on the prevention of the progression of existing caries. Parents, teachers, doctors and dentists joined together to improve the oral health level of children in this study.

We used a combination of primary, secondary and tertiary preventive methods to generate our comprehensive oral health care model. The primary prevention included oral health education for parents and teachers in kindergarten and topical fluoride use for children. The secondary prevention included oral health examination twice every year for early diagnosis and therapy. The tertiary prevention included dental treatment.

The results of this study showed that the oral health status of the control group and the test group at the time of recruitment was not significantly different. However, many of the oral health indices were significantly different at the post-intervention evaluation survey time point, including dt, mt, ft, ratio of the (dt + ft)/ft, ds, ms and fs ($P < 0.001$). In addition, the difference of incidence between the two groups was statistically significant ($P = 0.025$). The awareness rate ($P = 0.012$) and the proportion of children with a correct diet habit ($P = 0.026$) between the control group and the test group at the 1 year evaluation were significantly different. Taken together, these results indicate that the comprehensive oral health care model is effective in children diagnosed with s-ECC in our sample population in urban China.

In addition, in the test group, the dt, ft, dmft and the ratio of the (dt + ft)/ft, ds, fs and dmfs at 1 year were significantly higher than those at baseline ($P < 0.001$). In the control group, the ft, the ratio of the (dt + ft)/ft, fs and dmfs at 1 year were significantly higher than those at baseline ($P < 0.001$).

Although the children in the control group did not receive comprehensive oral health care, the parents of these children were informed about the results of their oral health examination and were advised to take their children to the hospital to receive dental treatment. Some parents took their children to the hospital to receive dental treatment, but they might not have received comprehensive oral health care, such as oral health education and fluoride application. The control group results revealed that only the proportion of filled tooth surfaces increased, while the proportion of decayed tooth surfaces did not significantly change. Therefore, dental treatment could only increase the filled proportion, but it did not prevent caries. Other preventive methods need to be combined in order to obtain better results.

There are several limitations in this study. First, the period of this study was only 1 year. Longer studies are needed to assess the exact impact of the model. Second, more indices, such as the microbial level, should be investigated, in order to evaluate the effectiveness of the comprehensive oral health care model. Third, inclusion of additional strategies, such as pit and fissure sealant or other types of topical fluoride agents may be more effective in preventing s-ECC. In conclusion, we demonstrated the effectiveness of the comprehensive oral health care model to prevent s-ECC in children.

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Conflicts of interest

The authors reported no conflicts of interest related to this study.

Author contribution

Dr Yan Si and Dr Yan Guo for the study design, for collecting the clinical data, for data inputting and analysis, and for writing the manuscript; Dr Chao Yuan for collecting the clinical data; and Dr Tao Xu and Dr Shuguo Zheng as the director of the research.

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The manuscript should be written clearly and concisely and be double-spaced on 21 x 29 cm white paper with at least 2.5 cm margin all around. All pages should be numbered, beginning from section of title page, and followed by abstract, introduction, materials and methods, results, discussion, acknowledgements, references, figure legends and figures/tables. Non-standard abbreviations should be defined when first used in the text. Use a standard font such as Times New Roman or Arial to avoid misrepresentation of your data on different computers that do not have the unusual or foreign language fonts. For units, the Journal recommends the use of the International System of Units (SI Units). For authors whose native language is not English, the Journal strongly recommends improving the English in the manuscript by consulting an English-speaking scientist before submission.

Title page should include: full title (a brief declarative statement of the major findings of the research), full names of authors, professional affiliations and complete postal address, telephone and fax number, and email address of the corresponding author. If the work was supported by a grant, indicate the name of the supporting organisation and the grant number.

Abstract and keywords: 250 words presented in a concise form and including the purpose, general methods, findings, and conclusions of the research described in the paper. A list of 5 keywords or short phrases (a few words per phrase) suitable for indexing should be typed at the bottom of the abstract page. Avoid vague or overly general terms. If necessary, the keywords will be adjusted to the standards of the Journal by the editors without consulting the authors.

Introduction: should begin with a brief introduction of background related to the research and should be as concise as possible. The rationale of the study should be stated.

Materials and Methods: should be described clearly and referenced in sufficient detail. Description should be such that the reader can judge the accuracy, reproducibility, reliability, etc. of the work.

Results: should present the experimental data in tables and figures with suitable descriptions and avoid extended discussions of its relative significance.

Discussion: should focus on the interpretation and significance of the findings with concise objective comments. Speculation is to be based on data only. The text should be written with a logical connection between the introduction and conclusions.

Acknowledgements: should only recognise individuals who provided assistance to the project.

References: should be cited in the text using superscript numbers and typed in numerical order following a style below:

1. Sorensen JA, Engleman MT, Torres TJ, Avera SP. Shear bond strength of composite resin to porcelain. *Int J Prosthodont* 1991;4:17-23.
2. Renner RP, Boucher LJ. Removable Particle Dentures. Chicago: Quintessence, 1987:24-30.
3. White GE, Johson A van Noort R, Northeast SE, Winstanley B. The quality of cast metal ceramic crowns made for the NHS [abstract 48]. *J Dent Res* 1990;69(special issue):960.
4. Jones DW. The strength and strengthening mechanisms of dental ceramics. In: McLean JW (ed). *Dental ceramics: Proceedings of the First International Symposium on Ceramics*. Chicago: Quintessence, 1983:83-41.
5. Rosenstiel S. The Marginal Reproduction of Two Elasto meric Impression Materials [Master's thesis]. Indianapolis: Indiana University, 1997.

Figures and Tables: should be numbered consecutively with Arabic numerals, with each one displayed on a separate page. Photographs should be of excellent quality with a width of 8 cm or 17 cm. All figures and tables should be cited in the text. Please refer to a current volume of this Journal for general guidance.

Legends for all figures, including charts and graphs, must be typed together on a separate page and should be understandable without reference to the text, including a title highlighting the key results and a key for any symbols or abbreviations used in the figure.

Case reports

Authors should describe one to three patients or a single family. The text is limited to no more than 2500 words, and up to 15 references.

Revised Manuscripts

All revisions must be accompanied by a cover letter to the Editor. The letter must detail on a point-by-point basis the contributors' disposition of each of the referees' comments, and certify that all contributors approve of the revised content.