Clinical effect of 3.0% hydrogen peroxide containing bleaching patch with primer in a double-blind randomized controlled trial

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Abstract

**Background:** To clinically evaluate the efficacy and safety of a primer that contains taurine and self-bleaching patches containing 3.0% hydrogen peroxide.

**Methods:** Overall, 55 participants were selected in this double-blinded randomized clinical trial between March and May 2019. Bleaching patches containing 3.0% hydrogen peroxide were attached using the primer on the labial surface of the upper six anterior teeth for 30 min once daily. $\triangle E^*$ values of color changes were measured using Shade Eye NCC for determining the efficacy of bleaching on days 3, 5, 7, and 10 before and after attachment. The safety was assessed using gingival index and visual analog scale for tooth sensitivity and gingival irritation, respectively.

**Results:** $\triangle E^*$ values were visibly detected from day 7 after the attachment of patches, and the bleaching effect was identifiable. No statistically significant difference was observed in the gingival index ($p = 0.069$), tooth sensitivity ($p = 0.983$), and gingival irritation ($p = 0.518$).

**Conclusions:** When the self-bleaching patches using 3.0% hydrogen peroxide with the primers were attached for 30 min once daily, visible bleaching effect was observed from day 7 of attachment, and it was verified to be safe for use without any significant adverse effect.

**Clinical Relevance:** This study was conducted after securing safety for clinical trials.

**Trial registration:** ISRCTN63650330

**Background**

Dental bleaching is a technique to restore the teeth discolored by intrinsic or extrinsic factors to their original brightness or to make them brighter. This is a conservative and relatively safe technique to restore the tooth color without physical damage to the teeth.

The bleaching methods can be divided into in-office bleaching (OB), which is conducted in the dental clinic, and over-the-counter (OTC) bleaching, which is conducted by the patients at their homes. OB that uses highly concentrated chemicals is inconvenient and requires several clinic visits as well as special equipment owing to its technical characteristics and high costs. In contrast, OTC bleaching is designed for direct application by the users; therefore, it is a method that could overcome the discomfort associated with OB.

There are some requirements of OTC bleaching such as taking precautions to avoid harm to the human body because chemicals are used in OTC bleaching. Therefore, various bleaching ingredients and products at varying concentrations ensuring the efficacy and safety of each drug are being developed. Different concentrations of carbamide peroxide or hydrogen peroxide are used in OTC bleaching. A clinical trial developed a method involving application of 10% carbamide peroxide and 6.5% hydrogen peroxide in different forms [1, 2]. However, bleaching products sold in Korea cannot contain > 3.0%
concentration of hydrogen peroxide \[3\]; therefore, prolonged time and period of attachment are required to obtain the bleaching effect. In addition, the most common adverse effects are gingival irritation and tooth sensitivity. Various methods are used to reduce such adverse effects \[4–6\]; generally, desensitizers are frequently used. The primer used in this study contained sweeteners, taurine, etc., thus increasing the attachment between the bleaching patches and the surface of the teeth as well as decreasing sensitivity and irritation in the oral hard and soft tissues \[7\].

OTC bleaching is a procedure used by nonprofessionals; therefore, it is necessary to ensure user convenience. Foreign or existing products are in the form that use preloaded trays, patches, gel, etc. Preloaded tray has some disadvantages, including difficulty in insertion into the mouth, drooling during application, swallowing the chemicals, or difficulty in talking. Gel requires a special container and is easy to swallow during application; therefore, it does not ensure safety. Patches are more convenient to use than preloaded tray or gel. However, they are associated with inconveniences such as being able to be removed using a toothbrush.

The consumers’ requirements of a bleaching product are as follows: excellent bleaching effects, safety, short time and period of application, easy to use, and cost effective. Among these, the consumers specifically want the products to be less complicated to use, require only a short period of application, and show immediate bleaching effects. Therefore, the purpose of this study is as follows. First, a patch containing primer and 3.0% hydrogen peroxide was applied once a day for 30 minutes to measure changes in tooth color before and after whitening, and the effective application time for whitening was reduced. Second, I tried to confirm the safety and convenience of using the whitening patch.

The hypothesis of this study is that the application of a patch containing a 3.0% peroxidation number with a primer has a whitening effect in a short period of time.

**Methods**

**Ethical approval**

After obtaining approval from the Bioethics Committee (IRB No. KNU 2019-0009) of Kyungpook National University, recruitment and clinical experiment were conducted between March and May 2019.

**Study design**

This is a double-blinded randomized clinical trial that referred to the Consolidated Standards of Reporting Trials 2010 guideline from design to completion \[8\]. The random allocation ratio was 1: 1 for each. Prior to enrollment in the study, a mechanics researcher who was not involved in the clinical part of the study prepared a random assignment table and sealed the assigned procedure in an envelope with a serial number. We also concealed a sealed random assignment table in a third location until the end of the study to maintain a double-blind study of all researchers and participants who participated in the clinical part. Participants were given a personal identification number by a blinded researcher at the time of study
enrollment, and then 30 minutes-control (n = 31), 30 minutes-based on a pre-generated random assignment table, respectively. They were assigned to the experimental group (n = 30), 60 minutes-control group (n = 32), 60 minutes-experimental group (n = 32). At the end of the study, we examined the dividends of the analysis group (Intention-to-treat, ITT) and the plan adaptation analysis group (Per-protocol, PP) as intended before the random allocation table was unsealed. In this study, we refer to the CONSORT (CONsolidated Standards of Reporting Trials) 2010 guideline\textsuperscript{16}) and the Quasi-drug Dental Whitening Agent Efficacy Test Guideline\textsuperscript{17}) of the Food and Drug Administration, from the research and design stages to report preparation. I registered after the fact with the Clinical Research Information Service (CRIS).

Sample size

G-power was used to calculate the minimum number of samples to compare the presence or absence of color changes and side effects from the military and perspective. The experimental group is for confirming the appropriate whitening time and safety of 3.0% hydrogen peroxide, and the control group uses the same patch without hydrogen peroxide. G*power (version 3.1.9.2) was used\textsuperscript{9}; total 42 participants were selected with each group comprising 21 participants when the effect size was $f = 0.25$\textsuperscript{10}; and the significance level was 0.05, power was 0.99, the number of groups was two, and the number of repeated measurements was five. Considering a dropout rate of 30%, 56 participants with 28 in each group were recruited.

Participants

After recruitment by snowball sampling, of the 73 candidates who understood the aims and objectives of the study and voluntarily agreed to participate in the study, 55 participants who met the selection criteria were finally enrolled through a dental checkup by a dentist (Table 1, Fig. 1)\textsuperscript{3}. The study was conducted in accordance with the Declaration of Helsinki, and the study was explained to the participants and their consent was obtained before participation.

Table 1 Inclusion and exclusion criteria
Inclusion

- Having good general and adequate oral health
- Having all natural teeth of Vita Classical Shade Guide A2-A3
- Willing to return for follow-up evaluation
- Signing the informed consent document

Exclusion

- Having 1 of the 6 anterior teeth restored more than 1/6 of the labial surface
- Having orthodontic treatment or tetracycline-stained teeth
- Presence of gross pathology on the soft or hard tissues in the oral cavity
- Presence of gingivitis or moderate or advanced periodontal tissues
- Having more than two caries lesions requiring immediate treatment
- Having used teeth whiteners within the last 6 months
- Smokers

Bleaching procedure

The control group was attached with a primer and patch that did not contain the active ingredient, and the experimental group was attached with a primer and patch containing the active ingredient. Each group was instructed to attach the allocated primer and patches on the labial surface of the upper six anterior teeth for 10 days once daily and then to remove them after 30 min (Table 2). They were further instructed to record a self-checklist after bleaching. The oral hygiene management of the participants was standardized, and the precautions to be taken during the experiment were informed verbally as well as through written form.

Table 2 Trial groups and treatment materials

| Groups   | Primer                                                                 | Patch                                                                 |
|----------|------------------------------------------------------------------------|----------------------------------------------------------------------|
| Control  | Water, ethanol, PVP, glycerine, taurine, ferric oxide, potassium phosphate, silica, titanium oxide, etc. | Hydrogen peroxide (3.0%), water, ethanol, glycerine, castor oil PVP, ethyl cellulose, sodium saccharin, sodium acid pyrophosphate, flavor, etc. | 0.0% |
| Experiment | Water, glycerine, ethanol, PVP, taurine, ferric oxide, potassium phosphate, silica, titanium oxide, etc. | Hydrogen peroxide (3.0%), water, ethanol, glycerine, castor oil PVP, ethyl cellulose, sodium saccharin, sodium acid pyrophosphate, flavor, etc. | 3.0% |

Evaluation of efficacy
For color measurement, a colorimeter (Shade Eye NCC, SHOFU Co., Kyoto, Japan) was used to determine \( \Delta E \) value \( \Delta E^* = \sqrt{(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2} \) along with use of the standard color table (Vita classical shade guide, Vita Zahnfabrik, H. Rauter GmbH & Co, KG, Bad Sackingen, Germany). Each measurement was conducted by the same dentist using the recorder in the same environment. At each measurement after whitening, the color of the teeth was determined using the mean value obtained from three repeated measurements per tooth with a tip located 1.0 mm right above the center of the labial surface of the upper anterior teeth, and the average value of the six anterior teeth determined the tooth color of the participant.

**Safety evaluation**

At each measurement, a dentist evaluated the oral health condition and the gingival index (GI) of the participants [11]. When the symptoms of adverse reactions occurred above the moderate level, acute gingivitis occurred, or GI was >2, the experiment was suspended. Each time the participants noticed any of these symptoms, they were instructed to mark the degree on visual analog scale (VAS) [12] and describe the other symptoms. If severe pain was marked on VAS or the symptoms interfered with daily life, the experiment was suspended.

**Statistical analysis**

Before analysis, the normality was confirmed by Shapiro–Wilk test; then, each analysis was conducted parametrically. Repeated measures ANOVA and paired \( t \)-test were conducted to determine the changes in the color and GI in each group, respectively. Color changes between the groups were compared using independent \( t \)-test. SPSS (23.0 for windows, USA) program was used for analysis, and the statistical significance level was 0.05.

**Results**

**Efficacy of bleaching**

\( \Delta L^*, \Delta a^*, \Delta b^*, \) and \( \Delta E^* \) values according to the attachment of the bleaching patches showed significant differences. \( \Delta L^* \) values were 2.50 ± 1.29, 3.11 ± 1.80, and 4.25 ± 1.98 on days 5, 7, and 10, respectively \( (p < 0.001) \). \( \Delta a^* \) values were –0.06 ± 1.25 on day 7 and –0.35 ± 1.32 on day 10 \( (p < 0.001) \). \( \Delta b^* \) was 2.09 ± 1.80 on day 10 with significant changes in the color \( (p < 0.05) \). Regarding \( \Delta E^* \) value, subtle changes in the color began to occur from day 5 \( (p < 0.05) \), and on day 7, it was >3.0, the standard National Bureau of Standards unit, with visibly identifiable changes in color \( (p < 0.001; \text{Table 3}) \).

**Safety of bleaching**

**Gingival index**

No significant difference was observed before and after the procedures (Table 4).
Subjective symptoms

During the entire experimental period, six subjects in the control group (24.0%) and seven in the experimental group (23.3%) experienced tooth sensitivity, gingival irritation, or discomfort caused by the attachment of the patches at least once, with no significant difference ($p > 0.05$; Table 5). Regarding the VAS scale evaluation on tooth sensitivity and gingival irritation, no significant difference was observed before and after the experiment ($p > 0.05$; Table 6).

Table 3 Color changes in bleaching after 3–10 days
|       | Control group | Experimental group | \( p \text{ value}^\dagger \) |
|-------|---------------|--------------------|------------------|
| \( \Delta L^* \) |               |                    |                  |
| 3 days | 0.81 ± 1.95   | 1.17 ± 1.03        | 0.408            |
| 5 days | 0.81 ± 1.85\(^a\) | 2.50 ± 1.29\(^b\) | 0.000            |
| 7 days | 0.79 ± 1.72\(^a\) | 3.11 ± 1.80\(^b\) | 0.000            |
| 10 days | 0.87 ± 2.03\(^a\) | 4.25 ± 1.98\(^b\) | 0.000            |
| \( p \text{ value}^\dagger \) | 0.982         | 0.000              |                  |
| \( \Delta a^* \) |               |                    |                  |
| 3 days | 0.45 ± 0.78   | −0.06 ± 0.95       | 0.038            |
| 5 days | 0.50 ± 0.83   | 0.06 ± 1.09        | 0.105            |
| 7 days | 0.51 ± 0.77\(^a\) | −0.06 ± 1.25\(^b\) | 0.046            |
| 10 days | 0.37 ± 0.70\(^a\) | −0.35 ± 1.32\(^b\) | 0.013            |
| \( p \text{ value}^\dagger \) | 0.620         | 0.106              |                  |
| \( \Delta b^* \) |               |                    |                  |
| 3 days | 0.59 ± 1.48   | −0.08 ± 1.63       | 0.120            |
| 5 days | 0.69 ± 1.49   | 0.53 ± 1.77        | 0.717            |
| 7 days | 0.69 ± 1.56   | 1.13 ± 1.65        | 0.312            |
| 10 days | 0.77 ± 1.95\(^a\) | 2.09 ± 1.80\(^b\) | 0.011            |
| \( p \text{ value}^\dagger \) | 0.975         | 0.307              |                  |
| \( \Delta E^* \) |               |                    |                  |
| 3 days | 1.10 ± 1.33   | 1.18 ± 1.24        | 0.354            |
| 5 days | 1.18 ± 1.43\(^a\) | 2.56 ± 1.28\(^b\) | 0.014            |
| 7 days | 1.17 ± 1.54\(^a\) | 3.31 ± 1.63\(^b\) | 0.000            |
| 10 days | 1.22 ± 1.93\(^a\) | 4.75 ± 1.85\(^b\) | 0.000            |
| \( p \text{ value}^\dagger \) | 0.634         | 0.000              |                  |

The data are presented as mean ± standard deviation

\(^\dagger\)P values indicate the overall significance over time in each group based on repeated measures ANOVA
Table 4. Changes in gingival index

|               | Control group | Experimental group | p value†  |
|---------------|---------------|--------------------|-----------|
| Baseline      | 0.03 ± 0.19   | 0.08 ± 0.28        | 0.078     |
| 10 days       | 0.03 ± 0.19   | 0.06 ± 0.23        | 0.069     |
| p value†      | 0.986         | 0.074              |           |

The data are presented as mean ± standard deviation

†P values indicate the overall significance over time in each group based on paired t-test

‡P values of <0.05 compared with the control group based on independent t-test

Table 5 Distribution of participants who experienced subjective symptoms during the 10 days

|                  | Total | Control group | Experimental group | p value†  |
|------------------|-------|---------------|--------------------|-----------|
| No               | 42    | 19 (76.0)     | 23 (76.7)          | 0.874     |
| Yes              | 13    | 6 (24.0)      | 7 (23.3)           | 0.912     |
| Tooth sensitivity| 2     | 1 (16.7)      | 1 (14.3)           | 0.898     |
| Gingival irritation| 2 | 0 (0.0)      | 2 (28.6)           | 0.067     |
| Discomfort       | 9     | 5 (83.3)      | 4 (57.1)           | 0.114     |

N(%) by frequency analysis

†P values of <0.05 compared with the control group based on independent t-test

Table 6. Visual analogue scale (VAS) of tooth sensitivity and gingival irritation
| VAS scale          | Control group | Experimental group | \( p \) value\( ^\dagger \) |
|-------------------|---------------|--------------------|-----------------------------|
| Tooth sensitivity | 0.03 ± 0.18   | 0.03 ± 0.16        | 0.983                       |
| Gingival irritation| 0.03 ± 0.18   | 0.06 ± 0.23        | 0.518                       |

The data are presented as mean ± standard deviation

\( ^\dagger \) \( p \) values of <0.05 compared with the control group based on independent \( t \)-test

**Discussion**

Humans always wish to improve their quality of life. Particularly, the interest in appearances is increasing with the development in society and increase in income. In this respect, bleaching aesthetically increases self-satisfaction and is chosen as a method to ensure good impression on others. Therefore, it is expected that the demand for bleaching will increase in the future and will also cause a change in the bleaching methods.

We assessed the efficacy and safety of bleaching in the control and experimental groups using bleaching patches containing 3.0% hydrogen peroxide that were applied for 30 min once daily for 10 days.

\( \Delta L^* \) value was 2.50 ± 1.29 (\( p < 0.001 \)) at 5 days after the attachment of the patches, indicating a significant color variation compared with that reported in previous studies [3, 13, 14]; this color variation was lower than that reported by Jung et al. [15]. Considering the similarity in the experimental conditions between the studies, it is considered that the bleaching is affected by how tightly the patches are attached.

\( \Delta a^* \) value was −0.06 ± 1.25 at 7 days after the attachment of the patch (\( p < 0.05 \)), which was similar to the results of previous studies [13, 15, 16]. Alternatively, although the color change was lower than those reported by Wen et al. [17] and Meireles et al. [18] (\( p < 0.05 \)), it is believed that the result of this study is also significant, considering that there were differences in the bleaching ingredients and concentrations.

\( \Delta b^* \) value was 2.09 ± 1.80 at 10 days after the attachment, with significant color change verified (\( p < 0.05 \)); however, this color variation was lower than those reported by previous studies [13, 16-18].

\( \Delta E^* \) value was 2.56 ± 1.28 on day 5 with a visibly identifiable level of change (\( p < 0.05 \)), 3.31 ± 1.63 on day 7, and 4.75 ± 1.85 (\( p < 0.001 \)) on day 10, showing a higher level of color change over time. This was at a similar level as that reported in some studies [19, 20] but lower than that reported in a majority of others [15, 21-25]. According to these results, it could be verified that the efficacy of bleaching is affected by the duration of application and the concentration. Based on these facts, it was verified that if bleaching is performed for 30 min once daily for >7 days using 3.0% hydrogen peroxide, the bleaching effect can be obtained at a visibly identifiable level.
The final color variation in this study was 4.75 ± 1.85, which was similar to that reported by Robert & Xiaojie [26]. Sulieman et al. [27] reported that to obtain a bleaching effect using various concentrations of hydrogen peroxide, repeatedly applying low-concentration of hydrogen peroxide several times is more effective, and in case of high concentration, prompt color changes can occur; however, the concentration, time, duration of exposure, and safety might be more advantageous for color changes and its maintenance. In addition, application of high concentration hydrogen peroxide does not result in a significant difference in color changes [28].

Regarding the safety of bleaching patches, symptoms of tooth sensitivity occurred in two individuals (15.4%), gingival irritation in two (15.4%), and discomfort caused by attachment of patches in nine (69.2%), and such results did not affect dropouts. This corresponds to a study wherein most subjects complained of tooth sensitivity and discomfort, but it was at a minor level and did not act as a contributing factor toward discontinuing the trial [25, 26]. Moreover, the result was much lower than that reported by Bizhang et al. [16]. Accordingly, it can be said that the bleaching condition in this study ensured safety because it did not result in tooth sensitivity or gingival irritation in the subjects.

The patches used in this study could be more tightly attached on the surface of teeth using the primer and were easily detachable without tools. Conversely, a previous study [14] reported that there was inconvenience in removing some remaining patches using a toothbrush; however, apart from this study, there is no study mentioning user convenience of using a tray or gel. Therefore, the patches used in the study were easy to attach and detach.

There are a few limitations of this study. First, the duration of applying the bleaching patches was limited to 30 min; therefore, the bleaching effect with extended duration of application was not compared. Second, how the active ingredients of the primer affect the bleaching effect was not measured because its control group was not selected. Therefore, further studies are suggested to determine the efficacy of bleaching patches with the increase in time by including a control group of 60 min.

**Conclusions**

Bleaching patches containing 3% hydrogen peroxide are effective when attached for 30 min once daily for a minimum of 5 days. If these are applied for up to 10 days in the same manner, a higher level of bleaching effect is obtained, providing options to the users. Using these bleaching patches together with a primer ensured safety and convenience because the application and detachment of the patches were possible without the aid of a special tool. These facts provide the ground for the effective and safe use of the bleaching patches containing 3% hydrogen peroxide with the primer.

**Abbreviations**

Office bleaching; OB, Over-the-counter; OTC, Gingival index; GI, Visual analogue scale; VAS
Declarations

Ethics approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee (IRB No. KNU 2019-0009) of Kyungpook National University.

Consent to publish: Patients signed informed consent regarding publishing their data and photographs.

Availability of data and material: Informed consent was obtained from all study participants.

Competing of interests: The authors declare that they have no conflict of interest.

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Authors’ contributions: All authors contributed to the study conception and design. All authors read and approved the final manuscript.

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**Figures**

![Figure 1](image_url)
Flow chart of the study

Supplementary Files

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- CONSORT2010Checklist1019.doc