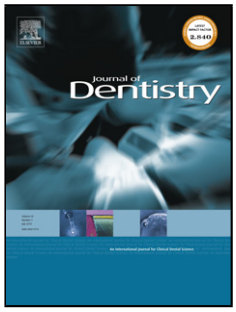

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Authors: Botelho Michael George, Chan Alex Wai Kwok, Newsome Philip Richard Holmes, McGrath Colman Patrick, Lam Walter Yu Hang

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A randomized controlled trial of home bleaching of tetracycline-stained teeth

Short title : Bleaching of tetracycline stained teeth

Botelho Michael George[a*], **Chan Alex Wai Kwok**[b], **Newsome Philip Richard Holmes**[c], **McGrath Colman Patrick**[d], **Lam Walter Yu Hang**[e]

[a,e] Prosthodontics, Faculty of Dentistry, The University of Hong Kong, Prince Philip Dental Hospital, Sai Ying Pun, Hong Kong

[b,c] Private Practise, Hong Kong, China

[d] Dental Public Health, Faculty of Dentistry, The University of Hong Kong, , Prince Philip Dental Hospital, Sai Ying Pun, Hong Kong

Correspondence author:

Botelho MG

Prosthodontics, Faculty of Dentistry, The University of Hong Kong

34 Hospital Road, Prince Philip Dental Hospital, Sai Ying Pun, Hong Kong

Tel: (852) 2859 0412 Fax: (852) 2858 6114 E-mail: botelho@hku.hk

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A randomized controlled trial of home bleaching of tetracycline-stained teeth

ABSTRACT

Objectives: To investigate the effectiveness of two home bleaching modalities on whitening of tetracycline-stained teeth (TST).

Methods: A randomized controlled trial on the bleaching effect of 15% carbamide peroxide gel loaded in *tray* and 6.5% hydrogen peroxide *strip* in subjects with TST was performed. Eligible subjects were judged independently by two assessors, and randomly assigned into the *tray* or the *strip* group. Lightness (L*), redness (a*) and yellowness (b*) were measured with colorimeter at baseline, one, two and three months. Any adverse reaction associated with bleaching were also recorded. Overall colour changes (ΔE) were analysed by one-sample and independent t-test/Wilcoxon test at significance level $\alpha=0.05$.

Result: Twelve and fourteen participants were allocated to the *tray* and the *strip* group respectively. Both groups experienced noticeable and significant L*a*b* improvement at the end of the trial in comparison to the baseline ($p<0.05$). Significant improvement was observed in the first month for the *tray* group ($p<0.05$) and in the first two months for the *strip* group ($p<0.05$). While greater lightness improvement was observed in the *tray* group over the s*trip* group in the first month ($p=0.02$), the reverse was noticed in the second month ($p=0.01$). There was no difference between two groups at the end of this trial ($p<0.05$) and no significant adverse reactions were observed.

Conclusion: Over a three-month period, 6.0% hydrogen peroxide strip performed equally well as the 15% carbamide peroxide tray delivery system in TST.

Clinical Significance: Home bleaching systems produce noticeable tooth whitening effect in subjects with tetracycline-stained teeth.

1. Introduction

Tetracyclines are broad-spectrum antibiotics used for treatment of a range of common infections [1]. However, they may incorporated into developing tooth tissue and are discoloured by light induced oxidization and may deteriorate dental aesthetics significantly [2]. The prevalence of tetracycline stained teeth (TST) has been estimated to be 3-6% [3] and up to 23% in one national survey [4]. This can be generalized or localized and range in colour from mild yellow to grey and dark brown. The clinical presentation is dependent on the type of tetracycline, its dose, length of medication, and period of development of the tooth tissue [3, 5-7].

Clinical management of TST includes the use of bleaching [8], composite resin/porcelain laminate veneers [9] or full coverage metal-ceramic/all ceramic crowns to improve the aesthetic appearance. Bleaching is the most conservative treatment option without sacrifice of sound tooth substances and subjects' satisfaction and oral health related quality of life has been improved after bleaching [10, 11]. Moreover, bleaching systems based on carbamide peroxide and hydrogen peroxide have been shown to be clinically safe with no irreversible side effects and have minimum biological cost [12-14]. Bleaching agents may be administered professionally [15] or by patients at home [16].

The quinone rings in tetracyclines that are responsible for red discoloration can be altered to less coloured molecules [17, 18]. Tray based peroxide home bleaching systems have been shown to lighten the appearance of TST when used for prolonged periods. Using 10% carbamide peroxide gel for a 6-month period in a tray delivery system, Haywood *et al* found that the tooth whitening effects were long lasting up to 90 months and that patients gave positive feedback [19, 20]. They also observed that severe discoloration in the gingival third of the tooth gave a poor prognosis for total tooth whitening. In a similar design study, Matis *et al* compared the effects of different concentrations of carbamide peroxide (10%, 15% and 20%) on tetracycline stained teeth also for a 6-month period [21]. They showed that most rapid whitening occurred in the first month. There was some relapse of the tooth whitening effects after bleaching, mostly 3 months after bleaching. However, improvements in the redness and lightness are still observed at 5 years [22]. Supporting the observation of Haywood *et al* [19], they found that the darker the teeth at baseline, the more difficult it was to lighten them.

Polyethylene strips have been used for delivery of bleaching peroxide and their direct contact with teeth may reduce overall peroxide dose and treatment time [23]. These strips may be easier to use by the patients compared to other delivery systems and eliminate the need of fabricating a custom tray [24]. Hydrogen peroxide bleaching strips used for six months has been shown to significantly whiten teeth with tetracycline staining [25]. Bleaching strips have been compared to 10% carbamide peroxide tray delivery system (equivalent to 3.6% hydrogen peroxide) in non-TST and the strips produced a comparable (strips with 5.3% hydrogen peroxide) [26] or even greater (strips with 6.5% hydrogen peroxide) [27] whitening effect when compared to the tray system. For TST, Kugel *et al* found that the 6.5% hydrogen peroxide strip system demonstrated significantly greater tooth whitening at 1- and 2-month and experienced a more rapid whitening effect in comparison to 10% carbamide peroxide tray delivery system [28]. Effects of increased tooth whitening with higher concentrations of bleaching agents have been reported on both non-TST [26, 29, 30] and TST [21].

Tetracycline staining has been a significant issue in Hong Kong and China [4]. Our hypothesis was both the tray and strip systems are effective in bleaching teeth with tetracycline staining and the objectives of this study are to prove this hypothesis and as a pilot study to compare the tooth whitening effect of a strip system (6.0% hydrogen peroxide) and a tray system (15% carbamide peroxide equivalent to 5.4% hydrogen peroxide) of similar hydrogen peroxide concentration in subjects with TST in a randomized clinical trial.

2. Materials and Methods

A randomized controlled trial was performed on the tooth whitening effects of two bleaching modalities, a *tray* based system using 15% carbamide peroxide and a *strip* based system using 6.0% hydrogen peroxide, on tetracycline stained teeth (TST). This trial was approved by the Ethics committee of the Faculty of Dentistry, the University of Hong Kong. Snowball sampling was used to recruit subjects, which was performed by word of mouth and written notices via staff and students of the University teaching hospital, Prince Philip Dental Hospital (PPDH) over a 6-month period. Participants' selection and data collection were all performed in PPDH.

2.1 Selection criteria and participants

Potential participants were invited for a clinical examination and were screened for eligibility according to the inclusion and exclusion criteria (Table 1). The presence of tetracycline staining teeth in the maxillary anterior region were judged independently by two assessors (MB and AC) and where inconsistent opinion was found, third assessor (PN) opinion was sought [4]. Those who did not meet the selection criteria or refused to participate this trial were offered other treatment as appropriate. Written consents were obtained from all selected participants after verbal and written explanation of the trial.

2.2 Intervention and trial design

Enrolled participants received a dental prophylaxis and an alginate impression (Aroma Fine Plus, GC Corporation, Tokyo, Japan) of the maxillary arch were made and poured in dental stone (Dentstone KD, Saint-Gobain formula, France). From this a clear maxillary positioning jig (Biocryl®, 3mm thickness, Great Lakes Orthodontics, Tonowanda, NY, USA) was fabricated so that the disposable tube of colorimeter (ShadeVision System, X-Rite Inc. Grandville, MI, USA) could be accurately re-positioned into the location cone of the jig to measure the labial middle third tooth colour of a selected tooth [17, 31, 32]. Baseline colour of the maxillary right central incisor and if this was restored the maxillary left central or lateral incisor was measured by a colorimeter which adopted the Commission Internationale de l'E´ clairage (International Commission on Illumination, CIE) L*a*b* three dimensional colour space. Axis L* is a measure of the lightness of an object and range from zero (perfect dark) to 100 (perfect reflecting diffuser). Axis a* is a measure of redness (positive) or greenness (negative) while axis b* is a measure of yellowness (positive) or blueness (negative). In CIELAB (1976) 's definition, the overall colour changes delta E (ΔE) can be calculated by the square root of the changes in L*a*b* ($\Delta E = [(\Delta L^*)^2 + (\Delta a^*)^2 + (\Delta b^*)^2]^{1/2}$) [33].

Participants were then randomly assigned to either the *tray* group or the *strip* group by a research assistant tossing a coin (allocation ratio 1:1). At this time the clinicians instructed the participants on the bleaching product, how it should be used and what adverse symptoms they may expect. For the participants assigned to the *tray* group, a full maxillary arch bleaching tray (Drufosoft 1.5mm thickness, Dreve-Dentamid GMBH, Unna, Germany) was fabricated on the stone model. Gel reservoir was painted on the labial surface of the anterior

teeth 1 mm terminated from the attached gingiva on the stone cast using two layers of spacer (Pink Rubber Sep, Kerr Corporation, Orange, CA, USA). The tray has gingival scalloping extended 2 to 3 mm past the attached gingiva but they did not engage undercuts or terminate on the top of the rugae. Participants were instructed to inject 15% carbamide peroxide bleaching gel in a syringe (Nupro White Gold™, Dentsply Professional, York, USA) into the labial surface of maxillary incisors and canines and wear the tray up to 2 hours or overnight during the 3-month trial period. For the *strip* group, participants were instructed to place the gel side of the maxillary strips containing 6.0% hydrogen peroxide (Crest Whitestrips™, Procter & Gamble, Cincinnati, USA) against the labial surface of maxillary incisors and canines twice daily for 30 minutes during the 3-month trial period. All participants were requested to report any adverse reaction associated with bleaching that they experienced and were addressed accordingly. Participants were advised avoid tobacco use and consume staining foods and drinks such as curry and coffee etc. during the trial period.

Participants were clinically reviewed by one reviewer who was blinded to their treatment group at one-, two- and three-months. The primary outcome measures were the changes in L*a*b* (i.e. adjusted colorimeter values) and the calculated overall colour changes ΔE compared to baseline. Three colorimeter readings were taken and averaged. The colorimeter was calibrated for each subject's measurement. The secondary outcome was any significant adverse reaction associated with bleaching reported by the participants and assessed clinically by the reviewer.

2.3 Sample size calculation

Recruiting adult subjects with untreated tetracycline stained teeth (TST) was recommended [22] however was anticipated to be difficult, therefore the objective of this clinical trial was to determine the effectiveness of strip and tray based bleaching modalities on TST. ΔE value (just noticeable difference) more than 2 will normally be noticeable to an experienced observer [33]. The standard deviation of TST at baseline were around 2 [21]. The effect size is therefore equivalent to 1.0. For one sample t-test with α=0.05 and 80% power, 10 subjects will be needed. Twenty percent more subjects were recruited for potential drop-out.

2.4 Statistical analysis

Continuous variables were tested for normality by Kolmogorov–Smirnov test. For normal distributed variables, means were analysed using two-sided parametric one sample t-test and

independent t-test for intra- and inter-group comparison respectively. For non-normally distributed variables, means were either log converted to normal distribution or medians were analysed using two-sided non-parametric one-sample Wilcoxon test and Mann-Whitney U test for intra- and inter-group comparison respectively. Categorical variables were analysed by Fisher's exact test. Significance level was set at $\alpha=0.05$. All data were analysed using Statistical Package for Social Science (SPSS) 23.0 (IBM, New York, USA).

3. Results

Thirty-six subjects were screened for possible inclusion in this study, from these 26 were enrolled. Ten subjects were excluded because either the discoloration was not tetracycline in origin or time conflict (Figure 1). Among the enrolled participants, fourteen recalled a history of tetracycline ingestion. Twelve and fourteen participants were randomly distributed into the *tray* and *strip* groups respectively. The socio-demographic and baseline tooth colour of two groups were compared and no significant difference was found ($p>0.05$) (Table 2). Each group has one participant that cannot attend the two-month review, otherwise there was no missing data. For the *tray* group, eight (66.7%) and four (33.3%) of participants the tested teeth were maxillary right and left central incisors respectively. For the *strip* group, five (35.7%) maxillary right central incisors, eight (57.2%) maxillary left central incisors and one (7.1%) maxillary left lateral incisor were tested. There were no significant adverse reactions other than mild transient sensitivity reported by both groups of participants.

3.1 Intra-group comparison

For both the *tray* and the *strip* groups, tooth colour have been found to be lighter, decreased redness and yellowness (increased L*, decreased a* and decreased b*) when compared to the baseline, and these changes were significant at the end of this 3-month trial ($p<0.05$) (Table 3). The overall colour changes ΔE were significant ($p<0.05$) and noticeable (i.e. greater than value of 2) in each monthly reviews. Changes in L*, a* and b* were significant from baseline to 2 months and from baseline to 3 months (Table 3 and 4). For the *tray* group, most L*, a* and b* changes were found in the first month ($p<0.05$). For the *strip* group, significant L* and a* changes were found in the first month and second month and significant b* changes was found in the second month ($p<0.05$) (Table 4).

3.2 Inter-group comparison

Inter-group comparison of tooth colour changes found that while greater lightness (ΔL*) improvement was observed in the *tray* group over the *strip* group in the first month (p=0.02), reverse was noticed in the second month (p=0.01) (Table 3). Both comparison have effect sizes greater than one. Despite the *tray* group has greater overall colour changes ΔE than the *strip* group at the end of this trial (10.11 *vs.* 8.23), no significant difference was found between two groups (p>0.05) and the effect size were 0.40 only. Clinically, the overall colour difference (1.88) between two groups was smaller than the just noticeable difference.

A post-hoc power analysis was performed for the two-tailed inter-group comparison of the overall colour changes ΔE at significance level α=0.05 (Table 4). The null hypothesis was the tray and strip systems are equally effective in bleaching tetracycline stained teeth (TST). The power of this pilot study was inadequate to correctly reject this null hypothesis when the alternative hypothesis (i.e. superiority of one bleaching modality) was true. Based on the 3-month result, with the value of 2 or more as just noticeable difference (JND) for experienced observer, sample size required at 80% power should be 68 subjects per group. In view of the difficulty to recruit adult subjects with untreated TST, for lay person the JND was 4 or more [33], the sample size required at 80% power will reduces 18 subjects per group.

4. Discussion

There are several limitations with this study. The difficulty in collecting a large enough sample of eligible subjects with tetracycline staining teeth (TST) to make comparison between two bleaching modalities meaningful. While there was adequate power for intra-group comparison, the power for inter-group comparison was inadequate and may lead to accept the null hypothesis (i.e. no difference) while there was a real difference between two bleaching modalities. A snowballing technique was used to gather eligible subjects and a 6-month period was used to gather the subject pool. Ideally a longer period for recruitment could have been used however, it was felt the speed of recruitment had dried up at 6 months.

Patient-centred outcome measures (PROMs) such as oral health related quality of life (OHRQoL) associated with the bleaching modalities were not assessed and compared in this trial. Standardized effect sizes (ES) of previous study on oral impact on daily performance

(OIDP) range from 0.34 to 0.75 [10], a sample size of 175 (ES 0.3) was therefore required for a two-tailed comparison at significance level α=0.05 [34]. Moreover, blinding of two bleaching modalities were impossible to the participants. However, potential bias to the tooth colour measurement was minimized by the use of a colorimeter with high reliability and accuracy [35] as well as positioning jig [17, 31, 32].

In this study the labial middle third of the testing tooth was measured since bleaching of the cervical third of TST may take up to a year [22, 36]. While participants were instructed to follow the treatment regimen and avoid tobacco use and/or consume staining foods and drinks, their compliance may decrease over an extended period of time. Moreover, the labial middle third of a tooth exhibited the most consistent results when the precision of measurement of different tooth areas was evaluated [31, 37]. Despite whitening effect has been observed at the cervical third of TST in this trial, the result should be limited to the labial middle third of TST.

The mean overall colour change ΔE reported was 5.5 or more at 1 month and greater than 8.0 at 3 months for both the tray and strip bleaching systems in this study. Colour change ΔE of 4 or more will normally be visible to the average person [33]. In dental literature, ΔE of 1.0 and 3.7 was suggested as the perceptibility (PT) and acceptability threshold (AT) respectively. PT means 50% of observers noticed there is a difference in colour while AT means 50% of observers considered unacceptable to the colour difference. [38-42]. While many studies used CIELAB 1976 colour difference formula, concerns has been raised on the use of this formula since human visual perception are not uniform [33]. PT and AT based on more updated formula CIEDE 2000 was found to be 1.30 and 2.25 respectively [43]. Therefore the bleaching effect of both modalities on TST were noticeable and acceptable to participants. However, the *tray* group loaded with 15% carbamide peroxide in this study has smaller colour changes than Matis *et al*'s tray group with same concentration of carbamide peroxide (mean ΔL* +9.13; mean Δa* -1.70; mean Δb* +0.32). Furthermore, decrease in the yellowness was observed only in 6-month review in Matis *et al*'s study. This may be due to different measurement techniques since they first matched participants' teeth to a shade guide and then measured the colour of shade guide by a colorimeter. In a meta-analysis of bleaching strip, similar trend of tooth colour changes (increased mean L* 2.04, decreased mean a* -0.79 and decreased mean b* -2.31) was observed in two-week's time [44]. These lower values are most likely related to the increased bleaching time in the current study (one-

month result) and the darker colour of TST at baseline allowing a relatively larger amount of change.

At the end of this trial, the *tray* group (mean ΔE=10.11) exhibited greater colour improvement than the *strip* group (mean ΔE=8.23); this trial did not have adequate power (10% only) to reject the null hypothesis (i.e. two modalities are equally effective) when the alternative hypothesis (i.e. superiority of one bleaching modality) was true. However the clinical significance of this mean differences (1.88) may be low, since it was smaller than the just notifiable difference (JND) (2 or more) and AT (2.25). Two modalities were also found equally effective in non-TST for 5.3% hydrogen peroxide strip and 10% carbamide peroxide tray delivery system (equivalent to 3.6% hydrogen peroxide)[26]. Experienced observer may observe differences (7.84 *vs* 5.53) in the bleaching effect between two treatment modalities in the first month only. This study chose strip (6.5% hydrogen peroxide) and tray (15% carbamide peroxide equivalent to 5.4% hydrogen peroxide) systems that had more equivalent bleaching concentrations to the one by Kugel *et al* [28] and hence the results showed that the whitening effect between the two groups was not statistical significant different over the study period.

Tooth bleaching involves a series of colour parameters, of which lightness L* is generally considered as the primary parameter and also the most used to assess the effectiveness of a bleaching procedure [45]. Some studies [32-34] regarded yellowness b* the most important indicator of tooth whitening in bleaching [46-48]. Ishikawa-Nagai *et al* used 10% carbamide peroxide for tooth bleaching and found the total colour change had a strong, moderate and low correlation with b*, L* and a*, respectively [49]. In both groups of the current study, the whitening effect was manifested mainly by an increase in lightness (increased L*), to a less extent, by a reduction in yellowness (decreased b*) and redness (decreased a*). This may be related to the darker hue of TST varying from yellow or grey to brown. Kwon *et al* have reported the increase in lightness tends to be greater for teeth with lower initial L* value [50] which supports the observation of Haywood *et al.* and Matis *et al*. that darker TST did not lighten as well [19, 21].

This study showed for both systems the majority of the bleaching of TST occurred during the first month, which agrees with the results of Matis *et al* [21, 22]. The onset of bleaching effect was more rapid in the *tray* group, and ΔL* in *tray* group at 1-month which was significantly greater than the strip group. Furthermore Matis *et al* also reported over the

subsequent two months further whitening did occur supporting the clinical impression that prolonged bleaching can be effective in improving the appearance of TST suggesting that bleaching times at least up to 3 months are appropriate for TST [21]. The patients in the current study reported no unexpected signs or symptoms with only mild transient tooth sensitivity the most common symptom reported and is consistent with other studies which demonstrated its safe longer term use [28, 48, 51].

5. Conclusion

The results of this randomized controlled trial suggested that a 3-month regime of both the 6% hydrogen peroxide strips and 15% carbamide peroxide tray system were effective in whitening of tetracycline stained teeth.

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

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Table 1. Inclusion and exclusion criteria of this randomized clinical trial on the tooth whitening outcomes.

Inclusion criteria	Exclusion criteria
• Tetracycline stained maxillary anterior teeth (agreed by two independent assessors) • Maxillary anterior teeth were sound or minimally restored • Able to attend over a 4-month period	• Subject who was under 18 or unable to give consent • Subject who was medically unfit for dental treatment and reviews • Subject who was pregnant and/or lactating • Uncontrollable oral diseases and/or with oral infections • History of tooth whitening treatment • Smoker • Allergy to hydrogen peroxide or carbamide peroxide

Table 2. Socio-demographic and tooth colour (L*a*b*) profile of the *tray* and the *strip* group at baseline

	Tray group Mean (SD)	*Strip group* Mean (SD)	p-value
Socio-demographic profile			
Age	28.7 (5.9)	30.4 (3.1)	0.388[^]
Gender (Female)	66.7%, n=8	85.7%, n=12	0.365[+]
Ethnic (Chinese)	100%, n=12	100%, n=14	N/A
Tooth colour profile			
L*	59.9 (6.5)	62.9 (4.5)	0.167[^]
a*	8.0 (1.9)	9.1 (4.6)	0.542[#^]
b*	13.4 (4.4)	15.1 (3.6)	0.286[^]

[+]Fisher's exact test; [^]Independent t test; [#]log-normality

Table 3. Tooth colour changes (i.e. adjusted values) of the *tray* and the *strip* group during the trial period. P-values of inter-group comparisons were presented.

	Tray group Mean (SD)	*Strip group* Mean (SD)	Inter-group p-value	Standardized effect size[#]	Post-hoc power analysis[$]
ΔE					
0 - 1 month	7.84 (3.88)[^]	5.53 (4.16)[^]	0.16[+]	+0.56	0.28
1 – 2 month	2.68 (1.29)[^]	2.96 (1.74)[^]	0.66[+]	-0.16	0.07
2 – 3 month	3.22 (2.54)[%]	2.56 (1.51)[^]	0.61[@]	+0.26	0.16

0 - 2 month	8.28 (3.24)^	7.55 (5.01)%	0.68+	+0.15	0.07
0 - 3 month	10.11 (3.42)^	8.23 (4.69)^	0.26+	+0.40	0.10
ΔL*					
0 - 1 month	6.64 (3.55)^	3.01 (3.48)^	**0.02**+	+1.02	-
1 – 2 month	-0.08 (1.64)	2.09 (1.86)^	**0.01**+	-1.17	-
2 – 3 month	2.11 (2.82)%	0.70 (2.19)	0.23@	+0.50	-
0 - 2 month	6.92 (3.22)^	5.16 (3.56)^	0.22+	+0.49	-
0 - 3 month	8.76 (3.87)^	5.61 (4.38)^	0.07+	+0.72	-
Δa*					
0 - 1 month	-1.63 (1.49)%	-2.19 (4.09)%	0.67@	+0.14	-
1 – 2 month	-0.13 (1.19)	-0.79 (1.09)^	0.17+	+0.55	-
2 – 3 month	-0.26 (1.18)	-0.37 (1.19)	0.82+	+0.09	-
0 - 2 month	-1.84 (1.03)%	-3.17 (4.95)%	0.57@	+0.27	-
0 - 3 month	-2.25 (1.50)%	-3.39 (4.38)%	0.94@	+0.26	-
Δb*					
0 - 1 month	-2.50 (3.09)^	-0.91 (2.36)	0.15+	-0.51	-
1 – 2 month	0.13 (2.33)	-0.98 (1.21)^	0.17+	+0.48	-
2 – 3 month	-0.44 (1.83)	-0.34 (1.53)	0.88+	-0.05	-
0 - 2 month	-2.56 (3.30)^	-1.87 (2.48)^	0.56+	-0.21	-
0 - 3 month	-2.78 (2.90)^	-2.12 (2.29)^	0.52+	-0.23	-

+p-values obtained from independent t-test; @p-values obtained from Mann-Whitney U test

^One sample t-test, $p<0.05$; %One-sample Wilcoxon test, $p<0.05$

#Standardized effect size = mean difference in tooth colour change / standard deviation of tooth colour change

$Two-tailed post-hoc power analysis at significance level $\alpha=0.05$

Table 4. Significant intra-group tooth colour changes (ΔL*, Δa*, Δb*) of the *tray*

and the *strip* groups during the trial period. Percentage changes were presented in bracket.

Tray group	← **0 - 1 month** →	← **1 - 2 month** →	← **2 - 3 month** →
	ΔL*, ***Δa****, Δb*	-	***ΔL****
	(75.8%, 72.4%, 89.9%)		(24.1%)

← **0 - 3 month** →
ΔL*, ***Δa****, Δb*
(All 100%)

← **0 - 2 month** →
ΔL*, ***Δa****, Δb*
(79.0%, 81.8%, 92.1%)

Strip group	← **0 - 1 month** →	← **1 - 2 month** →	← **2 - 3 month** →
	ΔL*, ***Δa****	ΔL*, Δa*, Δb*	-
	(53.7%, 64.6%)	(37.3%, 23.3%, 46.2%)	

← **0 - 3 month** →
ΔL*, ***Δa****, Δb*
(All 100%)

← **0 - 2 month** →
ΔL*, ***Δa****, Δb*
(92.0%, 93.5%, 88.2%)

One sample t-test, p<0.05; ***One-sample Wilcoxon test, p<0.05***

Figure 1. **Flowchart of subject recruitment of this randomized clinical trial on the tooth whitening outcomes.**