Special Reproduction of the Final Report of the Clinical Trial

"Clinical Efficacy of a Toothpaste with Aluminium Lactate and Chlorhexidine (Lacalut® aktiv) on Plaque Formation and Gingivitis"

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Introduction

Toothpastes are an ideal carrier for active pharmaceutical agents because teeth cleaning is the most common form of oral hygiene practised in Europe (Frandsen 1986). The active pharmaceutical agents in toothpaste should work to prevent caries and act as a prophylactic agent against gingivitis. Besides fluorides, which represent the most common and effective prophylactic agents against caries, metal ions, essential oils, aminfluoride/tinfluoride and Triclosan have all demonstrated their effectiveness as antibacterial agents in toothpastes (Addy 1986, Mandel 1988).
However, as a result of the various different ingredients in toothpastes (abrasive materials, detergents, flavor agents, preserving agents and humectants), some of these individual active agents may reciprocally inactivate themselves so that not all substances that have demonstrated their worth in simple *In vitro*-Systems are equally effective in the *In vivo*-Situation (Addy et al. 1983). It is very difficult to demonstrate the efficacy of one particular agent in a complex toothpaste mixture. Therefore the complete preparation should always be examined as alone the presence of any given agent is no guarantee for its efficacy in the overall combination (Addy et al. 1990).

Aluminium lactate is a lactic acid salt with astringent, protein-coagulating and slight haemostatic properties (Fiedler 1967). A coagulating membrane is expected to form on the gums' surface that protects the gums from exogenous irritations for a short time (Goodman & Gilman 1955, Fiedler 1967). The aluminium lactate has an anti-inflammatory and pain-relieving effect, whereby the most effective results were obtained with a concentration of 0.5% (Grauber & Waegelein 1950), which continued for around 3 to 4 hours (Wannenmacher 1961). The astringent effects of the aluminium lactate can also cause protein substances to precipitate in the dentin canals that inhibit the transmission of the stimulus and thus contribute to the desensitization of over-sensitive tooth necks (Higuchi et al. 1996).
Chlorhexidine (digluconate) is considered the most effective active agent in the fight against plaque and gingivitis and is also called the "gold standard" against which all other antimicrobacterial agents must be measured.
In the past, the use of chlorhexidine in toothpastes was given only very limited attention even though this agent is considered the gold standard in the prevention of plaque and gingivitis (Jones 1997). This was because of studies which indicated that chlorhexidine can be inactivated by the detergent sodium laural sulphate commonly found in toothpastes (Jenkins et al. 1991, Barkvoll et al. 1989). Nevertheless, two current *In vivo*-studies show no inhibition of the chlorhexidine (as a 0.2% mouthwash solution) when preceded by the use of toothpastes containing sodium laural sulphate (Van Strydonck et al. 2004, Van Strydonck et al. 2006).
A toothpaste containing aluminium lactate and chlorhexidine has been available on the market for over 60 years. Kämper (1942) reported many cases of successfully treated acute periodontal and gingival inflammation in patients who exercised poor or no oral hygiene after professional cleaning and the administration of an aluminium lactate toothpaste (Lacalut®). Keil (1969) describes a considerable improvement in the clinical situation of acute and chronic gingivitis once Lacalut®medical toothpaste was administered, an effect he could verify with histological and cytological examinations.
Once the data are scrutinized, however, it will be noticed that all examinations took place over 30 years ago or that there are no clinically controlled studies with a large number of trial participants.

Thus the goal of these double-blind, randomized, long-term (6 months) clinical trials with groups of trial participants being tested in parallel was to examine the antibacterial, plaque and gingivitis reducing effects of a toothpaste containing aluminium lactate and chlorhexidine (Lacalut® aktiv) compared to those of a toothpaste containing fluoride with no antibacterial agent (0.14% fluoride) on trial participants with gingivitis.

Material and Method

The clinical trial was begun after receiving the go-ahead from the Ethics Commission of the Albert-Ludwigs University Freiburg and was performed in compliance both with the ICH guidelines for Good Clinical Practice and the Declaration of Helsinki.

Description of the Trial participants

After a medical history was taken, information on the trial participants was acquired and a declaration of consent was signed by the trial participants, they were received into the clinical trial in a randomized manner according to the inclusion criteria (age: 18 – 80 years; sex: m + f; condition of teeth: ≥20 teeth, no removable prostheses; chronic gingivitis: GI (full mouth) ≥1) or exclusion criteria (women: pregnancy; medicaments: antibiotics during the previous 4 weeks; medicaments: blood thinners; participation in another clinical trial with medicaments or tooth care products, known incompatibility with or allergy to chlorhexidine, aluminium lactate or other components of the toothpastes).
The identification of moderate gingivitis as an exclusion criterion was done according to the gingival index according to Löe and Silness (1963).

Tested Products

The composition of the tested products is listed in table 1. The test toothpastes and the toothbrushes (Lacalut® med toothbrushes) were manufactured and delivered for the clinical trial to the Polyclinic Restorative Dentistry and Periodontology Department by Arcam, Michelinstraße 10, 66424 Homburg. All of the pastes were filled in identical, white, neutral 75 ml tubes. The coded tubes (A and B) were distributed according to a randomizing procedure (see test plan) and marked with the number of the test subject. The director of the clinical trial performed the decoding and the investigator once the testing was complete.

Design of the Clinical Trial

The schematic of the trial is shown in table 2. After a 2 - 4 week standardizing phase with one toothbrush and one toothpaste containing fluoride distributed (with no further antibacterial or astringent agents), 59 trial participants, in two groups of 30 and 29, cleaned their teeth either with a toothpaste containing aluminium lactate and chlorhexidine (Lacalut® aktiv) or with a reference toothpaste (containing fluoride, with no antibacterial agents).
Tests were carried out at baseline, after one month, three months and six months.
In order to determine the extent of gingivitis and plaque, in the course of these tests the

- gingival index according to Löe and Silness (GI) and the
- plaque index according to Quigley and Hein (1965) (PI) were measured. The extent of dental calculus formation was measured using the
- dental calculus index (CI) and the occurrence of discoloring measured using the staining index (SI). A plaque sample was taken at each follow-up examination to inspect the antibacterial effect. This probe was tested microbiologically for

- total number of bacteria (BC) and
- the number of colony-forming units (CFU).

The trial participants were also asked at each examination about the safety and the compatibility of the toothpastes and any unwanted occurrences were documented. The trial participants were given a questionnaire to complete regarding the taste of the toothpastes and their subjective feelings on using them.
No instruction was given on oral hygiene, as it was particularly important that no alteration in the frequency and manner of the particpants' existing oral hygiene occur.

Test Parameters

Gingival Index (GI):
The gingival index according to Löe und Silness (1963) was used as an inclusion criterion and for the follow-up examinations. It appraises the gingival state facially, orally, mesially and distally, according to both visual and invasive considerations and is classified in the following degrees:

Score 0	No inflammation of any kind
Score 1	Slight inflammation: slight changes of color and texture. No bleeding when probed.
Score 2	Moderate inflammation: moderate shine, redness, edema and hypertrophy. Bleeding when probed.
Score 3	More serious inflammation: obviousness redness and hypertrophy, tendency to spontaneous bleeding and ulceration.

The GI was measured at four locations on each of the 6 so-called Ramfjord teeth 16, 21, 24, 36, 41, 44. If one of these teeth was missing, the neighbouring tooth was measured instead.
The index was calculated from the sum of all measured values: 24.

Plaque Index (PI)
The plaque index was determined according to the criteria of Quigley and Hein (1962) in modification of Turesky et al. (1970) according to the staining of the plaque with an erythrosine solution at the six Ramfjord teeth 16, 21, 24, 36, 41, 44.

Score 0	No plaque
Score 1	Separate flecks of plaque at the cervical margin of the tooth
Score 2	A thin continuos band of plaque (up to one mm) at the cervical margin of the tooth.
Score 3	A band of plaque wider than one mm but covers less than one-third of the crown of the tooth.
Score 4	Plaque covers at least one-third but less than two-thirds of the crown of the tooth.
Score 5	Plaque covers two-thirds or more of the crown of the tooth

Dental Calculus Index (CI)
The dental calculus index (according to Volpe and Manhold 1991) assesses the extent of dental calculus formation on the lingual surface of the 6 lower-jaw front teeth. It is measured at each tooth after a thorough brushing and drying at three locations with a PA probe calibrated in millimetres and which measures the following: vertical, distal diagonal, mesial diagonal. The index is calculated as the sum of the 18 measurements.

Staining Index (SI):
The staining index determines the extent of staining on the buccal surfaces of the upper-jaw and lower-jaw incisors after cleaning. The staining is classified according to color (0=none, 1=yellow, 2=light brown, 3=brown, 4=grey, 5=black) and intensity (0=none, 1=slight, 2=moderate, 3=stronger, 4=very strong).

Safety, Compatibility and "Quality of Life"
On each visit the trial participants were asked if they had experienced any unwanted occurrences or side effects (allergic reactions, irritations, burning sensations, changes in taste, staining).

On completion of the trial the subjects were also asked to fill out a questionnaire in which they gave details on the taste of each toothpaste and their own "mouthfeel" with each.

Statistical Data Analysis

The decoding was performed once the final test was complete and the toothpastes were collated to the arrays. The data were evaluated using the Statistical Package of Social Science/SPSS 12.01 computer program. The average and the standard deviation of the clinical parameters at the different points in time were calculated for each toothpaste. The normal distribution of the test data was checked using the Kolmogorow-Smirnow test for each toothpaste. As the data were not distributed normally, non-parametric tests were applied. Differences between the two toothpastes were investigated using the Mann-Whitney U-test (unpaired groups), differences in the toothpastes between the baseline and the remaining points in time were determined using the Wilcoxon rank-sum test for dependent samples.

Results

Fifty-nine trial participants aged between 18 and 57 took part in the trial from start to finish, 30 in the test group and 29 in the reference group. As the gingival index baseline data shows, both groups were balanced at the start of the trial and there were no significant differences between them ($p>0.05$).

The averages and the standard deviations of the parameters examined at all points in time and the results of the statistical comparison of both groups are shown in table 3. As the microbiological data displays no uniformity and allowed no interpretation, these were not included in the evaluation.

In the reference group the gingival index sank from a value of 1.19±0.28 to 0.81±0.35 after one month and to 0.63±0.28 after 3 months. It then increased to 0.71±0.45 at the 6 month examination. At each of the points in time the gingival index showed a significant difference to the starting value ($p<0.001$; ***).

With the Lacalut® aktiv toothpaste the gingival index sank continuously from a starting value of 1.11±0.22 to 0.75±0.26, 0.59±0.25 and 0.44±0.27 after one, 3 and 6 months respectively. Just as with the control group, the test group also showed significant differences in the gingival index between the starting value and all of the values recorded at later points in time ($p<0.001$; ***).

A comparison of the two toothpastes showed that after 6 months the test group (Lacalut® aktiv) broke away from the reference group significantly ($p=0.001$; ***).

With regard to the plaque index, after one month the reference group showed a similar value to the starting value, 1.46±0.63 and 1.46±0.48 respectively. After 3 months the plaque index dropped slightly to 1.38±0.48 only to increase again to 1.62±0.64 after 6 months. No significant difference arose between the baseline and the later points in time ($p>0.05$; n.s.).

A continuous lowering of the plaque index was noted in the test group from 1.51±0.41 to 1.41±0.54, 1.42±0.49 and finally to 1.34±0.61. However, none of the reductions differed significantly from the starting value ($p>0.05$; n.s.).

Similarly, the two groups displayed no significant statistical differences in plaque index values ($p>0.05$; n.s.).

Dental calculus and staining were present in some participants at the start of the trial as no professional tooth cleaning was performed beforehand. These values remained very stable over the course of the 6 months; in particular there was no significant increase in dental calculus or staining (color and intensity).

Discussion

Use of the Lacalut aktiv® toothpaste showed significant increases in the gingival index main testing parameter at all points in time compared to the starting data. However, the reference group also showed significant differences in the gingival index compared to the baseline values such that there were no significant differences between the two groups after 3 months.

This phenomenon occurs frequently in toothpaste trials: while examining the effects of special (antibacterial) agents, the unknown variable of mechanical brushing is introduced. This effect is known as the Hawthorne effect. This states that the oral hygiene of trial participants improves simply by the fact of participating in the trial, of being equipped regularly with new toothbrushes and participating in regular examinations. Any possible antibacterial or other effect of any active agent is mostly smothered by the improved mechanical hygiene of the participants.

In the reference group the values of both the gingival index and the plaque index begin increasing again after 6 months – an effect also easily explained by the Hawthorne effect. This implies that the motivation of the reference group drops and that the data are no longer covered by very good oral hygiene. Instead the efficacy of the Lacalut® aktiv comes to the fore, so that after 6 months significantly lower values are recorded in the test group than in the reference group.

As no long-term clinical trials exist with the same toothpaste, a scientific comparison is not possible. The reductions in the toothpaste compared to the baseline data (reduction in the gingival index of 60%, reduction in the plaque index of 11%) and to the reference toothpaste with no active agent (reduction in the gingival index of 38%, reduction in the plaque index of 17%) indicate excellent efficacy of the two main agents in the toothpaste, aluminium lactate and chlorhexidine. Which of the two agents is more efficacious, whether synergies or interactions occurred or whether other ingredients in the complex toothpaste mixture may also have had an anti-inflammatory and plaque-inhibitory effect cannot be determined within the framework of this trial (test paste with two main agents against a reference toothpaste lacking both agents).

It is possible that the astringent properties of the agent aluminium lactate contributed to the tautening of the gums and the reduction in the tendency of the gums to bleed (Riethe et al. 1980). This is confirmed by the answers given to the "Quality of Life" questions posed to the participants. Twenty-five of the participants who used Lacalut® aktiv reported a tautening effect and spoke of having the feeling of cared-for gums compared to 14 participants in the reference group.

However, this tautening and reduction in bleeding tendencies of the gums through use of the aluminium lactate independent of the antibacterial effect of the toothpaste (most probably due to the effects of adding chlorhexidine gluconate, see Gaa et al. 1989) cannot be determined from the clinical indices of this study.

It can be said that the toothpaste formula Lacalut® aktiv has a considerable effect on gum bleeding or the general condition of gingivitis. Although different toothpaste trials with other toothpastes show improvements in the gingival and plaque indices compared to the baseline, most of these toothpastes tested showed no significant differences to the reference toothpastes used (Shapira et al. 1999; Winston et al. 2002). The reduction recorded in the gingival index of 60% is far greater than that in other studies and the 11% reduction in the plaque index is similar to the results recorded in other trials (i.e. 22.2% in the gingival index and 18.7% in the plaque index after 6 months with Mankodi et al. 2002; 16.2% in the gingival index and 14.4% in the plaque index after 3 months with Winston et al. 2002).

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