



Efficacy of fluoride varnish in preventing white spot lesions during treatment with fixed orthodontic appliances

A triple blinded randomized controlled trial

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Abstract:

Aim: The aim of this study was to evaluate the efficacy of a novel fluoride varnish (NFPV, Fluor Protector S) in preventing development of white spot lesions in adolescents undergoing treatment with fixed orthodontic appliances.

Material and methods: 185 patients aged between 12 and 18 years planned for orthodontic treatment with fixed appliance were randomized into varnish or placebo group. The varnish group received a varnish with the active ingredient ammonium fluoride and the placebo group received a similar varnish but without ammonium fluoride. All patients received treatment with fixed orthodontic appliance in the upper arch for a period of more than one year, and before bonding all patients had three intra-oral photos. Varnish in both groups was applied on the maxillary anterior teeth and premolars during every check-up at the orthodontic clinic (every 6 weeks). After debond, the composite on the teeth was carefully removed using carbide bur and three new intra-oral photos were taken. Finally, white spot lesions (WSL) were evaluated and scored on a monitor in a dark room using Gorelick scoring index.

Results: 66 patients of the 185 patients were debonded and represent the final number of patients included in present master thesis. The incidence of WSL after debond was 19.9% in the test group and 18.1% in the placebo group, respectively. No statistically significant difference between the groups was recorded.

Conclusion: Based on the limited amount of the patients in present master thesis, the null hypothesis was confirmed, there is no additional benefit to apply ammonium fluoride varnish during treatment with fixed orthodontic appliance to reduce the incidence of WSL.

Introduction:

Demineralization, decalcification, initial carious lesion and white spot lesion (WSL) are different names for the most common and significant adverse effect of orthodontic treatment with fixed appliance (1,2). WSL has an opaque white chalky appearance, which is caused by enamel subsurface demineralization, which in turn causes alterations in enamel optical properties (2). The reported incidence of patients developing at least one new WSL during orthodontic treatment ranged between 36% to 72.9% (3,4). It has also been reported that maxillary incisors are the most commonly affected teeth, more specifically the maxillary lateral incisors (3,5,6). The relation between orthodontic treatment with fixed appliance and the increase of incidence of white spot lesions is simply explained by the increase in retentive areas around the orthodontic brackets and wires, which elevate the plaque accumulation on the teeth surfaces (2). Not surprisingly, a proportional relation is found between the length of orthodontic treatment and development of WSL (4,7). These lesions jeopardize the final aesthetic results of the orthodontic treatment and decrease the patients' satisfaction after the treatment.



Figure 1 illustrating WSL

WSL occurs mainly because of the plaque accumulation around the orthodontic brackets, hooks and ligatures. Plaque contains bacteria (i.e. *Streptococcus mutans*) which digest carbohydrates resulting in a lower pH. The bacteria also secrete extracellular glucans which enhances plaque mass and colonization of bacteria. The low pH at the interface between plaque layer and tooth surface causes demineralization and increases the rate of diffusion of calcium and phosphate ions out of the tooth surface. When the pH increase, the diffusion of ions will be the opposite, resulting in a re-mineralization of the surface. If the rate of demineralization exceeds that of the re-mineralization, white spot lesions will start to develop. However, if the rate of the re-mineralization excess the de-mineralization, a healing of WSL will occur, unless the WSL develops to a cavity (2).

To establish re-mineralization of the enamel, several oral factors need to be coordinated. Saliva has a buffering capacity that counters the acid produced in plaque. This buffering capacity is derived from carbonic acid-bicarbonate system, phosphates and proteins. Saliva flow rate and buffering capacity are interrelated; an increase in the saliva flow increases the buffering capacity (2). The available amount of saliva might differ in separate areas of the oral cavity. Differences in saliva might explain why WSL are more common on the buccal surfaces of the maxillary incisors, as these surfaces seems to be less exposed to saliva, compared to other surfaces (2,5). Patients with poor oral habits seem also to be at risk for WSL after the insertion of fixed orthodontic appliance. Poor oral habits in combination with a frequent intake of carbohydrate rich diet increase the risk for developing WSL (2,3,5). All previously discussed factors influence the demineralization and re-mineralization, summarized in figure 2.

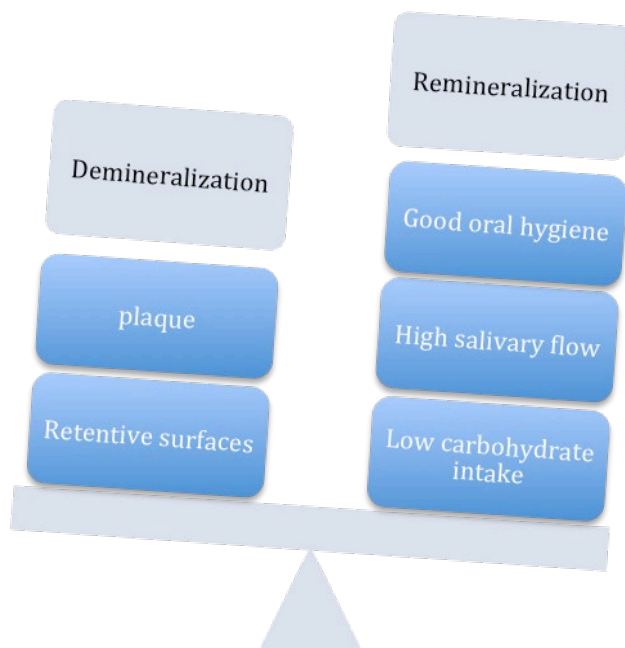


Figure 2 illustrating how remineralization takes place

With the introduction of fluoride as a preventive substance to decrease the development of carious lesions more than seventy years ago, dentistry turned into prevention to avoid carious lesions instead of reconstruction damaged dental tissues. Fluoride can inhibit the development of WSL by formation of fluoride apatite crystals which are more resistance to low PH (1,8). Fluoride also has direct inhibitory effect on the cellular enzymes and metabolism of the bacteria responsible for formation of WSL (8). Several studies have shown that the use of fluoride supplements reduce the numbers of the formation of new WSL in orthodontic patients (6,9,10). Fluoride mouth rinse, fluoride gel, high fluoride toothpaste and fluoride varnish are various approaches to administrate fluoride for prevention of WSL (1,6,8,9,11). A previous study was carried out in a double-blinded design, with a randomized placebo controlled design with two parallel arms to investigate the affect of 5000 ppm fluoridated toothpaste in one group and 1.450 ppm fluoridated toothpaste in the other group. All patients were planned to undergo orthodontic treatment with fixed appliance. Development of WSL was evaluated on the labial and buccal surface of maxillary incisors, canines and premolars after removal of the orthodontic appliance using intra-oral photos. Results from the study showed that 18.1% of the patients in the 5000 ppm group (test) had more than one WSL, while 26.6% of the patients in the 1450 ppm group (control) had more than one WSL, which was statistically significant (6). Another randomized placebo-controlled trial investigated the effect of a 1% fluorosilane varnish (Fluor Protector, Ivoclar Vivadent, Schaan, Liechtenstein) regularly applied around the bracket base in adolescents with fixed appliance. The study reported WSL incidence of 7.4% and 25.3% in the fluoride varnish group and the placebo varnish group respectively. The difference was highly statistically significant ($p < 0.001$) (9) .

The highest level of evidence is drawn from Cochrane reviews. The latest Cochrane review on preventive strategies for WSL in orthodontic patients with fixed appliance showed a moderate scientific evidence for professional fluoride varnish application during orthodontic treatment (10). However, the finding is based on a single study (9). High fluoride toothpaste and fluoride varnish seems to have a preventive effect on the development of WSL, but one method needs patient's compliance and the other method doesn't. So, in a situation where the patients comply with the instructions, high fluoride toothpaste is sufficient, while in a situation when a patient does not comply, the alternative might be professional fluoride varnish application.

WSL that develops on teeth surfaces during the orthodontic treatment may persist on teeth surfaces as

long as fourteen years after removal of the orthodontic appliance (12). Treatment of WSL after orthodontic treatment could be a challenging procedure. Multiple treatment alternatives are proposed as re-mineralization agents, bleaching, micro-abrasion and resin infiltration (13). However, in a previous systematic review on management of post-orthodontic WSL it was concluded that there is a lack of scientific evidence to support re-mineralization or camouflaging strategies, indicating the importance of preventive approaches (13).

Hypothesis:

The null hypothesis is that there is no statistically significant differences in incidence of WSL between a study group with fixed orthodontic appliance receiving ammonium fluoride varnish each check-up visit compared to a control group with fixed orthodontic appliance receiving a placebo varnish.

Aim:

The primary aim of the present study was to evaluate the efficacy of a novel fluoride varnish (NFPV, Fluor Protector S) in preventing the development of white spot lesions in adolescents undergoing treatment with fixed orthodontic appliances.

Material and Methods:

Subjects

185 healthy adolescents (12-18 years) of both genders from the general population referred to specialists for orthodontic treatment in Skåne Regional Council (Sweden) were planned to be consecutively recruited after informed individual and parental consent. Three clinics were involved in recruitment of the participants; Malmö University orthodontic department and two private orthodontic clinics, Ortodonti Syd in Hässleholm and Bernhold ortodonti in Helsingborg. The inclusion criteria was a scheduled treatment with fixed maxillary appliance according to a standard straight-wire concept (McLaughlin et al., 2001) during a period of at least 12 months. Exclusion criteria were severe chronic conditions such as asthma and allergy, neuropsychiatric disorders, regular use of oral antiseptics, patients planned for orthognathic surgery (since the patient will be operated during the treatment which will makes brushing more difficult after the surgery) and patients that will have restorations on the labial surface of the maxillary anterior teeth during treatment. In the event of long-term prescriptions of general antibiotics during the course of the study, this was recorded separately.

Randomization procedures

After the inclusion criteria were applied, the subjects were randomly allocated to a test or a placebo group by the clinicians with the aid of a computer program generating sequent numbers. Each group was assigned a colour either green or yellow. One of the trial staff (Mikael Sonesson) was privy to what the colours stand for and he was not involved in patient's allocation or treatment or outcome assessing. This procedure and steps insured elimination of selection bias during the enrolment of the participants by the clinicians and insured concealment. All subjects were recruited and enrolled from a community with a low natural fluoride content in the piped water (<0.3 ppm).

Study design

The study employed a triple blind, randomized placebo-controlled design with two parallel groups. The intervention started at onset of the fixed appliances and finalized at the time of debonding. The primary outcome was incidence of white spot lesions on the labial surfaces of the maxillary incisors, canines and premolars, as assessed from high-resolution digital photos.

All subjects were examined for orthodontic treatment planning reason prior to the onset of orthodontic fixed appliance bonding. During this examination, three standardized digital photos (one frontal and two laterals) were then exposed and stored on CD-discs for the comparisons with the status after debonding. At the time of debonding, at least 12 months after onset, the remaining composite material on the surfaces was carefully removed with a slowly rotating carbide bur followed by polishing with a rubber cup and pumice paste. After that, a new series of standardized frontal and lateral digital photos were taken and stored on a disc.

The pre- and post-treatment photos were then projected on a screen (Hewlett Packard ProBook 6650b, Palo Alto CA, USA) in a dark room. Then the incidence and the severity of enamel demineralization were registered by one blinded postgraduate student (SA) according to the index of Gorelick et al. (1982)(5). The incidence and severity were registered from digital photos, with aid of a 4-step score. The labial surfaces of the maxillary incisors, cuspids and premolars were the experimental sites and scored as: 1 = no white spot formation; 2 = slight white spot formation (thin rim); 3 = excessive white spot formation (thicker bands); 4 = white spot formation with cavitation (figure 3). When in doubt, the lower score is chosen. Unreadable follow-up photos (i.e. poor contrast, technical errors) were considered as dropouts. The examiner was blinded for the group assignment. A random sample of ten cases were re-assessed after one month in order to check the intra-examiner reliability.



Figure 3. Gorelick classification of WSL according to Gorelick et al. 1982

Clinical procedures

During the course of the orthodontic treatment, the patients were regularly checked every 6th week. At the end of each such occasion, the clinical staff dried the teeth with air and then applied either the test or the placebo varnish with a small brush in a thin layer around the base of the braces on the maxillary

teeth. The varnish was let to dry and the subjects were instructed not to eat or drink within 60 minutes after the application. The placebo varnish had an identical composition except for the ammonium fluoride. Taste, colour and handling properties were the same. The number of actual varnish applications was recorded in the digital records of each patient in order to keep track of the compliance with the protocol. All participants were strongly encouraged to brush their teeth twice daily with 1450 ppm fluoride toothpaste during the entire project. No other fluoride supplements, such as fluoride rinses, were recommended or prescribed.

Ethical considerations

The application of varnish were performed during ordinary appointments but half of the numbers of the participants got a varnish without the active substance (AmF). However, all the subjects were instructed to use ordinary tooth paste (1450 ppm) and had the opportunity to resign their participation and continue the orthodontic treatment without any explanation. The ethical application was approved by the Regional Ethical Research Authorities at Lund University (Dnr 2014/183). Both care givers and the patients were given a consent form and both signed it prior to the start of the intervention.

Statistics

The sample size was determined by a power calculation based on a previous trial with a similar design (9). With alpha (α) set at 0.05 (Type I error) and beta (β) to 0.20 (Type II error), 154 subjects (77 in each group) were needed to disclose a 15% difference between the groups. With an expected dropout rate of 20% over two years, it was considered appropriate to enrol a total of 185 subjects to the project. Fisher Exact test was used to determine any significant difference between the fluoride varnish group and placebo group at the level of individual tooth and at group level. Chi-Square test was used to determine any significant difference in relation to gender. Independent samples test, t-test for equality of means was used to determine any significant difference in relation to groups age and treatment duration.

Results:

Participant's enrolment, groups characteristics and intra-rater reliability

This master thesis followed the COSORT guidelines for randomised clinical trials except for the participants flow diagram since we did not have all data (14). One hundred and eighty patients were enrolled but only 66 patients were ready and debonded at the time of writing this master thesis. There was no statistically significant difference between the fluoride varnish group and placebo group in relation to age, gender and amount of WSL before bonding (Table 1). There was neither any significant difference between the orthodontic treatment time between the two groups (Table 1). To check the intra-observer reliability, ten cases were randomly selected for a second assessment of WSL. The assessments were performed 4 week after the initial assessment and the randomization of the cases were manage by using online website (<https://www.randomizer.org>). The intra-rater reliability was 0.97, which considered as excellent (15,16).

Clinical outcomes

No subjectively perceived side effects were reported during the trial. At a tooth level, there was no statistically significant difference between the groups regarding the amount or severity of WSL (Table 2). Before bonding the patients with fixed appliances, none of the subjects had any WSL. The total

incidence of WSL in both groups was 19.0% at teeth level. The incidence of WSL at tooth level was 19.9% and 18.1% in the varnish group and placebo group, respectively.

The most affected tooth with WSL was the maxillary right lateral incisor as 33% of them developed WSL. On the other hand, the least affected tooth with WSL was the upper right second premolar with an incidence equals 10.2%. Finally, none of the patients had a grade 4 WSL during the trial. A full presentation of the results can be found in Table 2.

Table 1 presenting groups characteristics and treatment duration

Group	Age (mean/SD)	Gender	Treatment duration (years/SD)
Varnish	14.0 years / 1.98	18 female, 15 male	1.48 / 0.39
Placebo	14.1 years / 1.51	22 female, 9 male	1.45/ 0.39
P value	P=0.899	P=0.175	P=0.781

Table 2 presenting the amount and grades of WSL at tooth level after debond

Group	Tooth	15	14	13	12	11	21	22	23	24	25
Varnish	Grade2 WSL	4	4	6	5	5	2	4	3	2	4
	Grade3 WSL	0	1	6	3	1	2	2	4	1	0
Placebo	Grade2 WSL	2	8	4	9	3	1	5	2	5	4
	Grade3 WSL	0	0	1	2	1	2	1	0	0	0
Total number of WSL per tooth		6	13	17	19	10	7	12	9	8	8
Percentage of WSL per tooth (tooth level)		10.2%	27.1%	28.8%	33.4%	16.1%	11.1%	20.4%	15.5%	17%	13.3%

Discussion:

The results of the present part-time evaluation of an on going randomized clinical trial (RCT), shows no differences in the prevention of WSL in patients with fixed appliance, treated with ammonium fluoride varnish compared to controls treated with a placebo varnish. In the health care sector, scientific research is done to identify interventions that provide the greatest patient benefit while utilizing resources in the most effective way. To evaluate effectiveness, the RCT is considered the highest standard and generate the highest level of evidence, followed by controlled trials (17,18). The advantages of using RCT-

methodology include elimination of bias in treatment assignment, specifically selection bias (without therapists or patient's preferences) and the confounding variables, hidden or variables out of control will be equalised in the groups (19). Thus all differences between the groups should be eliminated with proper randomization and concealment procedures. Three main solid methodological research planning were taken into consideration when preparing the present study: 1) randomized clinical trial, 2) triple blinded design and 3) prolonged observation period. Each of those points had a great advantage on the reduction of bias (19,20). One systematic review investigating the effect of improper concealment on estimating treatments effects in RCTs concluded that RCTs that did not report or incompletely reported a concealment approach yielded significantly larger estimates of treatment results (21). In our study, we insured a proper randomization and concealment since the clinicians were blinded from the beginning of the trial to the end, so they could not identify the group they are randomizing the patient to. The second point was the triple-blinded design, when neither the clinicians nor the patients nor the researchers/satiations could identify the intervention or the control group during the study time or during results interpretation. Blinding considered as one of the important methodological feature of an RCT to minimize bias and overoptimistic results and maximize the validity of the results (22). RCTs without double blinded design are reported to cause larger estimation treatment effects (21). Hence it is not always possible to apply the double or triple blinding design (22). In the present study, a triple-blinded design was used, which should strengthen the results.

The third point to discuss which added strength to our study was the prolonged observation period of the participants that almost eliminated the Hawthorne Effect. The Hawthorne Effect is defined as changes in patient or therapist behaviour when involved in a trial because of increased knowledge or interest or due to feeling observed in the trial (23). A recent systematic review (20) was assessed to elucidate whether the Hawthorne effect exists, explore under what conditions and estimates the size of any such effect. The conclusion confirmed the presence of such a phenomenon and that it causes overoptimistic results (false positive bias) in RCTs. The review also concluded that Hawthorne effect is almost diminished after the participants of the trial spend more than 6 months in the trial (20). In our study, the participants minimally spend one year in the trial, which means the Hawthorne Effect did not affect our trial results.

One of the main disadvantages of the present report is that the results are presented even though the trial is not ended yet. The power calculation that has been made before starting this study showed that the number of sample needed is 154 patients to reach the power. In this master thesis, only 66 patients were deboned and included in the analysis, which is under the power determined before the study. This could explain not founding a statistically significant difference between the groups. Another disadvantage is that only one examiner evaluated the intra-oral photos of the patients and scored the number and severity of the WSL. As a consequence, inter-rater reliability was not possible to perform. Another disadvantage of this trial is that the WSL were evaluated using intra-oral photos, which in some cases are not clear enough to diagnose the WSL. On the other hand, using the intra-oral photos instead of direct scoring decrease the clinical time needed for the scoring and also allow the performance of intra and inter- examiner reliability test.

In previous studies, the lateral incisors were the most affected teeth with WSL during treatment with fixed appliance (6,9) . This has been explained by that the lateral incisors usually have a palatally displaced position which makes cleaning more difficult during the orthodontic treatment. The second explanation is that the hooks of the orthodontic wires, the inter-maxillary elastics and the closing coils collects plaque in the area (3,6). In our study, the maxillary lateral incisors had more incidence of WSL than the other teeth.

The results of the present study is opposite to the results reported by Stecksén-Blicks et al. 2007 (9), who showed a reduction of the incidence of WSL after application of 1000 ppm fluoride varnish. The

difference between the studies could be explained by the diminished statistical power in our study and the differences in fluoride varnish formula that was used in the two different studies. In our study a novel fluoride varnish (NFPV, Fluor Protector S) containing 7700 ppm fluoride and ammonium was used and in the study of Stecksén-Blicks a varnish with lower fluoride concentration (Fluor Protector, Ivoclar Vivadent, Schaan, Liechtenstein) containing 1000 ppm fluoride as difluorosilane in a polyurethane varnish base was used. Even though the fluoride formula we used had a higher concentration of fluoride, we did not show any differences in the development of WSL between test and controls. This might indicate that the fluoride concentration not necessarily is the only variable that has to be taken into account when producing a varnish, also the other components in the varnish might influence the properties of the varnish. Also the diminished statistical power in this study could be an explanation why we did not find any significant difference between the groups. However, more proper conclusion could be drawn regarding the results after analysing all patients included in the present trial.

Patients with high caries experience or high decay-missing-filled index (DMFT) may have a higher risk for development of WSL during the treatment with fixed orthodontic appliance, but we did not have the data to investigate this question or even any evidence regarding this point.

Conclusion

Based on the limited amount of patients in present master thesis, the null hypothesis was confirmed, there is no additional benefit to apply ammonium fluoride varnish during treatment with fixed orthodontic appliance to reduce the incidence of WSL.

Reference list:

- (1) Chambers C, Stewart S, Su B, Sandy J, Ireland A. Prevention and treatment of demineralisation during fixed appliance therapy: a review of current methods and future applications. *Br.Dent.J.* 2013;215:505-511.
- (2) Chang HS, Walsh LJ, Freer TJ. Enamel demineralization during orthodontic treatment. Aetiology and prevention. *Aust.Dent.J.* 1997;42:322-327.
- (3) Chapman JA, Roberts WE, Eckert GJ, Kula KS, Gonzalez-Cabezas C. Risk factors for incidence and severity of white spot lesions during treatment with fixed orthodontic appliances. *Am.J.Orthod.Dentofacial Orthop.* 2010;138:188-194.
- (4) Richter AE, Arruda AO, Peters MC, Sohn W. Incidence of caries lesions among patients treated with comprehensive orthodontics. *Am.J.Orthod.Dentofacial Orthop.* 2011;139:657-664.
- (5) Gorelick L, Geiger AM, Gwinnett AJ. Incidence of white spot formation after bonding and banding. *Am.J.Orthod.* 1982;81:93-98.
- (6) Sonesson M, Twetman S, Bondemark L. Effectiveness of high-fluoride toothpaste on enamel demineralization during orthodontic treatment-a multicenter randomized controlled trial. *Eur.J.Orthod.* 2014;36:678-682.
- (7) Geiger AM, Gorelick L, Gwinnett AJ, Griswold PG. The effect of a fluoride program on white spot formation during orthodontic treatment. *Am.J.Orthod.Dentofacial Orthop.* 1988;93:29-37.
- (8) Buzalaf MA, Pessan JP, Honorio HM, ten Cate JM. Mechanisms of action of fluoride for caries control. *Monogr.Oral Sci.* 2011;22:97-114.
- (9) Stecksén-Blicks C, Renfors G, Oscarson ZD, Bergstrand F, Twetman S. Caries-preventive effectiveness of a fluoride varnish: a randomized controlled trial in adolescents with fixed orthodontic appliances. *Caries Res.* 2007;41:455-459.
- (10) Benson PE, Parkin N, Dyer F, Millett DT, Furness S, Germain P. Fluorides for the prevention of early tooth decay (demineralised white lesions) during fixed brace treatment. *Cochrane Database Syst.Rev.* 2013;12:CD003809.
- (11) Marinho VC. Cochrane reviews of randomized trials of fluoride therapies for preventing dental caries. *Eur.Arch.Paediatr.Dent.* 2009;10:183-191.
- (12) Shungin D, Olsson AI, Persson M. Orthodontic treatment-related white spot lesions: a 14-year prospective quantitative follow-up, including bonding material assessment. *Am.J.Orthod.Dentofacial Orthop.* 2010;138:136.e1-8; discussion 136-7.
- (13) Sonesson M, Bergstrand F, Gizani S, Twetman S. Management of post-orthodontic white spot lesions: an updated systematic review. *Eur.J.Orthod.* 2016 Mar 30.

- (14) CONSORT (2010) <http://www.equator-network.org/reporting-guidelines/consort/> (31 July 2017, date last accessed).
- (15) Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-174.
- (16) Fleiss JL. *Statistical methods for rates and proportions*. 2nd ed. : John Wiley; 1981. s. 38-46.
- (17) Moher D, Jones A, Lepage L, CONSORT Group (Consolidated Standards for Reporting of Trials). Use of the CONSORT statement and quality of reports of randomized trials: a comparative before-and-after evaluation. *JAMA* 2001;18:285:1992-1995.
- (18) O'Brien K, Craven R. Pitfalls in orthodontic health service research. *Br.J.Orthod.* 1995;22:353-356.
- (19) Bondemark L, Ruf S. Randomized controlled trial: the gold standard or an unobtainable fallacy? *Eur.J.Orthod.* 2015;37:457-461.
- (20) McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. *J.Clin.Epidemiol.* 2014;67:267-277.
- (21) Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408-412.
- (22) Karanicolas PJ, Farrokhyar F, Bhandari M. Practical tips for surgical research: blinding: who, what, when, why, how? *Can.J.Surg.* 2010;53:345-348.
- (23) Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". *J.Clin.Epidemiol.* 2001;54:217-224.