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Impact of Pro-Argin on the Oral Health-Related Quality of Life: A 24-Week Randomized, Parallel-Group, Multicenter Study

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Abstract: To assess the efficacy of Pro-Argin with respect to the oral health-related quality of life (OHRQoL) and cervical dentine hypersensitivity (CDH) in subjects with CDH for 24 weeks compared to a control group. Three study centers (one each in France, Germany, and Switzerland) included 273 subjects for 24 weeks. Patients with CDH involving at least two non-molar teeth and those with Schiff scores (cold air sensitivity scale) of 2 or 3 were included. The primary study parameter was a change in the OHRQoL from baseline to 24 weeks, as assessed by the Oral Health Impact Profile (OHIP)-49 questionnaire within and between the randomized groups. Patients were randomly assigned to the test group (TG) or the control group (CG). Prophylaxis paste and toothpaste in the TG contained 8% arginine and calcium carbonate. The toothpaste in the CG contained sodium monofluorophosphate. The level of significance was set at 5% ($p = 0.05$). The OHIP-49 at 24 weeks was analyzed using the analysis of covariance (ANCOVA). The mean OHIP-49 score after 24 weeks (adjusted for baseline) was significantly lower in the TG than in the CG ($p = 0.005$, ANCOVA). The OHIP-49 pain-related items adjusted for the baseline values also showed significant differences between the groups ($p = 0.025$, ANCOVA). The treatment over a period of 24 weeks using products based on the Pro-Argin technology showed a significant improvement in the OHRQoL compared to the placebo application.

Keywords: cervical dentine hypersensitivity; Pro-Argin; quality of life; patient health questionnaire

1. Introduction

Cervical dentine hypersensitivity (CDH) is defined as a short and sharp pain at the exposed dentine [1,2], which results from mechanical, thermal, osmotic, chemical, and/or evaporative stimuli. Characteristically, it is not associated with any other pathologic condition [3] related to the tooth or the periodontium. Gingival recession is a key predisposing factor [4] for CDH. The exposed dentinal surface is a consequence of gingival recession and may result from various etiological factors [5] or combinations [6] of these factors. Attrition,

abrasion, abfraction, erosion, and attachment loss [7] are the most important causes of CDH. Abrasive cleaning agents [8] can aggravate cervical abrasions.

The prevalence of CDH is between 3% and 98%. The age of patients with first-time CDH ranges between 20 and 40 years [9,10]. Patients may exhibit a higher prevalence of CDH (72.5%–98%) [11] after periodontal treatment. A recent epidemiological study [9,10], including 3187 European patients, reported variability in CDH prevalence among different countries (from 7.5% in Latvia and Estonia to 19.4% in Spain). Sex was also considered an influencing factor [12], with women showing a higher prevalence compared to men (60% vs. 40%). Buccal cervical surfaces of permanent teeth are the most frequently affected. Canines, premolars, and incisors are more frequently affected than molars [1,13]. Due to better prevention and longer life expectancy, an overall increase in CDH can be expected in the future with more emphasis on dentine hypersensitivity.

Based on the degree of discomfort, CDH may influence the quality of life (QoL) [14]. Knowledge about the influence of dentine hypersensitivity on oral health-related QoL (OHRQoL) is incomplete and requires further research. Clinical relevance oral diseases can lead to physical, psychological, and social disability [15]. The OHRQoL is a component of QoL. Validated questionnaires for the evaluation of oral health and the related quality of life [16] were developed, as these factors could not be analyzed clinically by the dentist alone. Slade and Spencer [17] developed the Oral Health Impact Profile (OHIP)-49 questionnaire to record multiple oral complaints and their influence on the OHRQoL. The 49 items of the OHIP can be used to evaluate and investigate psychometric characteristics and various dimensions of oral health. The English version of OHIP-49 was translated [18] into German in 2002. The OHIP-49 questionnaire is suitable for worldwide investigations [19], as it is currently available in many languages. Evaluations of the OHIP-49 have already shown that CDH is significantly correlated with the OHRQoL [20].

The Geriatric/General Oral Health Assessment Index (GOHAI) [21] is an additional questionnaire for the evaluation of the OHRQoL. It was developed by Atchison and co-workers in 1990. It is a 12-item self-administered questionnaire [22] that considers more functional aspects than the OHIP-49.

The main ingredients of the Pro-Argin™ technology are arginine in a concentration of 8% and calcium carbonate. In this combination, the hardly solvable calcium carbonate particles adhere to the highly solvable amino acid arginine. Both build together with bicarbonate, the basis of this technology, and can reduce the CDH by falling out on the surface and obliterating the dentinal tubules. After application and interaction with saliva, precipitates a mixture of arginine, calcium, bicarbonate, and phosphate, which adheres to the exposed dentin surface and the inner surface of the dentin tubules. Thus, the dentinal tubules obliterate, and an acid-resistant protective layer [23] is formed on the dentin surface.

A previous paper [24] showed that the application of prophylaxis products containing 8% arginine led to significant relief over 24 weeks when compared with control subjects. The proposed hypothesis was that the test agents led to a greater reduction in immediate and long-term CDH scores (Schiff score and Visual Analog Scale (VAS) score), mainly by sealing open dentinal tubules with a plug [25,26]. The present follow-up study focused on the efficacy of Pro-Argin with respect to the OHRQoL using in-office and at-home treatment approaches in the same population for more than 24 weeks.

Another interesting approach to reducing CDH and improving oral health-related quality of life is shown in a systematic review of recent clinical studies by Cicciù et al. [27] in 2019. This review described the extensive use of chitosan in dentistry. Chitosan is a marine-derived biomaterial and will be used in periodontology, implantology, oral surgery, orthodontics, and restorative dentistry. It can be applied as gels, solutions, dental materials, and in the form of brushes. Among other benefits, the active ingredient can reduce bleeding and probing depths, modify the oral biofilm, improve wound healing, reduce CHD, and increase remineralization.

2. Materials and Methods

2.1. Groups under Study

The primary outcome measure of this clinical trial was an improvement in the OHRQoL and CDH after the application of Pro-Argin (toothpaste and prophylaxis paste) to hypersensitive teeth. Three centers, including one each in France, Germany, and Switzerland, were involved as study centers. Only one or two calibrated dentists examined all patients in each study center. All patients were assigned to the test or control group. The subjects in the test group were treated with 8% arginine and calcium carbonate, while patients in the control group were treated with a placebo product of sodium monofluorophosphate. After randomization, the prophylaxis paste was applied to the corresponding groups at baseline. For this application, a white rotary cup (Kerr Hawe, Bioggio, Switzerland) filled with the prophylaxis paste was applied twice for three seconds at moderate speed ($\leq$3000 rpm). Patients were instructed to use a pea-sized amount of the study toothpaste to clean their teeth with the Stillmann tooth brushing technique for two minutes twice a day for the following 24 weeks. The returned pastes were weighed to check their compliance.

2.2. Selection Criteria

We included patients with CDH involving at least two non-molar teeth due to cervical erosion/abrasion or gingival recession. A significant stimulus response using the Schiff scale (Schiff cold air sensitivity scale) with a score of 2 or 3 after application of an air blast for one second was necessary for inclusion. The other inclusion criteria were male and female adults (18–70 years old) with suitable general health, no allergies to the study products, and availability for the entire duration of the study. The exclusion criteria were serious or chronic oral diseases; moderate and severe forms of periodontitis with or without previous therapy in the past 12 months; teeth with hypersensitivity due to other etiologies (deep or insufficient restorations, fixed or removable prosthetic restorations, pulpitis, orthodontic multiband, caries or enamel cracks, abnormal occlusal forces, degree of tooth mobility greater than one); medications including antiepileptic drugs, antihistamines, antidepressants, sedatives, tranquilizers, anti-inflammatory drugs or analgesics one month before the start of the study or during the study; also use of desensitizing preparations in the past three months including the application of highly concentrated fluorides; participation in other clinical studies or studies for desensitization products in the past 12 months; pregnant or nursing mothers and finally diseases that forbid a four-hour food break before and during each study appointment.

2.3. Study Design and Study Materials

The present study was a prospective, placebo-controlled, double-blind, randomized clinical trial. Before the clinical trial started, each study center received the test or placebo products (106 boxes per center). Each box was labeled with a randomization number and contained all study products for one patient. Each subject was provided with two cups of prophylaxis paste (pastes for single in-office application), eight tubes of toothpaste that were specially prepared for the study, one digital timer to ensure a cleaning time of at least two minutes, and seven toothbrushes (elmex® SENSITIVE PROFESSIONAL, Colgate-Palmolive Europe Sàrl, Therwil, Switzerland). The test products used were elmex® SENSITIVE PROFESSIONAL desensitizing paste (8% arginine, calcium carbonate, without fluoride) and elmex® SENSITIVE PROFESSIONAL toothpaste (8% arginine, 1450 ppm fluoride, monofluorophosphates). The placebo products included Nupro® (DENTSPLAY DeTrey GmbH, Germany) fluoride-free prophylaxis paste and an experimental sodium monofluorophosphate toothpaste with 1400 ppm fluoride and without any known desensitizing active ingredients.

2.4. Study Parameters

The OHIP-49 total score was used as the primary variable to describe the OHRQoL. OHIP-G53 was used in Germany and Switzerland, while OHIP-F49 was used in France. Only 49 original questions were needed with respect to the analytical statistics and their adequate comparability. A total of 9 out of the 49 original OHIP items were associated with the pain spectrum. The term 'pain-related/adjusted' summarizes the questions that refer to painful symptoms. Five answers were available in the form of a Likert scale. This means that the given answer possibilities could be more or less agreed upon [28]. The values of the items were added to calculate the total score (between 0 and 196). An increase in the scores was congruent with an increase in severity. Comparative values could be used to interpret the numerical results [23]. A minimal important difference (MID) of six points was considered for the evaluation of the OHIP-49 [29].

The secondary variables were the GOHAI scores, the Schiff scores (air blast sensitivity), and the VAS scores (tactile sensitivity). GOHAI scores varied from 12 to 60, according to the responses to 12 questions. Higher GOHAI values indicated a better OHRQoL [30]. The Schiff scores and the VAS scores were secondary parameters used to determine dentine hypersensitivity. These outcomes were published in a previous study [24].

2.5. Sample Size Calculation

The sample size was calculated under the assumption that OHIP-49 shows a clinically relevant difference of at least 6 points (21 in the test group and 15 in the control group) between the groups after 24 weeks. Achievement of this primary efficacy endpoint required a sample size of 286 (143 per group), considering a power of 80% and a significance level of 5% ($p \leq 0.05$). A standard deviation (SD) of 18 points was considered. Considering a moderate termination rate of 5%, 300 patients needed to be included.

2.6. Statistical Methods

Statistical analysis of the collected data was performed using IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). All efficacy endpoints were analyzed for the intention-to-treat (ITT) population. The level of significance was set at 5% ($p = 0.05$) for all statistical analyses. The OHIP-49 at 24 weeks was analyzed using analysis of covariance (ANCOVA) with the primary efficacy endpoint as the response and the group indicator, and the baseline OHIP-49 value as covariates. Results of the analysis of the OHIP-score using ANCOVA with baseline adjustment were confirmed with the Mann–Whitney U test, which compared the difference between the values at the endpoint (24 weeks) and the baseline values in the treatment group. Mean differences with the appropriate 95% confidence intervals (CIs) were detected. The secondary outcomes were evaluated using an appropriate ANCOVA analysis. Demographic variables were analyzed descriptively (mean, median, SD).

2.7. Ethical Principles

Each study center received its own ethics vote [24]. The ethics committee in Halle/Saale (Germany) approved the research project (GASAS-1105X/KKS-101) on 28 February 2012. The study was conducted in compliance with DIN EN ISO 14155:2011, the ICH Principles of Good Clinical Practice (CPMP/ICH/135/95 Step 5), and the revised Declaration of Helsinki.

2.8. Monitoring

Quality management of the clinical investigation was ensured by three local and independent coordination centers. The Coordination Centre for Clinical Trials (KKS) in Halle/Saale was commissioned to randomize all patients. The monitors supervised the execution of the clinical examination according to the protocol, the guidelines of the Good Clinical Practice, and the valid legal regulations.

2.9. Randomization

The investigator, the study monitor, all patients, and the statistician were blinded to the study products. Patient randomization was organized at the KKS in Halle/Saale based on stratification characteristics. The Schiff score (two or three) and the number of each study center (01, 02, 03) were used as stratification features. Stratification was performed according to block randomization using randomization lists. A randomized assignment list was created before patient recruitment. Subsequently, each randomized patient received an identification number. A box with blinded study products could be assigned to this number. Thus, the blinding of the investigator was maintained throughout the study.

2.10. Data Management

The University Hospital of Zurich provided the database system SecuTrial® for clinical studies. All collected data were saved in the SecuTrial®. This system created electronic case report files (eCRFs) for each patient. The eCRFs were regularly audited by the monitor to ensure compliance with the study protocol.

2.11. Timeline

The visit plan included five appointments for each subject (Table 1). Patients were screened according to the selection criteria, and an eCRF was created in the SecuTrial® for each subject. All collected data (anamnestic data, demographic characteristics, health status, medication, oral hygiene behavior, dental and periodontal status, Schiff score, VAS score, and the responses to the questionnaires) were entered into the eCRF during the entire duration of the study.

Table 1. Timeline (study flow chart).

Study Week Study Visit	−7/−14 V1	0 V2	4 (±3 Days) V3	8 (±3 Days) V4	24 (±3 Days) V5
Phase of Study	**Enrolment**	**Baseline**	**Home-Use Treatment**		**Termination**
Selection criteria	+	+			
Informed consent	+				
Demographics, ethnic characteristics	+				
General health status	+	+	+	+	+
Medical history	+				
Dietary habits	Handing out the report form	+ (Return of the report form)			
Concomitant therapy/treatment	+	+	+	+	+
Safety			Adverse events and serious adverse events		
Dental status	+	+	+	+	+
Schiff score, tactile stimulus and VAS [1]	+	+ [2]	+	+	+
QoL-questionnaire in the form of an interview (OHIP and GOHAI) [3]	+ (Only GOHAI)	+	+	+	+
Stratification and randomization		+			
Application of the prophylaxis paste		+			
Dispensing the toothbrush and the toothpaste		+	+	+	Products returned
Tooth brushing			≥ twice daily tooth brushing [4]		
Oral hygiene instructions		+		+	

[1] Initial tactile stimulus followed by Schiff score assessment. [2] Evaluation before the verification of dentine hypersensitivity and immediately after the application of the prophylaxis paste. [3] Completion before the assessment of the clinical parameters, particularly dentine hypersensitivity, except enrolment. [4] Oral hygiene instructions followed by supervised brushing according to the Stillmann technique with the assigned toothpaste. GOHAI: Geriatric/General Oral Health Assessment Index, QoL: quality of life, OHIP: Oral Health Impact Profile, VAS: Visual Analog Scale.

3. Results

The subjects were recruited between January 2012 and December 2014. The study centers in France, Germany, and Switzerland included a total of 298 subjects (France: n = 94, Germany: n = 101, Switzerland: n = 103). The dropout rate was 8.4% (France: n = 6, Germany: n = 3, Switzerland: n = 16). This implied a recall rate of 91.6%. Altogether, 273 patients (test: n = 137, control: n = 136) were available for the ITT analysis after 24 weeks. Five patients (test: n = 3; control: n = 2) did not comply with the protocol. Thus,

the per-protocol analysis set consisted of 268 evaluable patients. Non-compliance was confirmed when the patients returned more than 17 g of toothpaste per tube. Despite large sex-specific differences (59 males and 214 females), the sex distribution did not differ significantly between the treatment and the control group ($p = 0.769$; Fisher's exact test).

3.1. Analysis of the OHIP-49 Scores

A statistically significant difference ($p = 0.030$, ANCOVA) was detected between the groups for the first time after 8 weeks. The difference between the OHIP-49 scores at the endpoint and the scores at baseline represented the primary efficacy variable. It was analyzed in the ITT population (n = 273). Generally, lower OHIP-49 scores indicate better oral health-related conditions. Table 2 indicates the OHIP-49 scores at various visits. This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

Table 2. The OHIP-49 scores at various study visits.

Visit	Score (Mean ± SD)	
	Test Group (n = 137)	Control Group (n = 136)
Baseline	27.3 ± 18.5	24.9 ± 19.4
4 Weeks	21.6 ± 18.5	20.0 ± 18.8
8 Weeks	17.5 ± 15.6	19.4 ± 19.2
24 Weeks	16.0 ± 15.3	19.8 ± 20.2

OHIP: Oral Health Impact Profile, SD: standard deviation.

The OHIP-49 score after 24 weeks (adjusted for baseline) in the test group was significantly lower than the OHIP-49 score in the control group ($p = 0.005$, ANCOVA). The 95% CIs for the estimated mean difference in the OHIP-49 score between the test group and the control group after 24 weeks (adjusted for baseline) accounted for [−8.615; −1.513]. These findings confirmed that the OHIP-49 score was significantly lower in the test group than in the control group at the endpoint. The descriptive statistics are summarized in Table 3.

Table 3. Descriptive statistics and estimates of the OHIP-49 score at endpoint (dependent variable).

Descriptive Statistics				Estimates			
Group	**N**	**Mean**	**SD**	**Mean**	**SE**	**95% CI, Lower Bound**	**95% CI, Upper Bound**
Test	137	16.0	15.3	15.4 [a]	1.3	12.9	17.9
Control	136	19.8	20.2	20.4 [a]	1.3	17.9	23.0
Total	273	17.9	18.0				

[a] Covariates appearing in the model; OHIP-49 score at baseline = 26.1209. CI: confidence interval, SD: standard deviation, SE: standard error, OHIP: Oral Health Impact Profile.

Figure 1 represents that there were no significant center effects on the primary outcome (OHIP-49 score). Covariates appearing in the model are evaluated at the following values: OHIP-49 score at baseline = 26.2247.

Each of the three centers showed a significantly lower OHIP-49 score in the test group than in the control group ($p = 0.005$, ANCOVA). When the pain-related items of the OHIP-49 score were considered separately, patients in the test group showed a significantly lower score than those in the control group after 8 weeks ($p = 0.037$, ANCOVA) and after 24 weeks ($p = 0.025$, ANCOVA). The OHIP-49 was administered at baseline and after 4, 8, and 24 weeks of therapy. Changes in the OHIP-49 scores compared to the previous scores were analyzed as secondary effectiveness variables (Table 4).

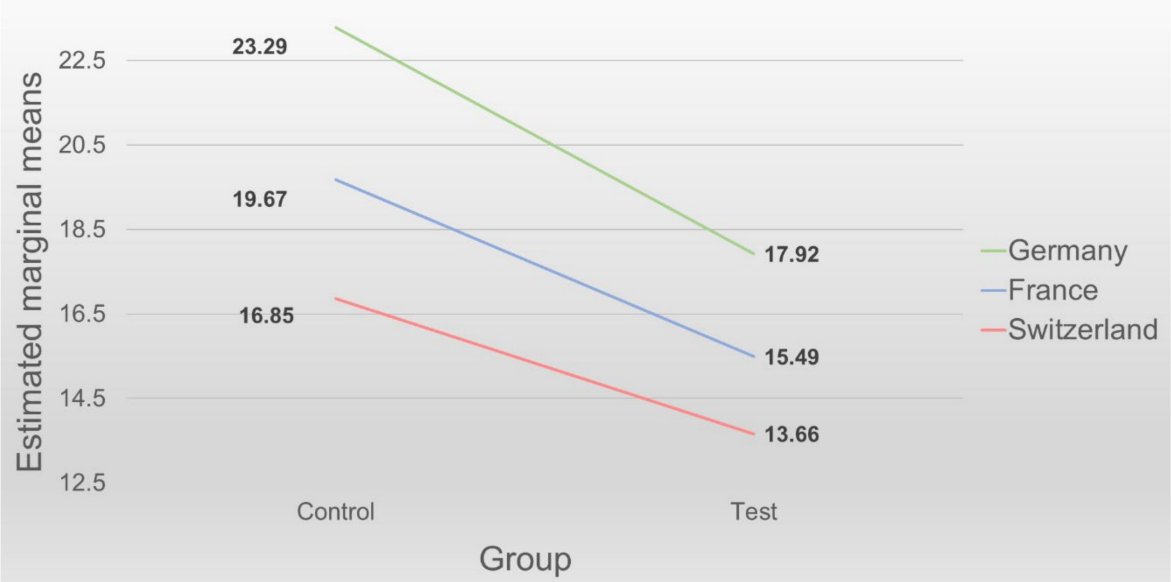

Figure 1. Estimated marginal means of the OHIP-49 scores at 24 weeks.

Table 4. Changes in the OHIP-49 scores during the treatment of 24 weeks.

Time Interval	Score (Mean ± SD)	
	Test Group (n = 137)	Control Group (n = 136)
Baseline to 24 weeks	−11.3 ± 17.8	−5.1 ± 16.8
4 Weeks to 24 weeks	−5.5 ± 13.8	−0.2 ± 15.5
8 Weeks to 24 weeks	−1.5 ± 13.4	−0.5 ± 13.4
Baseline to 8 weeks	−9.8 ± 14.8	−5.6 ± 14.4
4 Weeks to 8 weeks	−4.1 ± 10.1	−0.6 ± 13.2
Baseline to 4 weeks	−5.7 ± 15.1	−5.0 ± 11.6

OHIP: Oral Health Impact Profile, SD: standard deviation.

The OHIP-49 scores were statistically analyzed using ANCOVA and confirmed by the Mann–Whitney U test (Table 5).

Table 5. Comparison of the OHIP-49 scores, statistical tests, and corresponding *p*-values.

Parameter	Test Applied	*p*-Value
OHIP after 8 weeks (adjusted for baseline)	ANCOVA	0.030 *
OHIP after 4 weeks (adjusted for baseline)	ANCOVA	0.920
OHIP pain-related after 8 weeks (adjusted for baseline)	ANCOVA	0.037 *
OHIP pain-related after 4 weeks (adjusted for baseline)	ANCOVA	0.806
OHIP at baseline	Mann–Whitney U	0.184
OHIP after 4 weeks (unadjusted)	Mann–Whitney U	0.412
OHIP after 8 weeks (unadjusted)	Mann–Whitney U	0.563
OHIP after 24 weeks (unadjusted)	Mann–Whitney U	0.267
OHIP 24 weeks–baseline (unadjusted)	Mann–Whitney U	0.020 *
OHIP 24 weeks–4 weeks (unadjusted)	Mann–Whitney U	0.024 *
OHIP 24 weeks–8 weeks (unadjusted)	Mann–Whitney U	0.473
OHIP 8 weeks–baseline (unadjusted)	Mann–Whitney U	0.040 *
OHIP 8 weeks–4 weeks (unadjusted)	Mann–Whitney U	0.040 *
OHIP 4 weeks–baseline (unadjusted)	Mann–Whitney U	0.540

* Statistically significant ($p < 0.05$); ANCOVA: analysis of covariance, OHIP: Oral Health Impact Profile.

The OHIP-49 scores were significantly lower in the test group than in the control group ($p = 0.030$, ANCOVA) after 8 weeks of treatment. The same effect was observed when the pain-related items were considered separately ($p = 0.037$, ANCOVA).

3.2. Analysis of the GOHAI Scores

The GOHAI questionnaire was administered at screening, baseline, and at 4, 8, and 24 weeks after the application of the prophylaxis paste. Contrary to the OHIP-49, an increase in the values indicated an improvement in the oral health-related conditions (Table 6).

Table 6. Comparison of the GOHAI scores, statistical tests, and corresponding *p*-values.

Parameter	Test Applied	*p*-Value
GOHAI screening	Mann–Whitney U	0.442
GOHAI 24 weeks—baseline (unadjusted)	Mann–Whitney U	0.001 *
GOHAI 24 weeks—4 weeks (unadjusted)	Mann–Whitney U	0.002 *
GOHAI 24 weeks—8 weeks (unadjusted)	Mann–Whitney U	0.132
GOHAI 8 weeks—baseline (unadjusted)	Mann–Whitney U	0.057
GOHAI 8 weeks—4 weeks (unadjusted)	Mann–Whitney U	0.117
GOHAI 4 weeks—baseline (unadjusted)	Mann–Whitney U	0.506

* Statistically significant ($p < 0.05$); GOHAI: Geriatric/General Oral Health Assessment Index.

At the endpoint (24 weeks), the GOHAI scores were significantly higher in the test group than in the control group ($p = 0.005$, ANCOVA), which was similar to the baseline values ($p = 0.001$, Mann–Whitney U test), and the 4-week values ($p = 0.002$, Mann–Whitney U test).

4. Discussion

The present study assessed the efficacy of Pro-Argin technology (8% arginine and calcium carbonate) with respect to the OHRQoL when compared with a negative control over 24 weeks. Toothpaste with 8% arginine and calcium carbonate and its corresponding in-office desensitizing paste were compared with a pumice-based fluoride-free prophylaxis paste and an experimental sodium monofluorophosphate toothpaste. In general, all products were well tolerated during the entire treatment. The OHRQoL and CDH were evaluated at baseline and at 4, 8, and 24 weeks using the OHIP-49 and the GOHAI questionnaires (OHRQoL) as well as using the Schiff score and the VAS (CDH).

Bekes and co-workers [20] have elucidated that dentine hypersensitivity is significantly related to OHRQoL. However, most of the clinical studies focused exclusively on the clinical parameters, so only a few results were found that dentine hypersensitivity directly related to OHRQoL. Studies by Goh et al. [31] that are more recent have also shown an influence of dentine hypersensitivity on the OHRQoL. Therefore, the OHIP-49 is suitable for group comparisons in clinical studies. Another advantage of the OHIP-49 is that different investigators have to be calibrated exclusively for the clinical parameters. The difference between OHIP-49 scores after 24 weeks of treatment and the baseline scores was the primary outcome of the present investigation. The OHIP-49 formed the basis of the OHRQoL evaluation. A reduction in the OHIP-49 score was indicative of an improved oral condition. The Dentine Hypersensitivity Experience Questionnaire (DHEQ), formerly developed for assessing OHRQoL in the context of dentine hypersensitivity, as well as the short form of the OHIP (OHIP-14), could also have been considered for evaluation. However, the OHIP-49 was used in this clinical investigation due to its completeness and thus better comparability with regard to former investigations focusing on dentine hypersensitivity and quality of life [15,20]. According to the OHIP-49 scores, the test group (adjusted to baseline) showed a statistically significant improvement in the OHRQoL than the control group after 8 weeks ($p = 0.030$, ANCOVA) and after 24 weeks ($p = 0.005$, ANCOVA). These results were corroborated by the GOHAI questionnaire ($p = 0.001$, Mann–Whitney U test) after 24 weeks. The OHIP-49, its pain-relevant items, and the GOHAI questionnaire showed that the therapies in both randomization groups resulted in an improvement in the OHRQoL. In addition, the higher efficacy of the test product could be classified as clinically relevant. The overall improvement in both groups was also attributed

in part to an omnipresent placebo effect. In the case of a placebo effect, patients suggested a certain expectation of treatment success, such as a reminder of the improvement in symptoms after a visit to the doctor/dentist or after the intervention [32]. The placebo effect of the primary study parameter (OHIP-49 score) in the present study was 45%. Kirsch and Sapirstein [33] reported that the non-specific effects of clinical studies were up to 75%. The Hawthorne effect [34] was attributed to the considerable importance of these positive effects. Test subjects changed their natural behavior [35] due to the awareness that they were under observation. In the present study, regular recall appointments and dental care contributed to these positive effects. The use of a soft toothbrush, the instructions regarding an adequate brushing technique (Stillmann technique), and the recommendation of a moderate brush contact pressure [36] had a further positive effect on CDH and consequently on the OHRQoL.

The Schiff score and the VAS were used to evaluate dentine hypersensitivity [24] in the present study. Both are suitable for measuring CDH [37] in clinical trials. Patients in the present study showed a higher sensitivity for air blast stimuli than for probing [38,39], which is consistent with previous literature. Therefore, only the stimulus response with a Schiff score of 2 or 3 after a one-second air blast on the cervical area of the tooth was considered an inclusion criterion for this clinical investigation. The investigators were trained before patient recruitment measurement variability. In each study center, only the calibrated dentists (only one or two per center) examined all patients. Measurement errors were eliminated by the small number of examiners and their calibration. Thus, the Schiff score became a reliable and reproducible clinical parameter and was used as the stratification feature. Randomization ensured a random distribution of the patients among the trial groups in order to eliminate potential disruptive factors. These factors (confounders) such as age or body weight of the subjects might have had a positive or negative impact on the therapeutic effect. Therapeutic efficacy based on the sole effect [40] of the intervention can be determined by structural equality. Block randomization was performed for all patients in the KKS Halle/Saale. Randomization was planned for 300 patients (150 per treatment arm). The Schiff score (2/3) and the number of the study center (01/02/03) were used as stratification criteria. Using SAS version 9.1.3 (SAS Institute, Cary, NC, USA), a randomization list was compiled for each of the resulting six strata. The randomization algorithm assigned the patients to the therapy arms in a block-by-block manner. The blocks had a variable length of 6 or 10 subjects. At the end of the study, there was a group distribution of 136 control subjects and 137 test subjects. Systematic errors (bias) should be avoided by blinding [41] a scientific study. The randomization lists remained in the KKS until the end of the study. Thus, blinding was ensured for the entire duration of the study. The present clinical study was double-blind, implying that the investigator and the patient were not involved in the group distribution. The statistician, the sponsor, and the monitor were blinded to the data until the end of the therapy.

A major limitation of the present study was the absence of positive control, as recommended by Holland et al. [42]. The following trial could be used as a positive control. Samuel et al. [43] compared the effect of Pro-Argin with two positive controls, Gluma® (2-hydroxyethyl methacrylate and glutaraldehyde) and NovaMin® (5% calcium sodium phosphosilicate), after a single application and after 30 days. All three desensitizers led to a reduction in CDH, and Pro-Argin exhibited a significant reduction in the CDH values ($p < 0.016$). In addition, in further studies, the GOHAI questionnaire could be replaced by the DHEQ questionnaire to address the CDH more specifically and compare the results with the present findings.

The selection criteria in the present study were defined precisely. This made recruitment of the study population more difficult. The inclusion of molars and an increase in the age limit (>70 years) could have facilitated the recruitment process. Most of the excluded patients showed dentine hypersensitivity only in the molars. In Germany, 11 subjects (9%) fell into this category and had to be excluded. Only the anterior teeth were included, as the degree of destruction in the molars was too high. According to the press release no. 364 of

the Federal Statistical Office on 24.09.2009, life expectancy has continuously increased over the past decades. The life expectancy of newborn boys has increased by 5 months from 2010 to 2015, and the life expectancy of newborn girls has increased by 4 months (Federal Statistical Office Wiesbaden, press release no. 143 from 22 April 2015). Moreover, many of the screened patients (for example, 6 [4.9%] patients in Germany) could not be included due to their psycho-pharmaceutical anamnesis. The exclusion of these drugs was based on their direct correlation [9,10] with CDH.

5. Conclusions

In conclusion, according to the OHIP-49 scores, the Pro-Argin technology led to a statistically significant improvement in the OHRQoL of patients with CDH when compared with negative controls ($p = 0.020$, Mann–Whitney U test). During the entire duration of the study (24 weeks), the OHRQoL was represented by the difference in the sum values (termination−baseline) and reached an MID of six points.

Within the limitations of the present study, the use of desensitizing agents containing arginine in a concentration of 8% and calcium carbonate, named Pro-Argin technology, represents a viable option for reducing the discomfort related to CDH and could improve oral health-related quality of life and of effected patients significantly.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Details regarding where data supporting reported results can be found in the three study centers. (1) Department of Operative Dentistry and Periodontology, University School of Dental Medicine, Martin-Luther-University of Halle-Wittenberg; (2) Clinic of Conservative and Preventive Dentistry, Center of Dental Medicine, University of Zürich and (3) Service d'Odontologie, CHU de Clermont-Ferrand, University Clermont).

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