UNIWERSYTET MEDYCZNY
IM. PIASTÓW ŚLĄSKICH WE WROCŁAWIU

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# "Zasadność zastosowania profilaktyki antybiotykowej przed zabiegiem wszczepiania mini-implantów ortodontycznych"

Rozprawa na stopień doktora nauk medycznych

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Wrocław 2018

Składam serdecznie podziękowania Promotor
Pani Profesor Joannie Antoszewskiej-Smith
za inspirację, cenne uwagi, wszechstronną pomoc oraz
zaangażowanie w powstanie tej pracy

## 1. Streszczenie

Jednym z najważniejszych osiągnięć współczesnej ortodoncji jest uzyskanie zakotwienia absolutnego poprzez zastosowanie TISAD (Temporary Intraoral Skeletal Anchorage Devices). Wysoki odsetek mini-implantów zastosowanych z powodzeniem świadczy o dużej, jednak nie całkowitej skuteczności omawianej techniki. Wśród przyczyn przedwczesnej utraty mini-implantów na pierwszy plan wysuwają się infekcyjne stany zapalne otaczających je tkanek. Celem pracy była ocena wpływu profilaktyki antybiotykowej na stabilność mikro-implantów ortodontycznych. Na przeprowadzenie badań uzyskano zgodę Komisji Bioetycznej Uniwersytetu Medycznego we Wrocławiu nr 280/2012. Rozprawę doktorską stanowi cykl trzech publikacji o łącznym IF= 2,944; MNiSW= 71 pkt.

W pierwszej publikacji przeprowadzono przegląd systematyczny piśmiennictwa i meta-analizę w celu porównania skuteczności wzmacniania zakotwienia za pomocą metod konwencjonalnych względem TISAD. Z uzyskanych wstępnie 10038 artykułów zakwalifikowano ostatecznie 14 publikacji i wyekstrahowano dane łącznie 616 pacjentów dotyczące: mezjalnego przemieszczenia i angulacji zębów trzonowych, retrakcji i zmiany torku zębów siecznych oraz czasu leczenia, a następnie przeprowadzono ich meta-analizę. W kontekście kontroli zakotwienia, stwierdzono mniejszy mezjalny ruch zębów trzonowych o średnio 1,86 mm ($p<0,001$) przy wykorzystaniu TISAD, natomiast zmiana angulacji zębów trzonowych nie różniła się istotnie pomiędzy zakotwieniem konwencjonalnym, a szkieletowym. Zastosowanie TISAD umożliwiło również większą retrakcję zębów siecznych średnio o 1,37 mm ($p<0,001$), bez istotnych różnic w zmianie torku tych zębów pomiędzy obydwoma rodzajami zakotwienia. Ponadto, wykorzystanie zakotwienia szkieletowego umożliwiło skrócenie czasu leczenia przeciętnie o 4 miesiące ($p<0,001$). Uzyskane wyniki meta-analizy wskazują na wyższą skuteczność kliniczną TISAD, które powinno być metodą z wyboru w przypadkach wymagających absolutnej kontroli zakotwienia. Effectiveness of orthodontic miniscrew implants in anchorage reinforcement during en-masse retraction: A systematic review and meta-analysis.

W drugiej pracy dokonano przeglądu aktualnego piśmiennictwa w celu określenia najważniejszych czynników odpowiedzialnych za stabilność mini-implantów ortodontycznych. Analiza ujętych prac wykazała, że minimalna długość i średnica zapewniająca dobrą stabilizację wszczepu wynosi odpowiednio 8mm i 1,2 mm, natomiast rodzaj stopu oraz przygotowanie powierzchni mini-śruby nie odgrywają większej roli w kontekście jego stabilizacji. Pod względem czynników gospodarza piśmiennictwo wskazuje, że wiek i płeć nie oddziałują w istotny sposób na stabilność mikro-implantów. Wśród czynników zabiegowych wyniki badań wskazują na nieznaczną przewagę techniki samonawiercającej względem samogwintującej oraz procedury implantacji bez odsłaniania płata śluzówkowo-okostnowego, natomiast optymalnie moment obrotowy wkręcania mikro-śruby powinien mieścić się w zakresie 5-10 Ncm. Pojedyncze prace zawierały informacje o podawaniu antybiotyków w związku z zabiegiem wszczepiania mini-implantów, jednak autorzy w żaden sposób nie uzasadniali takiej praktyki.

Trzecia praca ma strukturę randomizowanego badania kontrolowanego, w którym oceniano wpływ zastosowania profilaktyki antybiotykowej na stabilność mini-implantów, częstość występowania stanów zapalnych wokół wszczepów, intensywność bólu pozabiegowego oraz czterokrotnie oznaczano poziomy prokalcytoniny i CRP w surowicy krwi w surowicy jako markerów stanu zapalnego. Po wstępnej selekcji wg ustalonych kryteriów do badań włączono 41 pacjentów Poradni Ortodoncji, którzy zostali losowo przydzieleni do grupy badanej lub kontrolnej, a do ostatecznej analizy uzyskano dane 38 uczestników (18 gr. badana, 20 gr. kontrolna). Uczestnicy otrzymywali 875mg amoksycyliny +125 mg kwasu klawulanowego oraz placebo odpowiednio w grupie badanej i kontrolnej na godzinę przed wszczepieniem mini-implantów ortodontycznych. Po jednej mini-śrubie utracili: jeden uczestnik w grupie badanej oraz dwóch w grupie kontrolnej, a proporcje uczestników z utraconym wszczepem pomiędzy grupami nie różniły się w sposób istotny statystycznie ($p=1,0$). Podanie antybiotyku nie zmniejszyło również częstości występowania stanu zapalnego wokół mini-implantów OR 1,22 (95% CI, 0,34-4,38, $p=0,795$) oraz intensywności bólu pozabiegowego ($p=0,798$). Badania poziomów prokalcytoniny oraz CRP wykazały brak istotnych statystycznie różnic w kolejnych pomiarach (PCT gr. badana $p=0,335$, gr. kontrolna $p=0,445$; CRP gr. badana $p=0,211$, gr. kontrolna $p=0,400$). Zastosowanie antybiotyku nie obniżyło w znaczący sposób poziomów PCT ($p=0,68$) i CRP ($p=0,908$). Uzyskane wyniki wskazują na brak korzyści klinicznych wynikających z zastosowania profilaktyki antybiotykowej przed zabiegiem wszczepiania mini-implantów ortodontycznych, zatem jej rutynowe zastosowanie nie jest wskazane. Oznaczanie systemowych poziomów PCT i CRP ma znikomą użyteczność w monitorowaniu stanów zapalnych tkanek otaczających mini-implanty.

Publikacje wchodzące w skład cyklu:

Antoszewska-Smith J, Sarul M, Łyczek J, Konopka T, Kawala B. Am J Orthod Dentofacial Orthop. 2017;151:440-455 IF: 1,472; pkt. MNiSW: 30

Fundamental factors related to orthodontic micro-implant stability: review of the literature. Łyczek J, Antoszewska-Smith J. Dent.Med.Probl. 2017;54:189-193. pkt. MNiSW: 11.000

Influence of antibiotic prophylaxis on the stability of orthodontic microimplants: A pilot randomized controlled trial. Łyczek J, Kawala B, Antoszewska-Smith J. Am J Orthod Dentofacial Orthop. 2018;153:621-631 IF: 1,472; pkt. MNiSW: 30

**2. Abstract**

One of the today`s most important achievements of orthodontics are Temporary Intraoral Skeletal Anchorage Devices (TISAD). High success rates associated with utilization of mini-implants states for significant, although not total effectiveness of this technique. Among various causes of premature loss of mini-implants, infectious inflammations of mini-screw surrounding tissues are of paramount importance. The aim of this dissertation was evaluation of the antibiotic prophylaxis on the stability of mini-implants. The research was granted a permission by Bioethical Comission of Wroclaw Medical University nr 380/2012. The dissertation consists of cycle of three publication with total IF= 2,944; MNiSW= 71 pkt.

The first publication is a systematic review and meta-analysis comparing effectiveness of anchorage reinforcement by conventional methods versus TISAD. Fourteen out of 10038 initially retrieved publications were eventually included in the study followed by extraction of data of 616 patients concerning: mesial molar movement, change of molar angulation, retraction of incisors, change of incisors` torque, total treatment time and their subsequent meta-analysis. In the context of anchorage preservation, less mesial molar movement was by average 1,86 mm ($p<0,001$) was observed with the use of TISAD, while the difference in molar angulation change was not significant between conventional and skeletal anchorage augmentation. Utilization of TISAD allowed more retraction of incisors by average 1,37 mm ($p<0,001$), whereas no significant differences in torque changes were stated between two anchorage types. Moreover, skeletal anchorage allowed reduction of treatment time by average 4 months ($p<0,001$). The results of the meta-analysis indicate higher clinical effectiveness of the TISAD, which should become method of choice in cases requiring absolute control of anchorage.

In the second publication the contemporary literature was screened in order to identify the most important factors related to mini-implants stability. The analysis of the included articles proved, that minimum length and diameter of the mini-screw should amount 8mm and 1,2 mm respectively, while the type of alloy or conditioning of the surface do not play major role in the context of mini-implant stability. In terms of host-patient characteristics, the findings of the literature show that age and sex do not influence on the TISAD stability in a significant manner. Among operative factors, the research results indicate slight advantage of self-drilling over self-tapping technique and a flapless surgical procedure, while the optimum placement torque ranges from 5 to 10 Ncm. Some authors mentioned administration of antibiotics in conjunction with mini-implantion, however none provided any justification of such approach.

The third publication was a randomized controlled trial, which evaluated the influence of the antibiotic prophylaxis on the stability of mini-implants along with frequency of inflammations, intensity of postoperative pain and quadruple procalcytonin and CRP as inflammatory markers serum levels testing. After initial selection according to established criteria, 41 patients of the Clinic of Orthodontic were included in the trial and randomly allocated to the study or control group, eventually resulting in data of 38 patients available for analysis ( 18 study group, 20 control group). The subjects were given 875mg of amoxicillin + 125mg of clavulanic acid or placebo one hour before mini-implant placement in the study and control groups respectively. One mini-screw was lost in one and two subjects in the study and control groups respectively and the proportions of subjects with lost mini-implants were not significantly different between both groups ($p=1,0$). Administration of antibiotic did not reduce the frequency of inflammations of the mini-implant surrounding tissues OR 1,22 (95% CI, 0,34-4,38, $p=0,795$) nor the intensity of postoperative pain ($p=0,798$). The analysis of procalcytonin and CRP levels did not show significant differences in consecutive measurements (PCT study gr. $p=0,335$, control gr. $p=0,445$; CRP study gr. $p=0,211$, control gr. $p=0,400$). Administration of antibiotic did not significantly reduce the procalcytonin ($p=0,68$) and CRP ($p=0,908$) levels. The obtained results indicate no benefit of introducing antibiotic prophylaxis prior to mini-implant placement, thus its routine utilization is not advocated. Measurements of systemic PCT and CRP proves of very little use in terms of monitoring of the condition of mini-implant surrounding tissues.

Publications included in the cycle:

Antoszewska-Smith J, Sarul M, Łyczek J, Konopka T, Kawala B. Am J Orthod Dentofacial Orthop. 2017;151:440-455 IF: 1,472; pkt. MNiSW: 30

Fundamental factors related to orthodontic micro-implant stability: review of the literature. Łyczek J, Antoszewska-Smith J. Dent.Med.Probl. 2017;54:189-193. pkt. MNiSW: 11.000

Influence of antibiotic prophylaxis on the stability of orthodontic microimplants: A pilot randomized controlled trial. Łyczek J, Kawala B, Antoszewska-Smith J. Am J Orthod Dentofacial Orthop. 2018;153:621-631 IF: 1,472; pkt. MNiSW: 30

**3. Wprowadzenie**

Opracowanie i wprowadzenie do praktyki klinicznej tymczasowego wewnątrzustnego zakotwienia szkieletowego (ang. Temporary Intraoral Skeletal Anchorage Devices, TISAD) w pierwszych dekadach XXI w. stanowi przełomowe osiągnięcie w zakresie kontroli zakotwienia. Uzyskane po raz pierwszy za pomocą tymczasowych implantów absolutne i niezależnie od współpracy pacjenta zakotwienie pozwoliło na znaczące rozszerzenie możliwości leczenia ortodontycznego, a także zwiększenie jego wydajności. Spośród różnego rodzaju wszczepów największą popularność zyskały mini-śruby charakteryzujące się wysoką skutecznością kliniczną, nieskomplikowaną procedurą implantacji oraz stosunkowo niską ceną. Szczegółowa diagnostyka oraz rzetelne szkolenie w procedurze implantacji pozwalają na zminimalizowanie ryzyka potencjalnych powikłań, np. uszkodzenia korzenia czy też złamania mini-implantu. Pomimo wielu zalet, kluczowym problemem związanym z zastosowaniem TISAD jest utrata stabilności i przedwczesne wypadnięcie wszczepów. W konsekwencji konieczne jest ponowienie zabiegu implantacji, co zwiększa inwazyjność oraz koszt leczenia, a w przypadku wielokrotnej utraty wszczepu uniemożliwia osiągnięcie celów terapii. W literaturze opisano rozmaite czynniki ryzyka utraty miro-implantów, do których należą między innymi lokalizacja w strefie ruchomej błony śluzowej w żuchwie, cienka blaszka kortykalna, zbyt małe rozmiary wszczepów czy nikotynizm. Tym niemniej, spośród zidentyfikowanych do tej pory czynników etiologicznych na pierwszy plan bezspornie wysuwa się stan zapalny tkanek otaczających mini-implant, w skutek którego dochodzi do degeneracji łoża kostnego, mechanicznej utraty stabilności i ostatecznie: wypadnięcia mini-śruby.

Jednym ze sposobów zapobiegania stanom zapalnym jest zastosowanie profilaktyki antybiotykowej przed wszczepieniem mini-implantów, jednak w literaturze światowej występuje całkowity brak badań dotyczących wprost tego zagadnienia. Jednocześnie istnieją prace, których autorzy opisują zastosowanie antybiotyków w związku z wszczepianiem mini-implantów ortodontycznych, ale bez podania jakiegokolwiek uzasadnienia takiej praktyki. W związku z brakiem obiektywnych badań oraz istotności omawianego problemu zdecydowałem o zdobyciu dowodów naukowych w tej dziedzinie.

Rozprawa doktorska składa się z cyklu 3 publikacji o łącznym IF= 2,944; MNiSW= 71 pkt

**Effectiveness of orthodontic miniscrew implants in anchorage reinforcement during en-masse retraction: A systematic review and meta-analysis.**
Antoszewska-Smith J, Sarul M, Łyczek J, Konopka T, Kawala B.
Am J Orthod Dentofacial Orthop. 2017;151:440-455
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**Fundamental factors related to orthodontic micro-implant stability: review of the literature**
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**Influence of antibiotic prophylaxis on the stability of orthodontic microimplants: A pilot randomized controlled trial.**
Łyczek J, Kawala B, Antoszewska-Smith J.
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IF: 1,472; pkt. MNiSW: 30

**4.0 Cele pracy**

Nadrzędnym celem rozprawy była ocena zasadności zastosowania profilaktyki antybiotykowej przed zabiegiem wszczepiania mini-implantów ortodontycznych jako metody zapobiegania rozwojowi peri-implantitis i wynikającej stąd przedwczesnej utracie wszczepów. Cele dodatkowe stanowiło porównanie skuteczności wzmocnienia zakotwienia przy zastosowaniu TISAD względem metod konwencjonalnych oraz przegląd czynników wpływających na stabilność mini-śrub.

4.1 Cel pracy **"Effectiveness of orthodontic miniscrew implants in anchorage reinforcement during en-masse retraction: a systematic review and meta-analysis**" stanowiło porównanie skuteczności wzmocnienia zakotwienia przy zastosowaniu TISAD oraz metod konwencjonalnych.

4.2 Celem pracy "**Fundamental factors related to orthodontic micro-implant stability: review of the literature"** była identyfikacja czynników wpływających za stabilność mini-implantów oraz czynników ryzyka odpowiedzialnych za ich przedwczesną utratę.

4.3 Celem pracy **"Influence of antibiotic prophylaxis on the stability of orthodontic micro-implants: a pilot randomized controlled trial"** była ocena wpływu zastosowania profilaktyki antybiotykowej na stabilność mini-implantów ortodontycznych, częstość występowania stanu zapalnego wokół wszczepów oraz intensywność bólu pozabiegowego i poziom białek wskaźnikowych stanu zapalnego tj. prokalcytoniny i CRP.

**5.0 Materiał i Metody**

5.1 W celu porównania skuteczności wzmocnienia przy pomocy TISAD oraz metod konwencjonalnych w pracy pt. **"Effectiveness of orthodontic miniscrew implants in anchorage reinforcement during en-masse retraction: a systematic review and meta-analysis"** przeprowadzono systematyczny przegląd piśmiennictwa oraz meta-analizę zebranych danych. Przeszukano bazy danych PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science przy pomocy słów kluczowych orthodontics and implant, micro-implant, microimplant, mini-screw, miniscrew, screw implant, temporary anchorage device, palatal implant, midpalatal implant, mini-plate, miniplate, en masse retraction za okres od stycznia 1990 do marca 2016 roku. Następnie przeprowadzono selekcję uzyskanych prac według ustalonych wcześniej kryteriów, a te włączone do analizy poddano ocenie jakości wg wytycznych grupy Cochrane i zmodyfikowanej skali New Castle-Ottawa. Następnie wyekstrahowano dane dotyczące utraty zakotwienia, zmiany angulacji zębów trzonowych, retrakcji zębów siecznych, zmiany torku zębów siecznych i czasu leczenia. Uzyskane dane poddano meta-analizie przy użyciu oprogramowania Statistica (wersja 12, Pakiet Medyczny wersja 3.0, StatSoft, Kraków, Polska).

5.2 W pracy pt. **Fundamental factors related to orthodontic micro-implant stability: review of the literature** dokonano przeglądu aktualnego światowego piśmiennictwa w celu identyfikacji czynników odpowiedzialnych za stabilność oraz przedwczesną mini-implantów. Używając słów kluczowych: micro-implants, mini-implants, micro-screws, mini-screws, TAD and TISAD, and stability, success rate and risk factor przeszukano bazy danych Medline, Scopus, Ebsco and Web of Science za lata 2000-2016. Z uzyskanych prac wyekstrahowano i skategoryzowano czynniki ryzyka przedwczesnej utraty mini-implantów.

5.3 Praca pt. **"Influence of antibiotic prophylaxis on the stability of orthodontic micro-implants: a pilot randomized controlled trial"** ma strukturę pilotażowego randomizowanego badania klinicznego, w którym porównano stabilność mini-implantów ortodontycznych i inne zmienne w sytuacji zastosowania profilaktyki antybiotykowej względem jej braku. Przed rozpoczęciem projektu badawczego uzyskano zgodę komisji bioetycznej Uniwersytetu Medycznego we Wrocławiu: nr 380/2012. Do badań włączano pacjentów Poradni Ortodoncji przy Katedrze Ortopedii Szczękowej i Ortodoncji Uniwersytetu Medycznego we Wrocławiu w okresie 11.2012-08.2015, którzy wymagali dystalizacji górnego łuku zębowego i spełniali następujące kryteria: dobry stan zdrowia ogólnego i jamy ustnej, brak alergii uogólnionych oraz na antybiotyki, brak chorób serca i nerek, nie przebyta antybiotykoterpia w ciągu dwóch miesięcy poprzedzających udział w badaniu. Pacjentów podzielono na rosnących i z zakończonym wzrostem wg aktualnej metody oceny dojrzałości kręgów szyjnych. Przydział do grup następował w momencie, gdy dwóch uczestników o tej samej płci oraz stadium rozwoju było gotowych do wszczepienia mini-implantów. Randomizacja polegała na rzucie monetą wykonywanym przez personel pomocniczy w osobnym pomieszczeniu, gdzie "zwycięzca" był przydzielany do grupy badanej, a "przegrany" do grupy kontrolnej. Farmaceutycznie przygotowane identyczne kapsułki z antybiotykiem (amoksycylina 875mg +125mg kwas klawulanowy) lub glukozą jako placebo były podawane uczestnikom odpowiednio w grupie badanej i kontrolnej na godzinę przed zabiegiem mini-implantacji. Następnie jeden i ten sam badacz nieświadomy przydziału pacjenta do danej grupy wszczepiał mini-implanty, a w późniejszym czasie oceniał następujące zmienne: stabilność wszczepów oraz stan tkanek je otaczających. Ponadto, od uczestników pobierano próbki krwi do oznaczania poziomu prokalcytoniny i białka CRP wg schematu: w dniu zabiegu przed implantacją, a następnie jeden, trzy oraz siedem dni po zabiegu w celu obiektywnego wykrywania ewentualnego stanu zapalnego. Pacjenci oceniali poziom bólu związanego z mini-implantacją jeden dzień po zabiegu za pomocą skali wizualno-analogowej (VAS) w przedziale od 0 do 100mm. Wyniki poddano analizie statystycznej

z zastosowaniem oprogramowania Statistica (wersja 12, Pakiet Medyczny wersja 3.0, StatSoft, Kraków, Polska) oraz Geepack (Generalized Estimating Equation Package, R Package, version 1.2-1)

**6.0 Wyniki**

6.1 Przeszukiwanie baz danych do pracy **"Effectiveness of orthodontic miniscrew implants in anchorage reinforcement during en-masse retraction: a systematic review and meta-analysis"** dało wstępny wynik 10038 artykułów, z których kryteria włączenia spełniło 14 publikacji. Randomizowane badania kontrolowane przeanalizowano zgodnie z wytycznymi Cochrane Collaboration, natomiast kliniczne badania kontrolowane oceniono przy pomocy zmodyfikowanej skali New Castle-Ottawa. Jakość włączonych badań oceniono na umiarkowaną. Dla celów meta-analizy uzyskano dane 616 pacjentów: 303 osoby o średniej wieku 19,43 w grupie badanej oraz 313 osób o średniej wieku 18,21 w grupie kontrolnej. Analiza przemieszczenia zębów trzonowych wykazała mniejszą o 1,86 mm utratę zakotwienia oraz przy zastosowaniu TISAD ($p<0,001$) oraz mniejszą zmianę angulacji zębów trzonowych, która jednak nie była istotna statystycznie ($p>0,05$). Wykorzystanie zakotwienia szkieletowego pozwoliło na większą retrakcję zębów siecznych średnio o 1,37 mm ($p<0,001$) oraz o $0,2^{o}$ większe ich przechylenie, jednak ten wynik nie osiągnął istotności statystycznej ($p>0,05$). Czas leczenia okazał się krótszy średnio o 4 miesiące przy zastosowaniu TISAD ($p<0,001$). Nie odnotowano działań niepożądanych związanych z zastosowaniem wszczepów ortodontycznych.

6.2 W pracy **"Fundamental factors related to orthodontic micro-implant stability: review of the literature"** kryteria wyszukiwania spełniły 44 publikacje. Otrzymane zmienne pogrupowano i sklasyfikowano w trzech kategoriach: a) związane z budową i charakterystyką mini-śruby, b) czynniki pacjenta-gospodarza, c) postępowanie zabiegowe i pozabiegowe. Wyniki badań dotyczących budowy i wielkości implantu wykazały, że minimalna długość i średnica zapewniająca dobrą stabilizację mini-śruby wynosi odpowiednio 8mm i 1,2mm, natomiast rodzaj stopu oraz przygotowanie powierzchni wszczepu nie odgrywają większej roli w kontekście jego stabilizacji. Analiza czynników gospodarza wskazuje, że wiek i płeć nie oddziałują w istotny sposób na stabilność mini-implantów. Pozytywnie na utrzymanie mini-śrub wpływa natomiast lokalizacja w szczęce oraz grubsza warstwa blaszki korowej i większa gęstość tkanki kostnej w miejscu implantacji. Wśród czynników zabiegowych wyniki badań wskazują na nieznaczną przewagę techniki samonawiercającej względem samogwintującej oraz procedury implantacji bez odsłaniania płata śluzówkowo-okostnowego, a optymalny moment obrotowy wkręcania mini-śruby powinien mieści się w zakresie 5-10 Ncm. Do predyktorów przedwczesnego obluzowania i wypadnięcia mini-implantów poszczególni badacze zaliczają między innymi lokalizację w żuchwie, cienką blaszkę korową, hiperdywergentny typ twarzy, średnicę wszczepu poniżej 1,0 mm oraz kontakt z korzeniem zęba. Tym niemniej, na pierwszy plan pośród czynników ryzyka przedwczesnej utraty mini-implantów wysuwa się stan zapalny, zgodnie wymieniony w znakomitej większości prac i potwierdzony meta-analizą, która wykazała 9-krotny wzrosty ryzyka wypadnięcia wszczepów w jego obecności. Pojedyncze prace zawierały informacje o podawaniu antybiotyków w związku z zabiegiem wszczepiania mini-implantów, jednak autorzy w żaden sposób nie uzasadniali takiej praktyki, podając jedynie rodzaj i dawkę stosowanego antybiotyku.

6.3 W pracy **"Influence of antibiotic prophylaxis on the stability of orthodontic micro-implants: a pilot randomized controlled trial"** do udziału w badaniach wstępnie zakwalifikowano 80 pacjentów Poradni Ortodoncji, z których 36 natychmiastowo odmówiło udziału w badaniach z powodu konieczności wielokrotnego pobierania próbek krwi. Kolejnych trzech pacjentów zostało zdyskwalifikowanych z udziału w badaniach z powodu wady serca, nasilonej alergii oraz alergii na penicyliny. Do randomizacji przystąpiło 41 uczestników, z których 21 alokowano do grupy badanej (antybiotyk), a 20 do kontrolnej (placebo). Dwóch uczestników z grupy badanej wycofało się z dalszego udziału po pierwszym pobraniu krwi obawiając się kolejnych, natomiast jeden został wykluczony z powodu podniesionego poziomu CRP (6,5mg/L) w pierwszej próbce krwi. Ostatecznie do celów analizy statystycznej uzyskano dane 18 uczestników w grupie badanej oraz 20 w grupie kontrolnej. Jeden oraz dwóch uczestników utraciło po jednym mini-implancie odpowiednio w grupie badanej i kontrolnej. Różnica uzyskanych odsetków sukcesu - 97,2 % w grupie kontrolnej oraz 95% w grupie badanej nie była znamienna statystycznie ($p=1,0$). Różnice w proporcjach pacjentów z utraconym przynajmniej jednym mini-implantem pomiędzy grupami również nie były znamienne statystycznie ($p=1,0$). Iloraz szans utraty przynajmniej jednego mini-implantu między grupą kontrolną, a badaną wyniósł OR 0.53, (95% CI, 0,0084-11,23; $p=1,0$). Brak stanu zapalnego wokół obu wszczepów zanotowano u odpowiednio 10 i 11 pacjentów w grupie badanej i kontrolnej. Zaczerwienienie tkanek otaczających mini-implant po przynajmniej jednej stronie zaobserwowano u 7 uczestników w obu grupach, natomiast zaczerwienienie i obrzęk u 1 oraz 2 pacjentów odpowiednio w grupie badanej i kontrolnej. Regresja logistyczna wystąpienia stanu zapalnego wokół przynajmniej jednego mini-implantu wykazała iloraz szans OR 1,22 (95% CI, 0,34-4,38) w grupie kontrolnej względem badanej, jednak wynik był nieistotny statystycznie ($p=0,758$). Poziomy bólu dzień po mini-implantacji wyniosły odpowiednio $8.5 \pm 0.75$ mm oraz $7.8 \pm 0.65$ mm w grupie badanej i kontrolnej, a ich

różnica nie była istotna statystycznie (p=0,798). Iloraz szans wystąpienia bólu poniżej 10mm w skali VAS wyniósł 1.174 (95% CI, 0,350-3,941) w grupie kontrolnej względem badanej, jednak różnica nie była istotna statystycznie (p=0,795). Średnie poziomy prokalcytoniny we krwi we wszystkich czterech badaniach w obu grupach wynosiły około 0,05 ng/ml, czyli znacząco poniżej normy dla osób zdrowych wynoszącej 0,1 ng/ml. Różnice w poziomach prokalcytoniny między kolejnymi badaniami nie były istotne statystycznie zarówno w grupie badanej (p=0,335), jak i kontrolnej (p=0,445). Uogólnione równanie szacunkowe wykazało, że w grupie badanej poziom prokalcytoniny był niższy o 0,001 ng/ml, jednak wynik nie był istotny statystycznie (p=0,68). Średnie poziomy CRP również zawierały się poniżej normy 5 mg/l we wszystkich badaniach w obu grupach. Analogicznie do poziomów prokalcytoniny, różnice w poziomach CRP między kolejnymi badaniami nie były istotne statystycznie zarówno w grupie badanej (p=0,211), jak i kontrolnej (p=0,400). Uogólnione równanie szacunkowe wykazało, że w grupie badanej poziom CRP był niższy o 0,015 mg/l, jednak wynik również nie był istotny statystycznie (p=0,908).

**7.0 Wnioski**

7.1 Meta-analiza zmiennych porównywanych w pracy **"Effectiveness of orthodontic miniscrew implants in anchorage reinforcement during en-masse retraction: a systematic review and meta-analysis"** wykazała mniejszą utratę zakotwienia przy zastosowaniu TISAD względem metod konwencjonalnych, średnio o 1,86 mm, co stanowi wynik istotny z klinicznego punktu widzenia. Jednocześnie wykorzystanie wszczepów pozwala na większą retrakcję zębów przednich oraz skrócenie czasu leczenia. Wyniki te wskazują zarówno na większą kontrolę, jak i efektywność przesunięć zębowych przy zastosowaniu TISAD, co świadczy o ich wyższej skuteczności w porównaniu z konwencjonalnymi metodami wzmacniania zakotwienia. Ponadto w bardzo licznej grupie pacjentów nie zanotowano powikłań związanych z TISAD, zatem powyższe wyniki przemawiają za ich częstszym stosowaniem, zwłaszcza w przypadkach wymagających największej kontroli zakotwienia.

7.2 Przegląd piśmiennictwa w pracy "**Fundamental factors related to orthodontic micro-implant stability: review of the literature"** umożliwił identyfikację najważniejszych czynników wpływających na stabilność mini-implantów ortodontycznych, które w ogólnym ujęciu można zaliczyć do trzech kategorii: związanych z pacjentem, budową wszczepu oraz postępowania około- i pozabiegowego. Zmienne kontrolowane przez klinicystę, a mające największy wpływ na stabilność mini-implantów to przede wszystkim odpowiednia średnica i długość wszczepów, które powinny wynosić co najmniej odpowiednio 1,2mm i 8mm oraz postępowanie kliniczne, a zwłaszcza procedura implantacji bez odsłaniania płata, umieszczanie wszczepów w błonie śluzowej związanej (dziąśle zębodołowym) oraz nieprzekraczanie siły 200g (200 cN) przy obciążeniu natychmiastowym. Natomiast podstawowym czynnikiem przedwczesnej utraty mini-implantu jest bezapelacyjnie stan zapalny otaczających go tkanek, prowadzący do degeneracji łoża kostnego, a w konsekwencji obluzowania i wypadnięcia wszczepu. Profilaktyka stanów zapalnych stanowi zatem kluczowy aspekt poprawy stabilności mini-implantów ortodontycznych.

7.3 W pilotażowym randomizowanym badaniu kontrolowanym **"Influence of antibiotic prophylaxis on the stability of orthodontic micro-implants: a pilot randomized controlled trial"** nie zaobserwowano poprawy stabilności mini-implantów na skutek zastosowania profilaktyki antybiotykowej. Ponadto, częstość występowania stanów zapalnych wokół wszczepów oraz nasilenie bólu pozabiegowego również nie uległy zmniejszeniu, zatem uzyskane wyniki wskazują na brak korzystnego wpływu profilaktyki antybiotykowej na kliniczny efekt zastosowania mini-implantów ortodontycznych. W związku z tym, a także mając na celu unikanie działań niepożądanych antybiotyków oraz zapobieganie narastania zjawiska antybiotykooporności, w praktyce klinicznej nie powinno się wdrażać profilaktyki antybiotykowej w związku z zastosowaniem mini-implantów ortodontycznych. Badania prokalcytoniny oraz białka CRP nie wykazały wzrostu ich poziomów zarówno na skutek ingerencji chirurgicznej w tkanki gospodarza podczas mini-implantacji, jak i stanu zapalnego powstałego wokół wszczepów. W pozytywnym ujęciu potwierdza to mikroinwazyjność zabiegu wszczepiania mini-śrub, jednak z drugiej strony wskazuje na brak możliwości wykrywania stanu zapalnego wokół mini-implantów i rokowania ich stabilności na podstawie pomiarów poziomów prokalcytoniny i CRP. W świetle uzyskanych wyników systemowe badania poziomów markerów stanu zapalnego mają znikomą użyteczność w związku z zastosowaniem wszczepów ortodontycznych.

**8.0 Załączniki: Publikacje i oświadczenia autorów**

8.1 **Effectiveness of orthodontic miniscrew implants in anchorage reinforcement during en-masse retraction: A systematic review and meta-analysis.**
Antoszewska-Smith J, Sarul M, Łyczek J, Konopka T, Kawala B.
Am J Orthod Dentofacial Orthop. 2017;151:440-455
IF: 1,472; pkt. MNiSW: 30

8.2 Oświadczenie autorów pracy

8.3 **Fundamental factors related to orthodontic micro-implant stability: review of the literature**
Łyczek J, Antoszewska-Smith J.
Dent.Med.Probl. 2017;54:189-193
pkt. MNiSW: 11.000

8.4 Oświadczenie autorów pracy

8.5 **Influence of antibiotic prophylaxis on the stability of orthodontic microimplants: A pilot randomized controlled trial.**
Łyczek J, Kawala B, Antoszewska-Smith J.
Am J Orthod Dentofacial Orthop. 2018;153:621-631
IF: 1,472; pkt. MNiSW: 30

8.6 Oświadczenie autorów pracy

8.2 Oświadczenie autorów

## Oświadczenie

Przyjmuję do wiadomości, że publikacja Joanna Antoszewska-Smith, Michał Sarul, Jan Łyczek, Tomasz Konopka, Beata Kawala.: Effectiveness of orthodontic miniscrew implants in anchorage reinforcement during en-masse retraction: a systematic review and meta-analysis Am.J.Orthod.Dentofac.Orthop. 2017 Vol.151 no.3; s.440-45 będzie składową rozprawy doktorskiej lek. dent. Jana Łyczka pt. "Zasadność zastosowania profilaktyki antybiotykowej przed zabiegiem wszczepiania mini-implantów ortodontycznych".

Miejsce Gniezno

Data 20.02.2018

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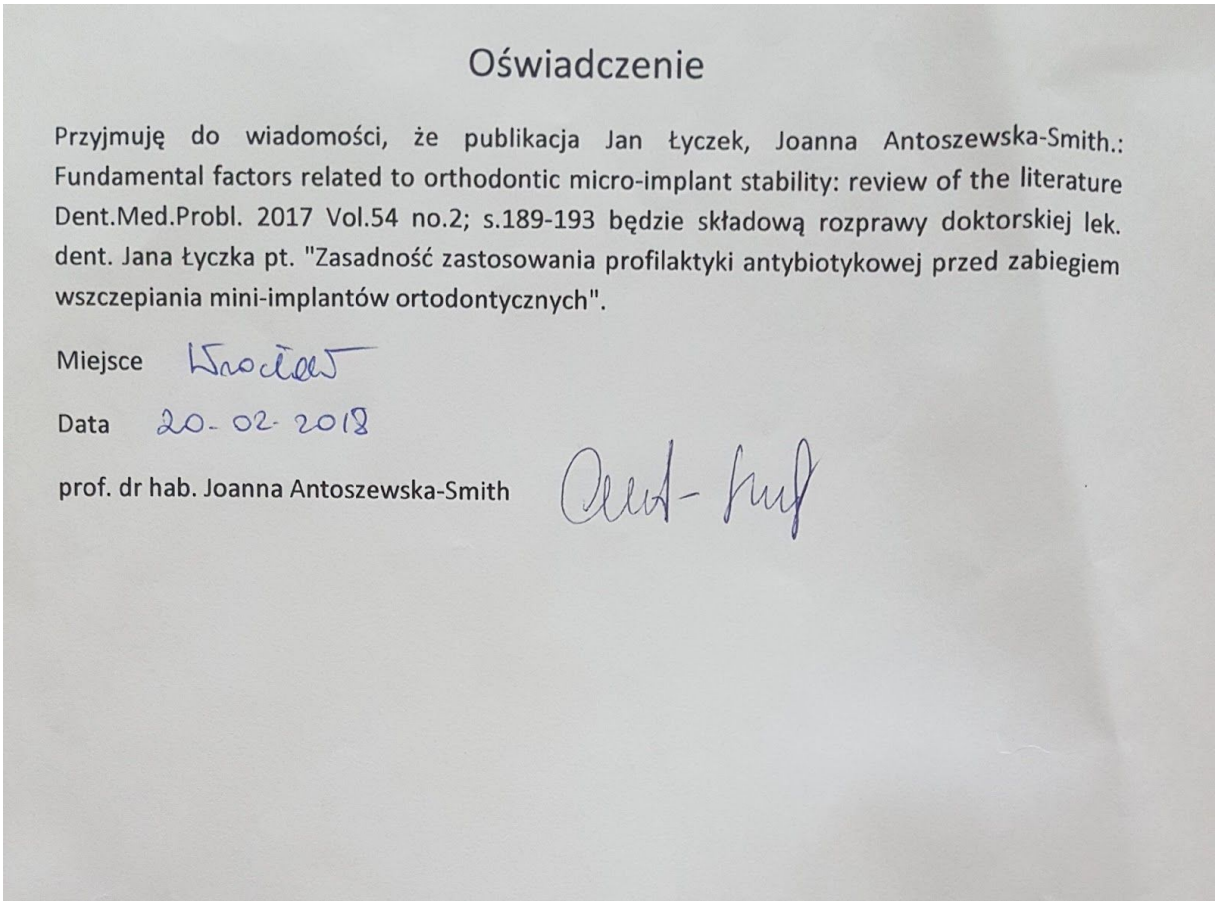
8.4 Oświadczenie autorów



## Oświadczenie

Przyjmuję do wiadomości, że publikacja Jan Łyczek, Joanna Antoszewska-Smith.: Fundamental factors related to orthodontic micro-implant stability: review of the literature Dent.Med.Probl. 2017 Vol.54 no.2; s.189-193 będzie składową rozprawy doktorskiej lek. dent. Jana Łyczka pt. "Zasadność zastosowania profilaktyki antybiotykowej przed zabiegiem wszczepiania mini-implantów ortodontycznych".

Miejsce Wrocław

Data 20-02-2018

prof. dr hab. Joanna Antoszewska-Smith

8.6 Oświadczenie autorów

## Oświadczenie

Przyjmuję do wiadomości, że artykuł Jan Łyczek, Beata Kawala, Joanna Antoszewska-Smith.: "Influence of antibiotic prophylaxis on the stability of orthodontic micro-implants: a pilot randomized controlled trial" przyjęty do publikacji w American Journal of Orthodontic and Dentofacial Orthopaedics będzie składową rozprawy doktorskiej lek. dent. Jana Łyczka pt. "Zasadność zastosowania profilaktyki antybiotykowej przed zabiegiem wszczepiania mini-implantów ortodontycznych".

Miejsce Wrocław

Data 20.02.2018

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# Effectiveness of orthodontic miniscrew implants in anchorage reinforcement during en-masse retraction: A systematic review and meta-analysis

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**Introduction:** The aim of this systematic review was to compare the effectiveness of orthodontic miniscrew implants—temporary intraoral skeletal anchorage devices (TISADs)—in anchorage reinforcement during en-masse retraction in relation to conventional methods of anchorage. **Methods:** A search of PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science was performed. The keywords were orthodontic, mini-implants, miniscrews, miniplates, and temporary anchorage device. Relevant articles were assessed for quality according to Cochrane guidelines and the data extracted for statistical analysis. A meta-analysis of raw mean differences concerning anchorage loss, tipping of molars, retraction of incisors, tipping of incisors, and treatment duration was carried out. **Results:** Initially, we retrieved 10,038 articles. The selection process finally resulted in 14 articles including 616 patients (451 female, 165 male) for detailed analysis. Quality of the included studies was assessed as moderate. Meta-analysis showed that use of TISADs facilitates better anchorage reinforcement compared with conventional methods. On average, TISADs enabled 1.86 mm more anchorage preservation than did conventional methods ($P < 0.001$). **Conclusions:** The results of the meta-analysis showed that TISADs are more effective than conventional methods of anchorage reinforcement. The average difference of 2 mm seems not only statistically but also clinically significant. However, the results should be interpreted with caution because of the moderate quality of the included studies. More high-quality studies on this issue are necessary to enable drawing more reliable conclusions. (Am J Orthod Dentofacial Orthop 2017;151:440-55)

The resistance to undesirable maxillary mesial molar movement while closing maxillary arch spaces after extraction of the first or second premolars is a key element of anchorage control and is obviously crucial for optimal treatment results.[1,2] Successful treatment of an adult with a full Class II malocclusion and maxillary dentoalveolar protrusion necessitating closure of the extraction spaces entirely from the front (by retraction of anterior teeth only) requires maximum anchorage achievable with various methods.[3]

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Submitted, February 2015; revised and accepted, August 2016.
0889-5406/$36.00

http://dx.doi.org/10.1016/j.ajodo.2016.08.029

Extraoral appliances, although efficient in anchorage control,[4] highly depend on the patient's compliance[5] and are therefore considered a fallible form of anchorage control with variable levels of outcome. Moreover, they have been associated with isolated cases of facial injury.[6,7] On the other hand, the effectiveness of intraoral appliances—eg, a Nance holding arch or transpalatal bar—has been questioned with prospective research alluding to limited benefits during active appliance therapy.[8]

Orthodontic implants or temporary intraoral skeletal anchorage devices (TISADs) are a compliance-free alternative to more traditional forms of anchorage. They are not attached directly to the teeth, unlike other methods of anchorage reinforcement. TISADs are regarded as simple to place and have reported survival rates ranging from 80% to 94%[9,10] and have therefore been advocated as the potential method of choice when anchorage reinforcement is necessary during treatment. However, there is some disagreement about the precise effects of

TISADs during space closure; several recent studies have demonstrated significant anchorage losses, whereas others found the opposite effect.[11-14] Moreover, there is conflicting evidence relating to their effectiveness vs alternative approaches to anchorage supplementation.

The aim of this systematic review and meta-analysis was to compare the effectiveness of TISADs and conventional anchorage augmentation during space closure by retraction of anterior teeth.

## MATERIAL AND METHODS

We performed this study according to PRISMA guidelines, and the main research question was defined in PICO format (Table I).

**Table I.** PICO format

| *Population* | *Subjects requiring absolute anchorage in maxillary arch* |
|---|---|
| Intervention | Retraction of anterior teeth with TISADs |
| Comparison | Retraction of anterior teeth with conventional anchorage |
| Outcome | Anchorage loss, change in angulation of maxillary molars, amount of incisors' retraction, change in angulation of maxillary incisors, and treatment duration |

### Eligibility criteria

1. Study design: randomized controlled trials (RCTs) and controlled clinical trials (CCTs).
2. Participants: orthodontic subjects requiring extraction of the maxillary first premolars and closure of the spaces without anchorage loss.
3. Interventions: study group, anchorage reinforcement with TISADs; control group, conventional anchorage reinforcement.
4. Exclusion criteria: language other than English, animal studies, case reports, case-series reports, literature reviews, lack of control group or fewer than 10 subjects in the study group, patients not treated with sliding mechanics, or comparison of anchorage loss after retraction of canines only.
5. Outcome measures: the primary outcome was anchorage loss defined as mesial movement of the maxillary first molars. Secondary outcomes were change in the angulation of the maxillary molars, amount of incisor retraction, change in the angulation of the maxillary incisors, and treatment duration.

### Search strategy, study selection, and information sources

The search strategy of the electronic databases, PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science (1990 to March 2016) is shown in Table II. Based on information from the titles and abstracts, relevant articles meeting the following inclusion criteria were selected: written in English, research on humans treated with extraction of the maxillary first premolars and retraction of all 6 anterior teeth with absolute anchorage, sliding mechanics used, and more than 10 subjects in the study group. Electronic searching was supplemented with review of the bibliography in each identified article. The following journals were manually screened: *European Journal of Orthodontics*, *Journal of Orthodontics*, *Journal of Clinical Orthodontics*, *Seminars in Orthodontics*, *American Journal of Orthodontics & Dentofacial Orthopedics*, and *Angle Orthodontist*. The literature search, assessment of relevance, risk of bias analysis, and data extraction were performed independently by 2 authors (J.A.S. and J.Ł.). All authors discussed disagreements until consensus was reached.

### Data extraction

The following data were extracted from the included studies: year of publication, sample size, age of the patients at the beginning of the treatment, types of appliances used for anchorage reinforcement, types and dimensions of the TISADs, amounts of mesial molar movement and tipping, amounts of incisor retraction and tipping, and treatment duration.

### Risk of bias in individual studies

The Cochrane Collaboration tool for assessing risk of bias in randomized controlled trials was applied using the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of assessors, incomplete outcome data, selective reporting of outcomes, and other potential sources of bias. The quality of the CCTs was assessed according to a modified Newcastle-Ottawa Scale (Appendix) comprising 3 sections.

1. "Selection," evaluating case definition, representativeness of cases, control selection, and definition of controls. Each aspect was assigned 1 mark, giving 4 marks in total.
2. "Comparability," appraising extraction patterns in the maxilla and the mandible; therefore, 2 marks could be obtained in this section.
3. "Outcome assessment," evaluating outcome measures, treatment changes, and blinding of assessors, giving 3 marks in total.

**Table II.** Search strategy

| *Database* | *Key words* | *Limits* |
|---|---|---|
| PubMed | orthodontics and implant or micro-implant or microimplant or mini-screw or miniscrew or screw implant or temporary anchorage device or palatal implant or midpalatal implant or mini-plate or miniplate or en masse retraction | English language, studies on humans, 1990 to March 2016 |
| EMBASE | orthodontics and implant or micro-implant or microimplant or mini-screw or miniscrew or screw implant or temporary anchorage device or palatal implant or midpalatal implant or mini-plate or miniplate or en masse retraction | English language, studies on humans, 1990 to March 2016 |
| Cochrane Central Register of Controlled Trials | orthodontics and implant or micro-implant or microimplant or mini-screw or miniscrew or screw implant or temporary anchorage device or palatal implant or midpalatal implant or mini-plate or miniplate or en masse retraction | English language, studies on humans, 1990 to March 2016 |
| Web of Science | orthodontics and implant or micro-implant or microimplant or mini-screw or miniscrew or screw implant or temporary anchorage device or palatal implant or midpalatal implant or mini-plate or miniplate or en masse retraction | English language, studies on humans, 1990 to March 2016 |

### Summary measures and approach to synthesis

Random-effects meta-analysis of the mean differences in mesial movement of the molars, tipping of the molars, retraction of the incisors, tipping of the incisors, and treatment duration was carried out. Randomized and controlled clinical studies were statistically evaluated both jointly and separately with subgroup analysis and significance established at $P < 0.05$. Results of the analyses are presented graphically with forest plots after comparisons of study designs, methodologies, participants, and types of anchorage to judge the clinical heterogeneity of the studies. The Cochrane Q test and $I^2$ statistics enabled evaluation of statistical heterogeneity of the collected data. All calculations were carried out with STATISTICA Medical Bundle software (version 3.0; StatSoft Polska, Krakow, Poland).

### Additional analysis

Sensitivity analysis was performed by drawing sensitivity plots to define the influence of specific studies on the total calculated effect. Funnel plot analysis involving Begg and Mazumdar[15] and Egger[16] asymmetry tests allowed assessment of publication bias.

## RESULTS

### Retrieved studies and data extraction

The PRISMA diagram depicting the flow of the 10,038 initially retrieved articles is presented in Figure 1. Review of the abstracts excluded 10,002 of them, leaving 36 full-text articles. Subsequently, 21 studies were found to be ineligible for further analysis because of insufficient sample size or lack of relevant outcome data. Two of the retrieved 15 eligible studies were based on the same sample of patients; therefore, only 1 was used in this systematic review.[11,12] Eventually, we obtained 7 RCTs and 7 CCTs, giving a total of 14 studies. A summary of the data extracted from the articles is shown in Table III, and the demographic structure of the pooled patient sample is given in Table IV. In total, 616 patients were included: 451 female and 165 male. Three hundred three patients were treated using TISADs (mini-implants, miniplates, or miniscrews). That group included 231 female and 72 male patients. The control group comprised 313 patients, 220 female and 93 male, treated with conventional anchorage reinforcement. The mean ages of the patients at the beginning of treatment were 19.43 years in the TISAD group and 18.21 years in the conventional anchorage group.

### Risk of bias within studies

The assessment of the risk of bias in the RCTs is presented in Table V and summarized in Figure 2. We assessed the risk of bias from randomization as low in the studies by Feldmann and Bondemark,[8] Benson et al,[11] Upadhyay et al,[13] Al-Sibae and Hajeer,[17] and Sandler et al,[18] who presented precisely described, rigorous randomization methods (computer-generated random numbers or external randomization center). Due to lack of information about the randomization process, we assessed the studies by Liu et al[19] and Victor

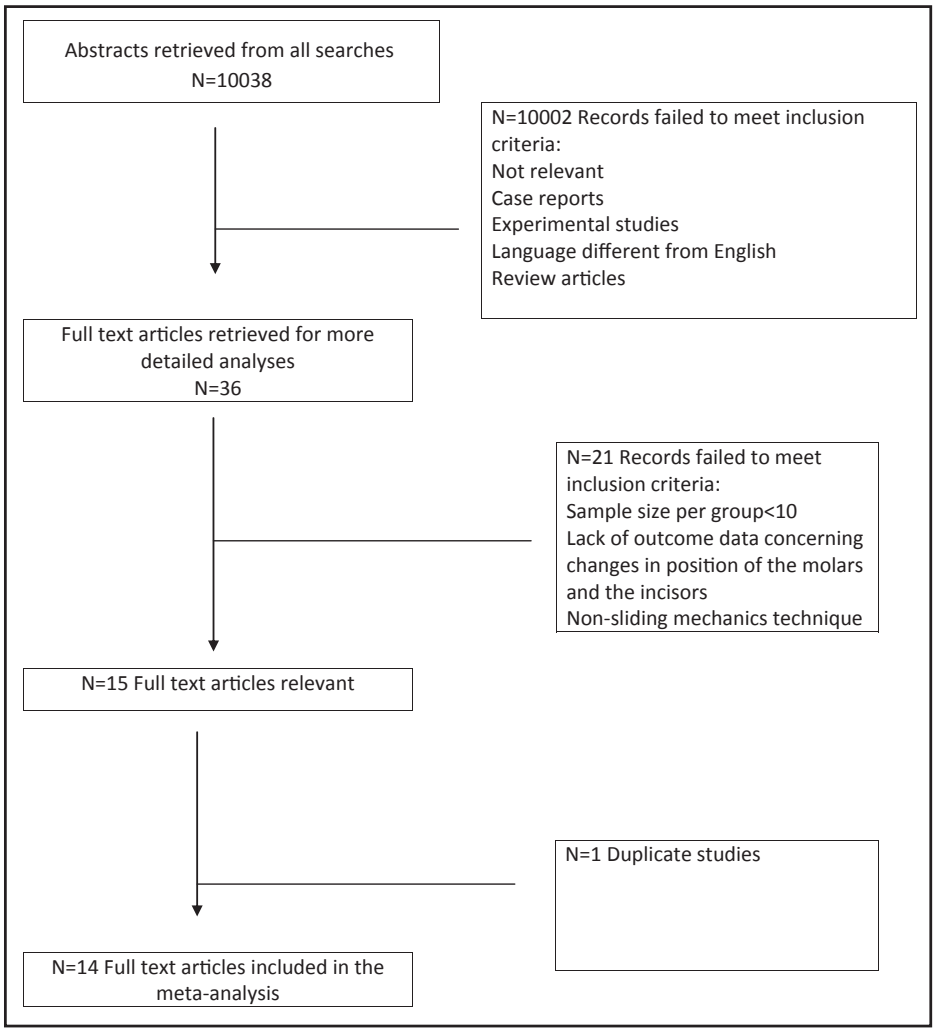


**Fig 1.** PRISMA diagram of article retrieval.

et al[20] as having an unclear risk of bias. For allocation concealment, the studies by Feldmann and Bondemark, Upadhyay et al, Al-Sibae and Hajeer, and Sandler et al were evaluated as having a low risk of bias, since opaque sealed envelopes were used in this respect. Because the type of anchorage reinforcement becomes obvious during its application, blinding of participants and personnel to the treatment method was not feasible. Thus, risk of bias had to be graded as high in all included studies. On the other hand, this shortcoming was partly overcome by blinding of the outcome assessment. Four studies, those of Benson et al, Upadhyay et al, Al-Sibae and Hajeer, and Sandler et al precisely described the blinding of assessors or the introduction of a person not involved in the study and unaware of its purpose. The other authors skipped that information; thus, the risk of bias remained unclear. All studies were assessed as having a low risk of bias from lack of complete data, selective reporting, or other threats to validity.

Results of the quality assessment of the included CCTs are shown in Table VI. Six studies acquired 4 marks in the section of selection. The article by Upadhyay et al[13] lost 1 mark for using various types of conventional anchorage reinforcement in the control group. For comparability, 3 studies—those of Kuroda et al,[9] Koyama et al,[21] and Lee and Kim[22]—achieved a maximum of 2 marks. The rest of the studies lost 1 mark in this section because of different extraction patterns. All CCTs obtained 2 marks out of 3 in the outcome assessment section, since none of the studies included blinding of assessors.

**Table III.** Data extracted from the enrolled studies

| Study | Diameter/ length (mm) of TISAD | Magnitude of force (G) | Mesial molar movement-anchorage loss (mm)* | | | Tipping of molars (°)* | | | Incisor distalization (mm)* | | | Incisor tipping (°)* | | | Treatment duration (mo) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Miniscrew | Miniplate | Hg/TPA | TISAD/Hg | | | TISAD/Hg | | | TISAD/Hg | | | Miniscrew | Miniplate | Hg/TPA |
| RCTs | | | | | | | | | | | | | | | | | |
| Benson et al,[11] 2007 | NR/6 mm | 450 | 1.5 | | 3 | NR/NR | | | −2.1/−0.7 | | | NR/NR | | | NR | | NR |
| Lai et al,[2] 2008 | Various | 300-350 | 1.3 | 1.4 | 2.5 | NR/NR | | | −6.9/−7.3/−5.5 | | | NR/NR/NR | | | 27.1 ± 4.2 | 31.4 ± 4.7 | 33.6 ± 7.2 |
| Upadhyay et al,[13] 2008 | 1.3/8 | 300-350 | −0.78 | | 3.22 | NR/NR | | | −7.22/−6.33 | | | −13.11/−16.83 | | | NR | | NR |
| Feldmann and Bondemark,[8] 2008 | 1.3/8 mm | NR | PI 0.1 | | Hg 2.0 | On −0.2 | Hg 0.8 | | On −3.9 | Hg −4.8 | | On −1.7 | Hg −1.9 | | NR | | NR |
| | | | On −0.1 | | TPA 1.0 | PI 0.7 | TPA 0.7 | | PI −4.7 | TPA −3.3 | | PI −3.0 | TPA −1.1 | | NR | | NR |
| Liu et al,[19] 2009 | 1.2/8 mm | NR | −0.06 | | 1.47 | NR/NR | | | −7.03/−4.76 | | | −13.53/−12.03 | | | 20.65 ± 5.06 | | 26.88 ± 6.54 |
| Lee and Kim,[22] 2011 | 1.6/8 mm | NR | 0.24 | | 2.2 | 0.49/−0.25 | | | −9.45/−7.10 | | | −16.20/−19.13 | | | 24.95 ± 4.55 | | 28.00 ± 8.37 |
| Koyama et al,[21] 2011 | 1.6/8 mm | 200 | 0.1 | | 2.1 | NR/NR | | | −6.2/−7.0 | | | −10.3/−11.1 | | | NR | | NR |
| Al-Sibae and Hajeer,[17] 2013 | 1.6/7 mm | 300 | −0.75 | | 1.76 | NR/NR | | | −5.92/−4.79 | | | −5.03/−7.94 | | | 12.9 ± NR | | 16.97 ± NR |
| Victor et al,[20] 2014 | 1.3/8 mm | 150 | NR | | NR | −0.88/3.38 | | | NR | | | −5.8/−5.8 | | | NR | | NR |
| Sandler et al,[18] 2014 | 1.6/8 mm | 100 | 0.99 | | Na 2.09 | NR | | | NR | | | NR | | | 26.83 (8.5-45.16) | | Hg 28.01 (17.46-38.51) |
| | | | | | Hg 1.99 | | | | | | | | | | | | TPA 27.43 (15.03-39.83) |
| CCTs | | | | | | | | | | | | | | | | | |
| Park et al,[25] 2008 | 1.3/8 mm | 150 | 0.26 | | 1.71 | −1.40/−0.17 | | | −8.58/−7.47 | | | −14.39/−19.29 | | | 25.6 ± 5.5 | | 28.6 ± 4.2 |
| Upadhyay et al,[14] 2008 | 1.3/8 | 300-350 | −0.55 | | 1.95 | −0.13/3.7 | | | −0.9/0.37 | | | −11.27/−10.83 | | | NR | | NR |
| Yao et al,[26] 2008 | Various | 300-350 | 0.88 | | 2.07 | NR/NR | | | −8.17/−6.73 | | | −13.56/−9.59 | | | 29.81 ± 6.41 | | 32.29 ± 6.46 |
| Kuroda et al,[9] 2007 | 1.3/8 | NR | 0.7 | | 3 | NR/NR | | | −9.3/−6.3 | | | −20.3/−14.0 | | | NR | | NR |
| Lee and Kim,[20] 2011 | 1.6/8 mm | NR | 0.24 | | 2.2 | 0.49/−0.25 | | | −9.45/−7.10 | | | −16.20/−19.13 | | | 24.95 ± 4.55 | | 28.00 ± 8.37 |
| Koyama et al,[21] 2011 | 1.6/8 mm | 200 | 0.1 | | 2.1 | NR/NR | | | −6.2/−7.0 | | | −10.3/−11.1 | | | NR | | NR |

*NR*, Not reported; *Hg*, headgear; *TPA*, transpalatal arch; *On*, onplant; *PI*, palatal implant; *Na*, Nance button.
*For linear measurements, + indicates mesial movement and–distal movement; for angular measurements, + indicates mesial tipping and − distal tipping.

**Table IV.** Characteristics of the samples in the included studies

| | *TISAD* | | | | | | *Conventional anchorage* | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Study* | *Female* | *Male* | *n* | *% female* | *Age at start of treatment (y)* | *Success rate (%)* | *Female* | *Male* | *n* | *% female* | *Age at start of treatment (y)* | |
| Benson et al,[11] 2007 | 20 | 6 | 26 | 76.92 | 15.70 | 75.00 | 18 | 7 | 25 | 72.00 | 14.80 | |
| Park et al,[25] 2008 | 14 | 2 | 16 | 87.50 | 22.50 | 87.00 | 11 | 3 | 14 | 78.57 | 22.90 | |
| Upadhyay et al,[14] 2008 | 10 | 5 | 15 | 66.67 | NR | 87.00 | 11 | 4 | 15 | 73.33 | NR | |
| Lai et al,[2] 2008 | 21 | 3 | 24 | 87.50 | 24.73 | NR | 16 | 0 | 16 | 100.00 | 21.70 | |
| Yao et al,[26] 2008 | 23 | 2 | 25 | 92.00 | 24.72 | NR | 20 | 2 | 22 | 90.91 | 22.23 | |
| Upadhyay et al,[13] 2008 | 20 | 0 | 20 | 100.00 | 17.60 | 93.00 | 20 | 0 | 20 | 100.00 | 17.30 | |
| Feldmann and Bondemark,[8] 2008 | 30 | 30 | 60 | 50.00 | 14.30 | 88.37 | 30 | 30 | 60 | 50.00 | 14.20 | |
| Kuroda et al,[9] 2007 | 11 | 0 | 11 | 100.00 | 18.50 | NR | 11 | 0 | 11 | 100.00 | 21.80 | |
| Liu et al,[19] 2009 | 14 | 3 | 17 | 82.35 | 19.71 | 88.00 | 14 | 3 | 17 | 82.35 | 21.65 | |
| Lee and Kim,[22] 2011 | 20 | 0 | 20 | 100.00 | 24.64 | NR | 20 | 0 | 20 | 100.00 | 22.16 | |
| Koyama et al,[21] 2011 | 13 | 1 | 14 | 92.86 | 24.80 | 86.00 | 12 | 2 | 14 | 85.71 | 25.00 | |
| Al-Sibae and Hajeer,[17] 2013 | 19 | 9 | 28 | 67.86 | 23.02 | 95.00 | 16 | 12 | 28 | 57.14 | 20.46 | |
| Victor et al,[20] 2014 | NR | NR | 10* | NR | NR | NR | NR | NR | 10* | NR | NR | |
| Sandler et al,[18] 2014 | 16 | 11 | 27 | 59.26 | 14.15 | NR | 21 | 30 | 51 | 41.18 | 14.26 | |
| Summary | 231 | 72 | 303 | 76.24 | 19.43 | 87.60 | 220 | 93 | 313 | 70.29 | 18.21 | |
| Incisor retraction | 215 | 61 | 276 | 77.90 | 19.97 | 87.60 | 199 | 63 | 262 | 75.95 | 19.02 | |
| Incisor tipping | 174 | 52 | 226 | 76.99 | 19.96 | 89.52 | 165 | 56 | 221 | 74.66 | 19.33 | |
| Mesial molar movement | 231 | 72 | 303 | 76.24 | 19.43 | 87.60 | 220 | 93 | 313 | 70.29 | 18.21 | |
| Molar tipping | 74 | 37 | 111 | 66.67 | 17.82 | 87.90 | 72 | 37 | 109 | 66.06 | 17.19 | |
| Treatment duration | 92 | 10 | 102 | 90.20 | 23.52 | 87.52 | 81 | 8 | 89 | 91.01 | 22.11 | |

*NR*, Not reported.
*Sex distribution was not described in the study.

**Table V.** Risk of bias of the RCTs

| Study | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias |
|---|---|---|---|---|---|---|---|
| Al-Sibae and Hajeer,[17] 2013 | Low | Low | High | Low | Low | Low | Low |
| Benson et al,[11] 2007 | Low | Unclear | High | Low | Low | Low | Low |
| Feldmann and Bondemark,[8] 2008 | Low | Low | High | Unclear | Low | Low | Low |
| Liu et al,[19] 2009 | Low | Low | High | Unclear | Low | Low | Low |
| Sandler et al,[18] 2014 | Low | Low | High | Low | Low | Low | Low |
| Upadhyay et al,[13] 2008 | Low | Low | High | Low | Low | Low | Low |
| Victor et al,[20] 2014 | Unclear | Unclear | High | Unclear | Low | Low | Low |

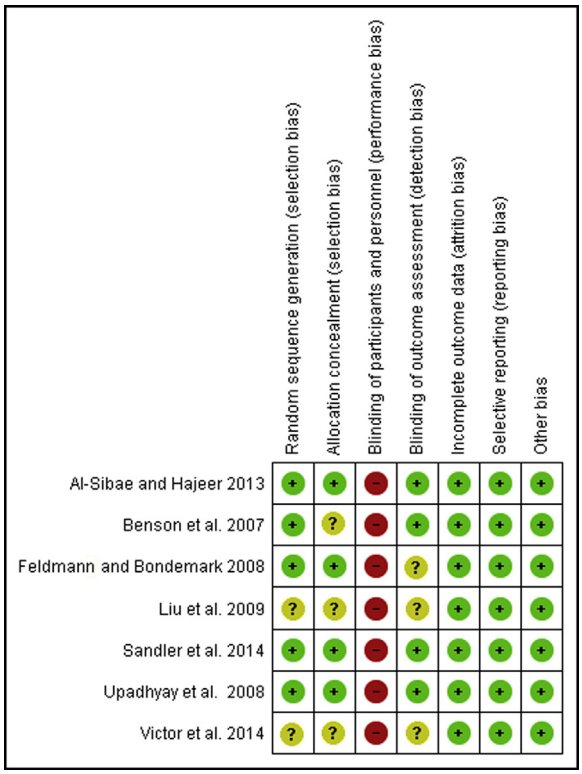


**Fig 2.** Risk of bias summary.

## PRIMARY OUTCOME MEASURE: MESIAL MOLAR MOVEMENT

The rate of mini-implants that served successfully throughout the treatment was 87.6%. The mean difference and 95% confidence interval (95% CI) in mesial molar movement between the TISADs and conventional anchorage is given in Figures 3 and 4 for total and subgroup analyses, respectively. In the total analysis, the TISAD group had significantly less anchorage loss than the control group ($P$ <0.001). Statistical heterogeneity analysis showed a Q statistics value of 34.57 with $P$ <0.001, $I^2$ = 65.28% and $T^2$ = 0.25, which show substantial heterogeneity. This is to a large extent due to the results of Upadhyay et al[13] that deviated from the calculated mean difference. Nevertheless, sensitivity analysis indicated that, after exclusion of this study, the initial result would be preserved at 96.29%. The Begg and Mazumdar[15] statistics resulted in tau b = −0.08 with $P$ = 0.714, meaning that the asymmetry tests did not show publication bias.

**Table VI.** Quality assessment of the CCTs according to the modified Newcastle-Ottawa Scale

| Study | Selection | Comparability | Outcome assessment |
|---|---|---|---|
| Park et al,[25] 2008 | **** | * | ** |
| Upadhyay et al,[14] 2008 | *** | * | ** |
| Lai et al,[2] 2008 | **** | * | ** |
| Yao et al,[26] 2008 | **** | * | ** |
| Lee and Kim,[22] 2011 | **** | ** | ** |
| Koyama et al,[21] 2011 | **** | ** | ** |
| Kuroda et al,[9] 2007 | **** | ** | ** |

*1 point; **2 points; ***3 points; ****4 points.

## SECONDARY OUTCOME MEASURES

### Tipping of the molars

Five studies allowed the analysis of molar tipping in 111 patients (74 female, 37 male; mean age, 17.82 years) in the TISADs group and 109 patients (72 female, 32 male; mean age, 17.19 years) in the control group. The TISADs success rate was 87.9%. In both total and subgroup analyses, the Raw Mean Difference (95% CI) was in favor of the TISADs group, although the differences were statistically insignificant ($P$ >0.05; Figs 5 and 6). The heterogeneity level was high: the Q statistics value equaled 39.2 with $P$ <0.001, $I^2$ = 89.8%, and $T^2$ = 4.13. The sensitivity analysis showed that exclusion of the study by Victor et al[20] from this meta-analysis would impact its result by 24%. Asymmetry tests

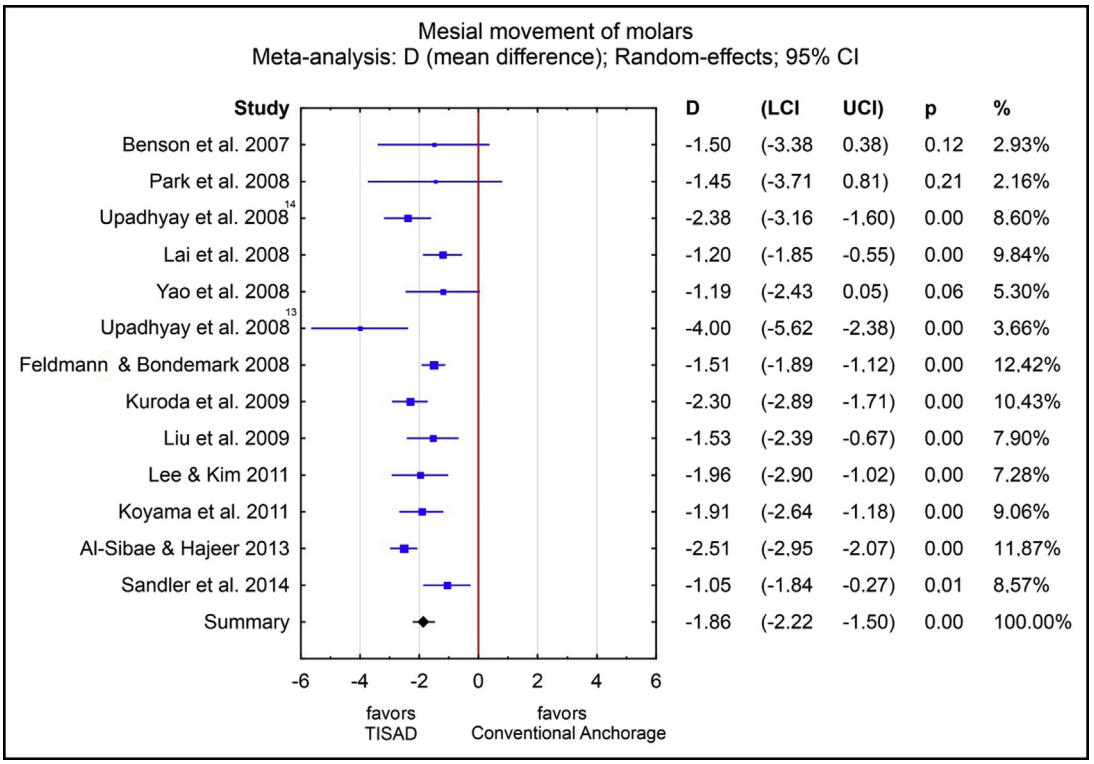


**Fig 3.** Mesial movement of molars meta-analysis.

did not show publication bias; the following values were obtained for the Egger[16] statistics: t = 0.26 with $P = 0.811$.

### Retraction of incisors

Twelve studies were qualified for the analysis of retraction of the incisors in 276 patients (215 female, 61 male; mean age, 19.97 years) in the TISADs group and in 262 patients (199 female, 63 male; mean age, 19.02 years) in the control group. The TISADs success rate was 87.6%. In both total and subgroup analyses, the RMD (95% CI) was in favor of the TISADs group,. and the differences were statistically significant ($P < 0.001$; Figs 7 and 8). A Q statistics value of 17.34 with $P = 0.098$, $I^2 = 36.55\%$, and $T^2 = 0.32$ indicated a moderate level of heterogeneity. Sensitivity analysis showed that the included studies had a similar impact on the calculated RMD. The Begg and Mazumdar[15] asymmetry test resulted in tau b = −0.06 with $P = 0.784$, showing no publication bias.

### Tipping of incisors

The analysis of tipping of incisors in 226 patients (174 female 52 male; mean age, 19.96 years) in the TISADs group and 221 patients (165 female 56 male; mean age, 19.33 years) in the control group was based on 11 studies. The TISADs success rate reached 89.5%. In both total and subgroup analyses, the RMD (95% CI) determined slightly more tipping in the TISADs group, but the differences were not statistically significant ($P > 0.05$; Figs 9 and 10). Heterogeneity was significant: the Q statistics value was 17.34 with $P = 0.002$, $I^2 = 64.53\%$, and $T^2 = 3.27$. The high level of incisor tipping heterogeneity most probably originated from various orthodontic techniques used for retraction of the anterior segment, with the different torque preservation means. Sensitivity analysis showed that the included studies had a balanced impact on the calculated RMD. The Begg and Mazumdar[15] asymmetry tests resulted in tau b = −0.02 with $P = 0.929$, showing no publication bias.

### Treatment duration

The analysis of treatment duration of 102 patients (92 female, 10 male; mean age, 23.52 years) in the TISADs group and 89 patients (81 female 8 male; mean age, 22.11 years) in the control group was based on 5 studies. The TISADs success reached 87.52%. The RMD (95% CI) values were statistically significant ($P < 0.001$) in favor of the TISADs group

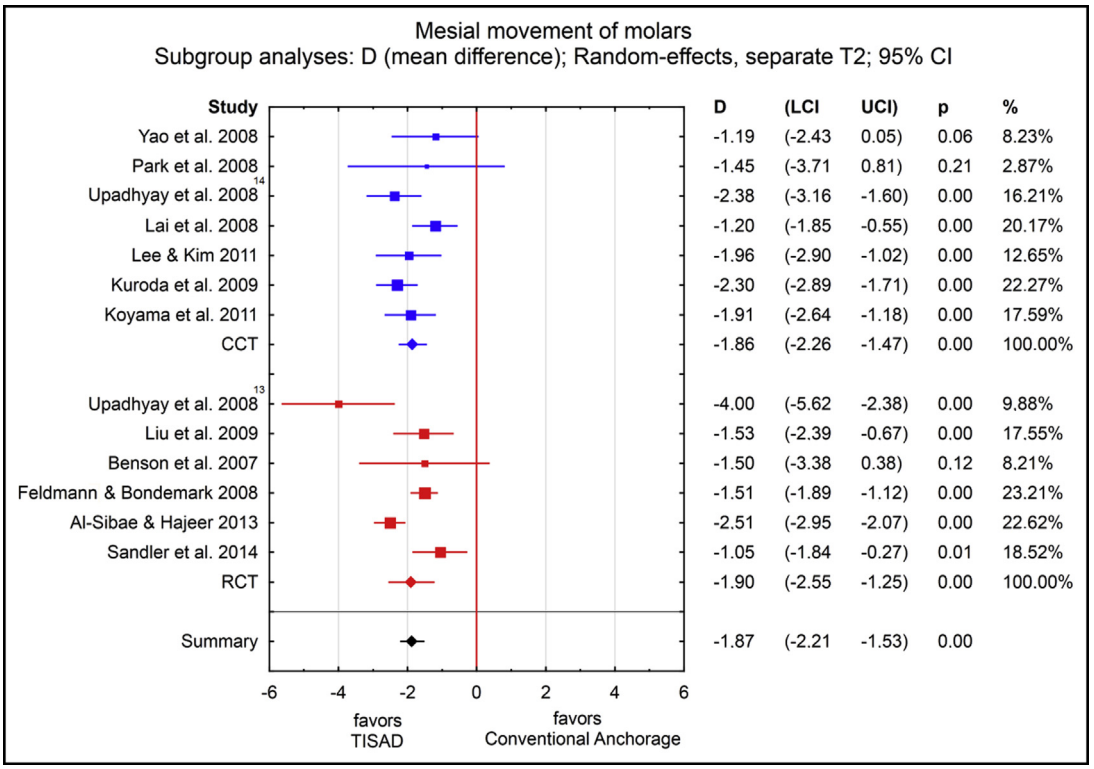


**Fig 4.** Mesial movement of molars subgroup analysis.

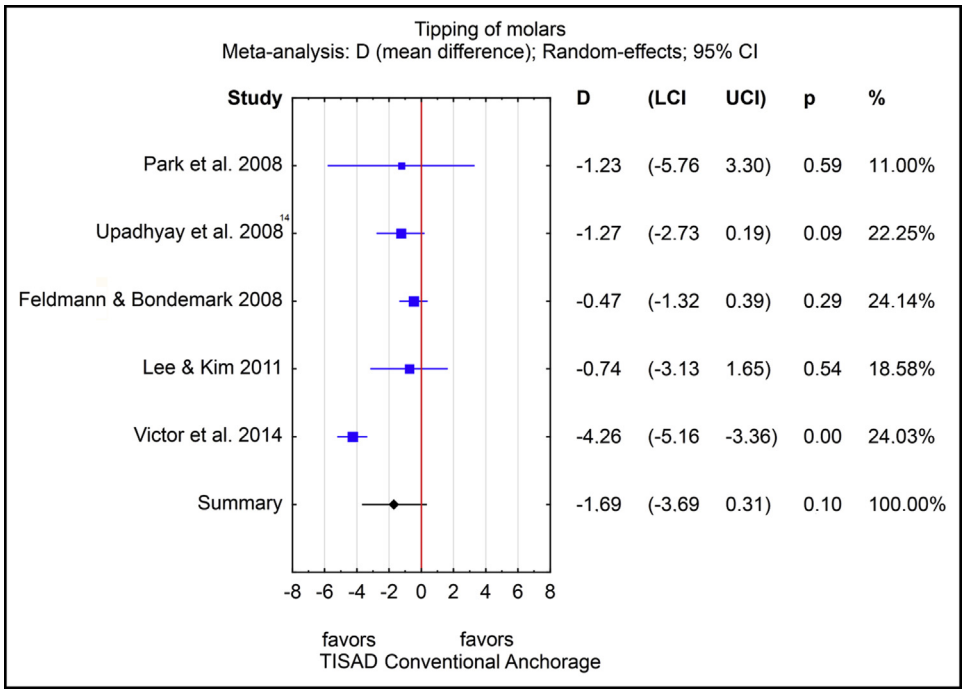


**Fig 5.** Tipping of molars meta-analysis.

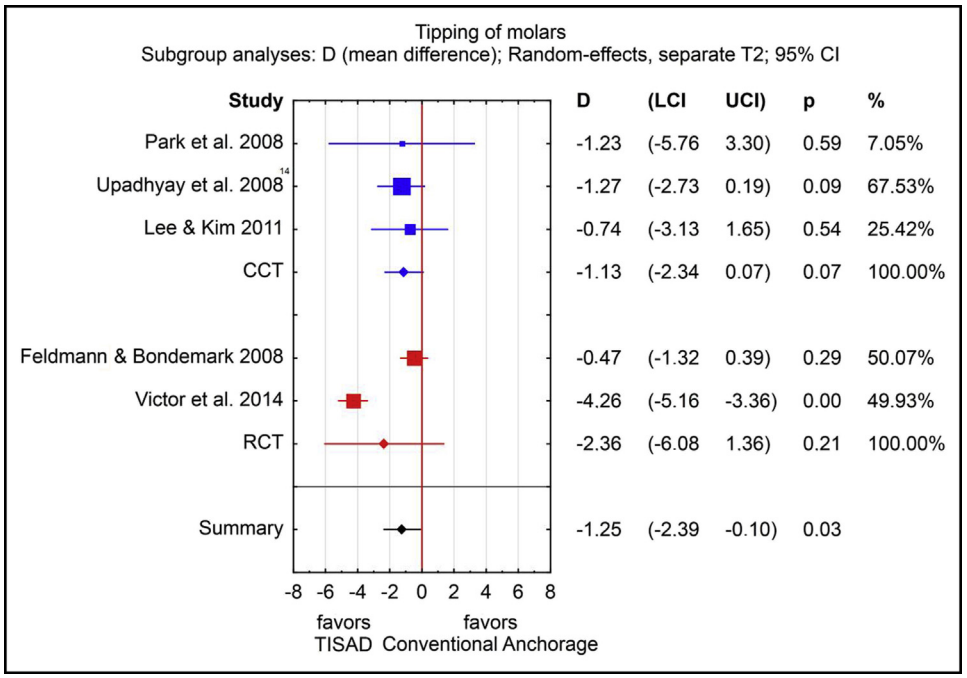


**Fig 6.** Tipping of molars subgroup analysis.

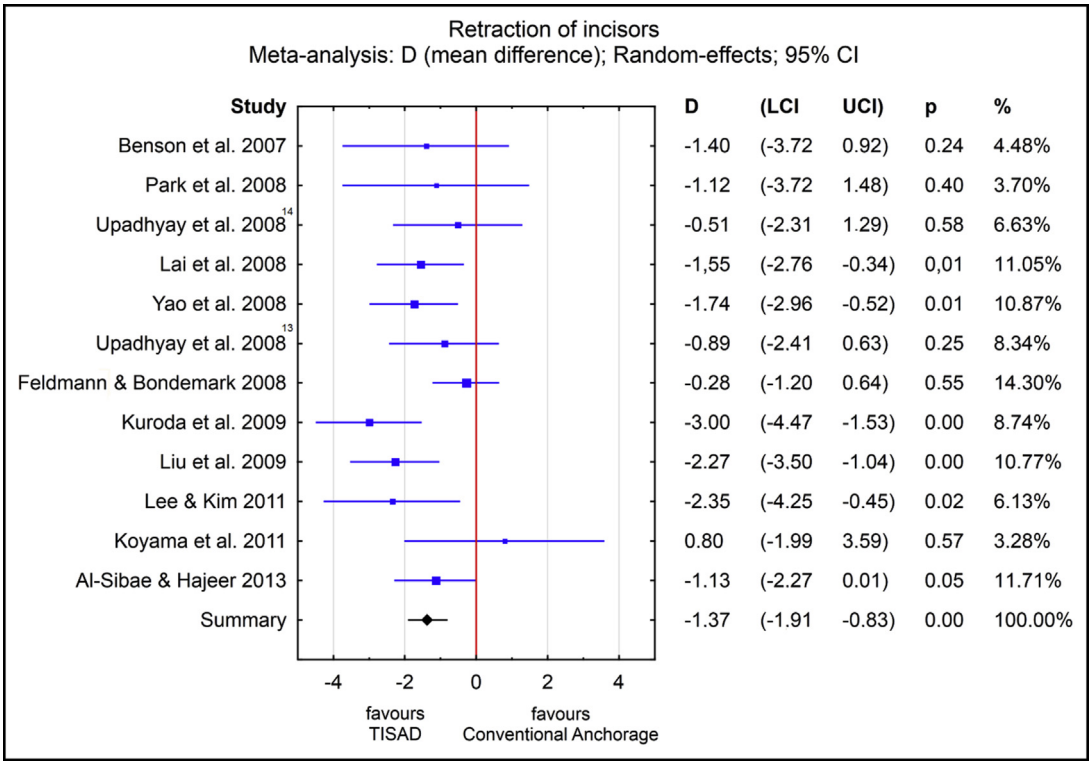


**Fig 7.** Retraction of incisors meta-analysis.

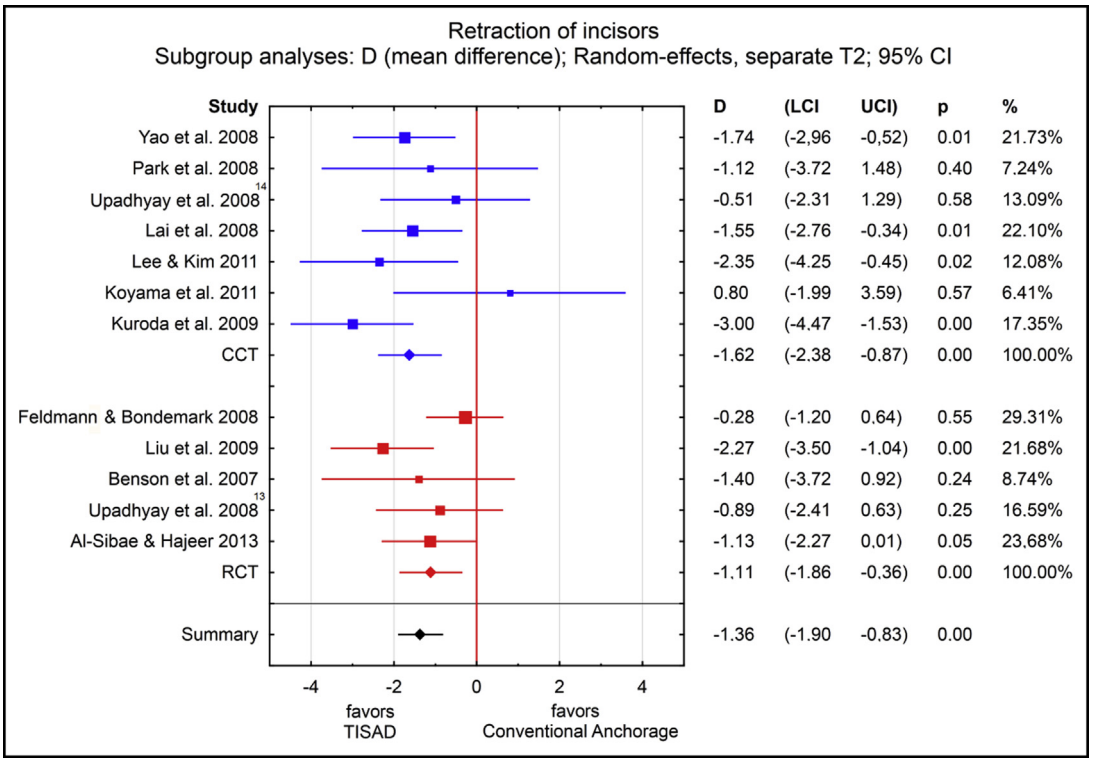


**Fig 8.** Retraction of incisors subgroup analysis.

(Figs 11 and 12). Subgroup analysis of the RCTs was not possible since there was only 1 RCT containing this outcome measure, and the result showed 6.23 months shorter treatment time in the TISADs group. A Q statistics value of 2.34 with $P = 0.655$, $I^2 = 0.0\%$, and $T^2 = 0.0$ indicated a low level of heterogeneity. Sensitivity analysis showed that the included studies had a balanced impact on the calculated RMD.

Asymmetry tests did not show publication bias, since the following values were obtained for the Begg and Mazumdar[15] statistics: tau b = 0.00 with $P = 1.0$.

## DISCUSSION

### Summary of the evidence

According to the Cochrane study assessment tool, 7 main aspects must be thoroughly screened to provide a reliable quality evaluation of RCTs. Randomization methods in the studies by Benson et al,[11] Feldmann and Bondemark,[8] Upadhyay et al,[13] Al-Sibae and Hajeer,[17] and Sandler et al,[18] were of high standard and met the criteria for robust randomization. The authors of the other studies broadly referred to random assignment; this resulted in an assessment of unclear risk of bias.

Anchorage augmentation required clinical application of devices, with a high risk of bias in all included RCTs because of impossible blinding of the patients and the personnel. However, that fact does not necessarily negate the validity of the study model, since blinding of the assessors may well compensate for unblinded patients. Unfortunately, blinding of the assessors was also troublesome in the studies because the presence or absence of a TISAD was instantly apparent in lateral cephalograms used for taking measurements. However, Benson et al,[11] Feldmann and Bondemark,[8] and Al-Sibae and Hajeer[17] overcame this impediment either by using extra radiopaque elements to obscure the TISAD in the cephalograms or by involving an assessor who was unaware of the purpose of the study. The study by Sandler et al[18] also provided a procedure for blinding an assessor by removal the Nance button 2 weeks before taking dental impressions; this was the time allowed for soft tissue healing and concealment of the anchorage augmentation method. The other authors did not mention blinding of the assessors, resulting in an unclear grade on this issue. Since many studies achieved a grade of unclear for randomization, allocation concealment, and blinding of assessors, we concluded that more scrutiny in adherence to RCT guidelines is needed in future

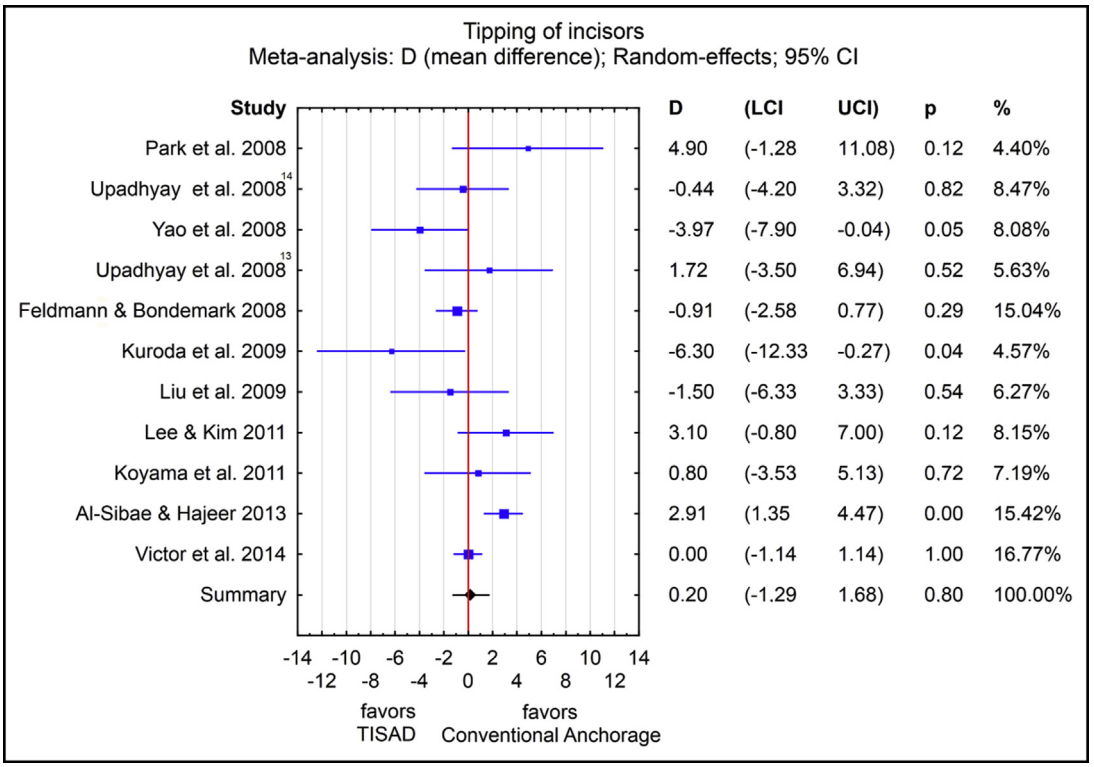


**Fig 9.** Tipping of incisors meta-analysis.

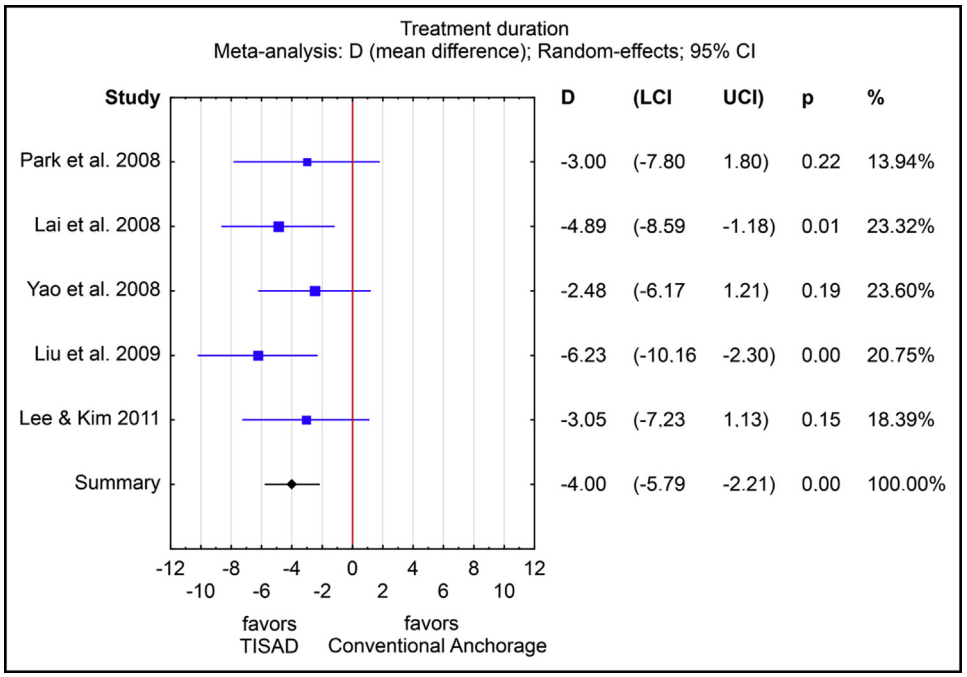


**Fig 10.** Tipping of incisors subgroup analysis.

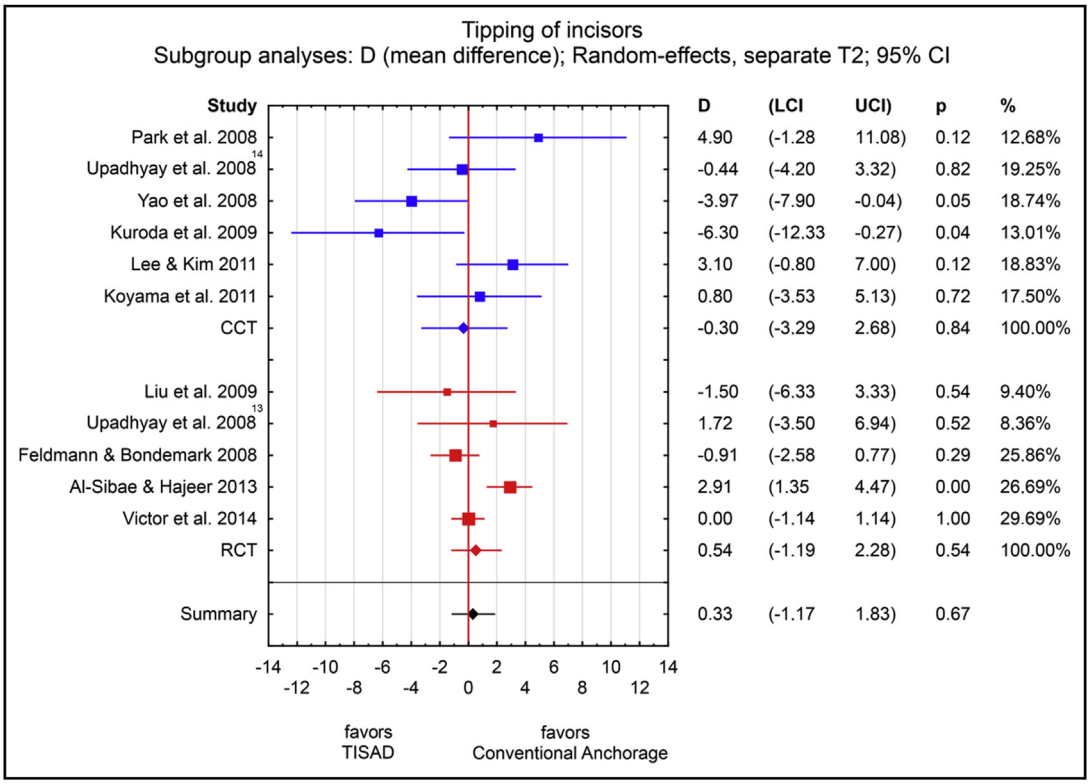


**Fig 11.** Treatment duration meta-analysis.

studies. These shortcomings attenuated the validity of the results; thus, we evaluated the quality of evidence from the RCTs as moderate.

For the CCTs, all studies except for one by Upadhyay et al[14] achieved a maximum of 4 marks in the selection section. Various types of anchorage augmentation used in the control groups in the other studies introduced undesired clinical heterogeneity. Most of the studies were graded with only 1 mark for comparability because their design involved several treatment strategies: eg, extraction of only maxillary premolars or 4 premolars. All CCTs achieved 2 marks out of 3 in the outcome assessment section since none of the studies included blinding of the assessors. We evaluated quality of evidence from the CCTs as moderate, since a more rigorous outcome assessment, especially blinding of the assessors, could have augmented the validity of the results.

### Primary outcome measure: Mesial molar movement

When choosing a treatment strategy with en-masse retraction, elimination of undesired mesial molar movement is the key issue in preserving the anchorage. Conventionally, in the pre-TISAD era, anchorage was reinforced with headgear, Nance holding arch, or transpalatal bar, which nonetheless caused significant loss of anchorage, most likely compromising the final results, especially in patients requiring absolute stability of the molars.[23,24] This is understandable considering the major drawbacks of these devices, such as the obvious biomechanical deficiencies of the transpalatal bar or the impossibility of full-time use of headgear. The results of our systematic review provide the evidence that undesirable mesial molar displacement is most efficiently minimized when TISADs are used for anchorage reinforcement. The efficiency of anchorage preservation, with TISADs prevailing over conventional methods by about 2 mm, seems to be noteworthy not only theoretically but also clinically. Furthermore, even distal movement of molars—anchorage gain—may be achieved with TISADs, as reported by Upadhyay et al.[13] This effect results from friction between the archwire and the bracket slot at the molars and depends on the size of the archwire. In general, we concluded that TISADs allow for better anchorage preservation compared with traditional anchorage reinforcement methods.

### Secondary outcome measures

Our meta-analysis showed slightly more distal tipping of the molars when TISADs were used, although

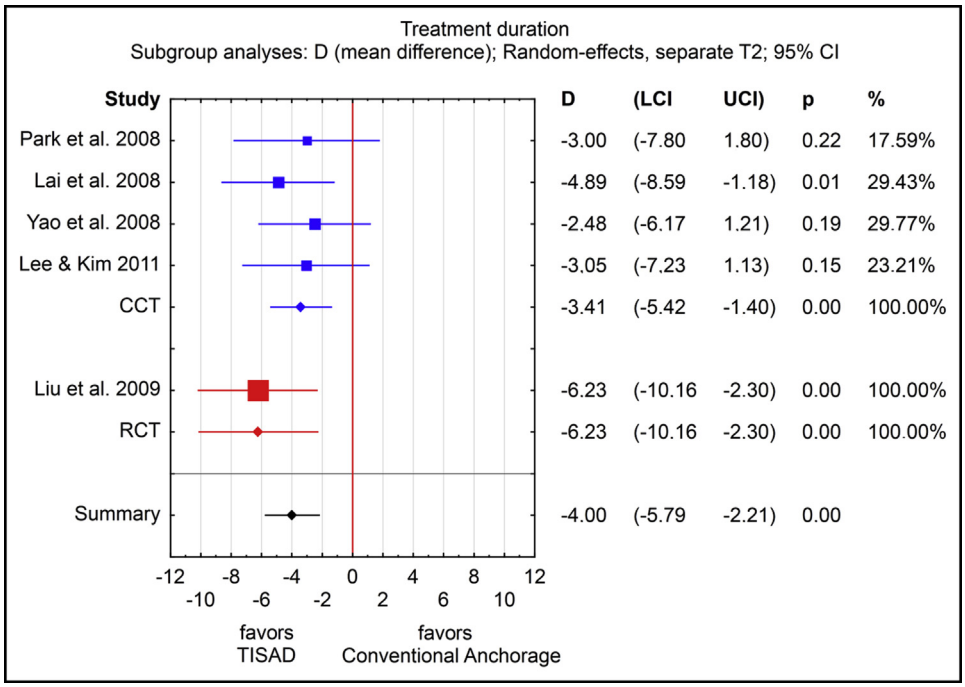


**Fig 12.** Treatment duration subgroup analysis.

the results were not statistically significant. Therefore, we concluded that there are no differences in molar tipping when comparing the 2 anchorage reinforcement methods. However, the distal tipping of molars in the TISADs group was consistent among all studies. The issue of molar angulation is especially important during treatment of high-angle patients, where mesial tipping of the molars promotes undesirable bite opening. The direction of angular changes depends on the force system acting on the teeth. TISADs keep the reactive forces away from the molars, which experience a favorable distal frictional force from the archwire. On the contrary, the reactive forces acting directly on the molars in conventional anchorage reinforcement methods with a tranpalatal arch or Nance plate result in mesial tipping of these teeth.

The range of incisor movement—planned dental displacement—was another investigated variable. Our meta-analysis showed that more retraction of the incisors may be achieved with TISADs, and this finding was substantiated by all studies except that of Koyama et al.[21] The amount of incisor retraction was closely related to the anchorage conditions: less anchorage loss provided by TISADs simultaneously gives more space for retraction of the incisors.

Our meta-analysis showed less tipping of the incisors in the conventional anchorage group; however, the difference was statistically insignificant. Thus, the result proved no difference in incisor inclination changes between the 2 groups. The alteration of incisor torque during retraction depends on several factors, such as the size of the archwire, the point of force application, and the presence of torquing bends. The dimensions of the working archwires used in the included studies ranged from 0.16 × 0.22 in[25] to 0.19 × 0.25 in[20]; the attachment hooks had different lengths, and some authors used torquing bends, whereas others did not. The wide variety of techniques prevents drawing clear conclusions about incisor torque preservation in treatment with TISADs or conventional anchorage reinforcement. However, it seems that these factors have a more significant influence on the torque of the incisors than the method of anchorage reinforcement.

Treatment duration was about 4 months shorter in the TISAD groups. Shorter treatment times were found in all included studies; this means that a slight treatment time reduction might be expected when TISADs are used. The shorter treatment time may be related to 1-step retraction in patients treated with TISADs, whereas the conventional Tweed-Merrifield technique requires retraction of the canines followed by retraction of the incisors.[25] However, Liu et al[19] pointed out that treatment time in the conventional anchorage samples may be deceptive, since part of the space is closed as a result

of anchorage loss, apparently reducing the duration of space closure. Otherwise, the advantage of shorter treatment time in the TISAD groups would probably be more emphasized.

Unfortunately, the data from the studies were insufficient to perform a meta-analysis of changes in vertical molar position, which is crucial when treating Class II malocclusions in high-angle patients. Molar extrusion forcing clockwise rotation of the mandible and resulting in further bite opening is an adverse side effect of conventional space closure. Some of this extrusion may be neutralized by mesialization of the molars, providing a bite-closing wedge effect; however, it is undesired in maximum anchorage patients.[23] Upadhyay et al[13,14] showed that the use of mini-implants produced intrusion of the molars, but the amount was not statistically significant. Anchorage with headgear showed the extrusion effect, which was supported by the study of Al-Sibaie and Hajeer.[17] In turn, Lai et al[2] found that the maxillary molars were significantly intruded only when miniplates were applied. Consequently, they recommended using miniplates in high-angle patients with Class II malocclusion. The results obtained by Yao et al[26] proving a decrease of the mandibular angle when using mini-implants also support the concept that intrusion of the maxillary molars could be followed by a counterclockwise rotation of the mandible, subsequently improving a Class II malocclusion. Although Kim et al[27] reported extrusion of the maxillary molars, they were neither banded nor bonded. Nonetheless, molar extrusion together with an increase of the mandibular angle observed by Yao et al in patients wearing high-pull headgear for anchorage reinforcement supports the evidence that high-angle patients require careful vertical control of the lateral segments as well as application of optimal force vectors.

### Limitations

The search strategy used was comprehensive with multiple database searches. However, non-English searches were not undertaken, risking an incomplete yield and possibly publication bias. Moreover, the number of clinical trials investigating the use of TISADs was limited. Most of the identified studies focused on objective measurements of outcome, typically cephalometric outcomes. Although this emphasis on cephalometric outcomes is important in the assessment of anchorage control, a more holistic assessment of the value of TISADs in clinical trials would also incorporate patient-centered outcomes. This focus on technical outcome measures is, however, typical of much dental research.[28] Further similar research should incorporate outcomes of relevance to both patients and clinicians.

## CONCLUSIONS

On the basis of this systematic review and meta-analysis, we concluded the following.

1. The use of TISADs enables better anchorage preservation compared with traditional reinforcement methods.
2. Tipping of both molars and incisors during space closure does not differ between the 2 anchorage reinforcement methods.
3. More retraction of the incisors may be achieved with TISADs.
4. Use of TISADs enables, to a small extent, reduction of the treatment time.
5. Due to the moderate quality of evidence, the results should be interpreted with some caution. More RCT studies strictly adhering to methodologic guidelines are necessary to improve the quality of available evidence for future analysis.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.ajodo.2016.08.029.

## REFERENCES

1. Melsen B, Bosch C. Different approaches to anchorage: a survey and an evaluation. Angle Orthod 1997;67:23-30.
2. Lai EH, Yao CC, Chang JZ, Chen I, Chen YJ. Three-dimensional dental model analysis of treatment outcomes for protrusive maxillary dentition: comparison of headgear, miniscrew, and miniplate skeletal anchorage. Am J Orthod Dentofacial Orthop 2008;134:636-45.
3. Wahl N. Orthodontics in 3 millennia. Chapter 15: skeletal anchorage. Am J Orthod Dentofacial Orthop 2008;134:707-10.
4. Güray E, Orhan M. "En masse" retraction of maxillary anterior teeth with anterior headgear. Am J Orthod Dentofacial Orthop 1997;112:473-9.
5. Cole WA. Accuracy of patient reporting as an indication of headgear compliance. Am J Orthod Dentofacial Orthop 2002;121:419-23.
6. Blum-Hareuveni T, Rehany U, Rumelt S. Blinding endophthalmitis from orthodontic headgear. N Engl J Med 2004;351:2774-5.
7. Samuels RH, Willner F, Knox J, Jones ML. A national survey of orthodontic facebow injuries in the UK and Eire. Br J Orthod 1996;23:11-20.
8. Feldmann I, Bondemark L. Orthodontic anchorage: a systematic review. Angle Orthod 2006;76:493-501.
9. Kuroda S, Sugawara Y, Deguchi T, Kyung HM, Takano-Yamamoto T. Clinical use of miniscrew implants as orthodontic anchorage: success rates and postoperative discomfort. Am J Orthod Dentofacial Orthop 2007;131:9-15.

10. Antoszewska J, Papadopoulos MA, Park HS, Ludwig B. Five-year experience with orthodontic miniscrew implants: a retrospective investigation of factors influencing success rates. Am J Orthod Dentofacial Orthop 2009;136:158.e1-10.
11. Benson PE, Tinsley D, O'Dwyer JJ, Majumdar A, Doyle P, Sandler PJ. Midpalatal implants vs headgear for orthodontic anchorage—a randomized clinical trial: cephalometric results. Am J Orthod Dentofacial Orthop 2007;132:606-15.
12. Sandler J, Benson PE, Doyle P, Majumder A, O'Dwyer J, Speight P, et al. Palatal implants are a good alternative to headgear: a randomized trial. Am J Orthod Dentofacial Orthop 2008;133:51-7.
13. Upadhyay M, Yadav S, Nagaraj K, Patil S. Treatment effects of mini-implants for en-masse retraction of anterior teeth in bialveolar dental protrusion patients: a randomized controlled trial. Am J Orthod Dentofacial Orthop 2008;134:18-29.e1.
14. Upadhyay M, Yadav S, Patil S. Mini-implant anchorage for en-masse retraction of maxillary anterior teeth: a clinical cephalometric study. Am J Orthod Dentofacial Orthop 2008;134:803-10.
15. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088-101.
16. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
17. Al-Sibaie S, Hajeer MY. Assessment of changes following en-masse retraction with mini-implants anchorage compared to two-step retraction with conventional anchorage in patients with class II division 1 malocclusion: a randomized controlled trial. Eur J Orthod 2014;36:275-83.
18. Sandler J, Murray A, Thiruvenkatachari B, Gutierrez R, Speight P, O'Brien K. Effectiveness of 3 methods of anchorage reinforcement for maximum anchorage in adolescents: a 3-arm multicenter randomized clinical trial. Am J Orthod Dentofacial Orthop 2014;146:10-20.
19. Liu YH, Ding WH, Liu J, Li Q. Comparison of the differences in cephalometric parameters after active orthodontic treatment applying mini-screw implants or transpalatal arches in adult patients with bialveolar dental protrusion. J Oral Rehabil 2009;36:687-95.
20. Victor D, Prabhakar R, Karthikeyan MK, Saravanan R, Vanathi P, Vikram NR, et al. Effectiveness of mini implants in three-dimensional control during retraction—a clinical study. J Clin Diagn Res 2014;8:227-32.
21. Koyama I, Iino S, Abe Y, Takano-Yamamoto T, Miyawaki S. Differences between sliding mechanics with implant anchorage and straight-pull headgear and intermaxillary elastics in adults with bimaxillary protrusion. Eur J Orthod 2011;33:126-31.
22. Lee AY, Kim YH. Comparison of movement of the upper dentition according to anchorage method: orthodontic mini-implant versus conventional anchorage reinforcement in Class I malocclusion. ISRN Dent 2011;2011:321206.
23. Geron S, Shpack N, Kandos S, Davidovitch M, Vardimon AD. Anchorage loss—a multifactorial response. Angle Orthod 2003;73:730-7.
24. Gjessing P. Biomechanical design and clinical application of maxillary anterior teeth of a new canine retraction spring. Am J Orthod 1985;87:353-63.
25. Park HS, Yoon DY, Park CS, Jeoung SH. Treatment effects and anchorage potential of sliding mechanics with titanium screws compared with the Tweed-Merrifield technique. Am J Orthod Dentofacial Orthop 2008;133:593-600.
26. Yao CC, Lai EH, Chang JZ, Chen I, Chen YJ. Comparison of treatment outcomes between skeletal anchorage and extraoral anchorage in adults with maxillary dentoalveolar protrusion. Am J Orthod Dentofacial Orthop 2008;134:615-24.
27. Kim SH, Hwang YS, Ferreira A, Chung KR. Analysis of temporary skeletal anchorage devices used for en-masse retraction: a preliminary study. Am J Orthod Dentofacial Orthop 2009;136:268-76.
28. Fleming PS, Koletsi D, O'Brien K, Tsichlaki A, Pandis N. Are dental researchers asking patient-important questions? A scoping review. J Dent 2016;49:9-13.

# Fundamental factors related to orthodontic micro-implant stability: Review of the literature

# Najważniejsze czynniki związane ze stabilizacją mikroimplantów ortodontycznych – przegląd piśmiennictwa

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Dental and Medical Problems, ISSN 1644-387X (print), ISSN 2300-9020 (online) *Dent Med Probl.* 2017;54(2):189–193

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**Funding sources**
none declared

**Conflict of interest**
none declared

Received on January 26, 2017
Revised on March 3, 2017
Accepted on April 12, 2017

## Abstract

The development and introduction of temporary intraoral anchorage devices (TISAD) in the beginning of the 21st century had a great impact on contemporary orthodontics. The enhancement of the scope of orthodontic treatment, improved efficiency, reduction of both the treatment time and need for the patient's compliance, all of these are the crucial advantages the TISAD have provided to our profession. However, there are also some limiting factors pertaining to this anchorage reinforcement technique which must be borne in mind prior to clinical application. Among some others, premature failure of the micro-implants is the most significant problem related to their utilization, as it entails a repetition of the insertion procedure, increasing the cost and duration of treatment and causing the patient's discomfort. Therefore, recognition of the factors related to the stability of orthodontic micro-implants is necessary for their efficient clinical application and maximum survival rates. Since over the last decade there has been noteworthy progress in the research investigating the issue of micro-implant stability, a review of the most current literature pertaining to this topic was the aim of our article, and ultimately providing clinical recommendations.

**Key words:** stability, micro-implants, success rates, micro-screws, TAD

**Słowa kluczowe:** stabilność, mikroimplanty, współczynniki sukcesu, mikrośruby, TAD

**DOI**
10.17219/dmp/70440

Temporary intraoral anchorage devices (TISAD) constitute a group of modern anchorage reinforcement tools which share a unique feature: the ability to provide absolute and compliance-free anchorage. The development of TISAD at the beginning of 21st century has noticeably extended orthodontic treatment efficacy along with the improvement of the patient's comfort. Nevertheless, as any other anchorage bolstering technique, use of TISAD bears some drawbacks, where loss of stability is the major one. Reported micro-implant success rates range from 75 to 94%, therefore roughly from 1 to 3 out of 10 inserted TISAD become mobile and cannot serve according to intent.[1–4] As a consequence, the failure of a micro-screw requires another implantation, increasing treatment cost, time and discomfort. Premature loss of orthodontic micro-implants has been a fundamental problem since their introduction to clinical practice, constantly calling for identification of the determinants favoring TISAD instability. The literature from the last decade deals with this issue substantially, thus the aim of this article was an evidence-based appraisal of the most crucial factors related to micro-implant survival, taking into account the most recent scientific findings. A search of the Medline, Scopus, Ebsco and Web of Science electronic databases was performed with all combinations of the key words: micro-implants, mini-implants, micro-screws, mini-screws, TAD and TISAD, and stability, success rate and risk factor. After reviewing the articles published from 2000 to 2016, we have summarized the most important findings in this paper. The determinants discussed were divided into 3 categories encompassing: the properties of a micro-implant, the patient's characteristics and management of TISAD.

## Design of a micro-implant

Table 1 summarizes the influence of the orthodontic micro-implant design on its stability. Micro-implants have the shape of a screw with a diameter 1.0–2.0 mm and a length 6–12 mm. The small dimensions are essential since they make possible TISAD placement in narrow interradicular spaces, thus providing an appropriate orthodontic force vector. However, it must be borne in mind that TISAD stabilization depends mostly on their primary stability, thus – theoretically – larger sizes, as opposed to smaller ones, will promote firmness of the micro-screws and there are reports in the literature indeed confirming such thesis. Miyawaki et al.[5] and Motoyoshi et al.[6] suggest that screws with a diameter equal to or smaller than 1.0 mm should be avoided, because their failure rate is significantly higher comparing to the screws with larger cross-section areas. The study of Wilmes et al.[7] supported this result, as the authors similarly found 1.1 mm screw stability fairly lower than 1.6 mm ones. In turn, Chen et al.[8] and Sarul et al.[9], while investigating the impact of micro-implant length, concordantly reported that screws 8 mm long are more stable than 6 mm ones. Last but not least, two independent meta-analyses by Crismani et al.[10] and Dalessandri et al.[11] have validated these outcomes and stated that sizes of minimum 1.2 × 8 mm and 1.3 × 8 mm, respectively, ensure sufficient primary stability of micro-screws. Therefore, micro-implants with at least such dimensions are advocated for most clinical applications, with exceptional use of the smaller TISAD in carefully selected cases.

As for the TISAD design, Migliorati et al. studied the micro-screw thread shape influence on stability.[12] They evaluated a geometrical TISAD relationship to describe the mechanical properties of miniscrews, calculated as the relationship between the mean thread depth and the pitch (D/P), expressed as a percentage. The authors proved that a higher percentage significantly correlates with better micro-implant stability. Chadad et al. also proved that etching and sandblasting the micro-implant's surface does not increase its stability, which again underscores the crucial role of the screw size.[13]

## Patient's characteristics

### Sex and age

A summary of the patient's characteristics' impact on the stability of micro-implants is presented in Table 2. Most of the researchers did not find significant differences between men and women in terms of micro-implant stability[14–18], which was entirely supported in 2 independent meta-analyses[10,11] evidently proving that sex does not affect micro-implant loosening.

In regard to age, Chen et al.[16] observed significantly more frequent micro-screw instability in 20 to 30 year-old patients, contrary to Lee et al.[17] who noted the highest success rates in such individuals. Apart from these 2 reports, the majority of the studies did not reveal any relationship of micro-implant stability and the patient's age;[4,5,14,15] again: 2 meta-analyses endorse such outcomes.[10,11] And although Dalessandri et al.[11] indicate a higher failure rate in patients under 20 years of age, the difference is minor and insignificant.

Table 1. Influence of micro-implant design on its stability

| Micro-implant design | Influence on the stability of the micro-implant |
|---|---|
| Diameter | diameter of at least 1–2 mm improves the stability of micro-implants |
| Length | length of at least 8 mm promotes the stability of micro-implants |
| Thread shape factor | higher values of thread shape factor increase the stability of micro-implants |
| Surface preparation | etching and sandblasting does not enhance the stability of micro-implants |

## Bone anatomy and histology

Micro-implants installed in the mandible have been reported to fail significantly more often than those placed in the maxilla.[14–18] Cheng et al. has suggested that the thick cortical plate in the mandible conduces to a rapid raise of the temperature during hole drilling, which may result in bone overheating.[15] Another issue resulting from greater cortical thickness is a risk of ischemia of the bone due to the high pressure exerted by the micro-implant.[19] Both the high temperature and high pressure result in necrosis and degeneration of the bone supporting the micro-implant, which subsequently loses primary stability and requires replacement. On the other hand, there are some studies that did not reveal any differences in micro-implant stability in the maxilla or the mandible. Chen et al.[20] stated that the quality of the bone itself rather than location is paramount for micro-screw fixation, which is in accordance with the studies published by Miyawaki et al.[5], who similarly concluded that cortical thickness overrides the issue of location itself. Nevertheless, the results of the meta-analyses clearly indicate that orthodontic micro-implants placed in the mandible have a higher risk of failure.[10,11] Thus, already at the stage of treatment planning, one needs to consider another anchorage reinforcement method, applicable when loosening of the TISAD in the mandible emerges.

The role of bone quality and quantity in achieving primary stability, so crucial for micro-screw survival, seems quite obvious. The ability to hold the screw in the bone is defined by parameters such as: 1. tightening torque and 2. pull out force. Experimental studies have revealed a positive correlation between these two variables and the thickness and density of the cortical plate and density of the cancellous bone,[21–24] further supported by the results of research on human cadavers.[25] Motoyoshi et al. have established that the critical thickness ensuring sufficient primary stability is 1 mm.[26] The results of the meta-analysis conducted by Marquezan et al.[27] confirmed a positive correlation between cortical bone thickness and the stability of micro-implants, though the authors emphasized the need for more high-quality clinical studies to support the final conclusion. Motoyoshi et al. demonstrated that the optimal placement torque values lie in the limit from 5 to 10 N/cm.[28] According to those authors, a lower number indicates insufficient mechanical fixation of the micro-screw, whereas a higher number reflects very strong pressure exerted by the implant on the bone, which may result in ischemic osteonecrosis. A meta-analysis by Meursinge Reynders et al. did not reveal any ideal micro-implant placement torque rate, however this may be partly caused by a very limited number of studies meeting the criteria and included in the analysis.[29]

Table 2. Influence of patient characteristics on the stability of micro-implants

| Factor | Influence on the stability of the micro-implant |
|---|---|
| Sex | sex has no influence on the stability of micro-implants |
| Age | age has no or very little impact on the stability of micro-implants |
| Location | micro-implants are more stable in maxilla compared to mandible |
| Bone quality and quantity | thicker cortical plate and higher bone density promote stability of the micro-implants |
| Placement torque | values ranging from 5 to 10 N/cm correlate with higher stability of the micro-implants |
| Nicotine addiction | smoking of 10 or more cigarettes a day impairs the stability of micro-implants |

## Susceptibility to inflammation

The detrimental influence of the inflammatory process of tissues surrounding the micro-implants has been widely emphasized as well.[2,5,15,20,30–32] Experimental studies show that a penetrating inflammatory process results in degeneration of the bone supporting the micro-implant that finally loses its stability.[32,33] Dalessandri et al. proved that peri-micro-implantitis entails an almost 9-fold increase of the risk of micro-screw failure and seems to be one of the most important factors responsible for this complication.[11] The phenomena may develop as a consequence of infection from oral micro-flora or may be caused by proximity or tight contact with the adjacent root.[34] Therefore, a fully aseptic and precise micro-implant placement procedure, along with meticulous hygiene of micro-screw surrounding tissues is paramount for a reduction of inflammation-related failures. As shown by Kuroda et al., the incidence of inflammations is higher when the micro-implant is placed in free mucosa, thus localization in attached gingiva is also recommended whenever applicable.[35]

## Nicotine addiction

Bayat and Baus showed that patients who smoke more than 10 cigarettes a day have a significantly higher risk of micro-implant failure than non-smokers or those who smoke less.[36] Therefore, a medical questionnaire should help to investigate the presence and intensity of nicotinism and the number of cigarettes smoked, which – if severe or high – ought to be considered while estimating the potential stability of micro-screws applied in a given individual.

# Management of TISAD

## Placement procedure

The influence of micro-implant management on its stability is shown in Table 3. There are multiple surgical protocols of micro-implant placement reported in the lit-

erature and the basic differentiation concerns pre-drilling (self-tapping) and drill-free (self-drilling) methods.[30,37] Experimental studies on dogs showed higher stability of the micro-implants placed with the drill-free approach, and subsequent histological analysis revealed more tight contact between the screw and the surrounding bone.[38] Similar results were obtained in clinical studies, which compared the success rates of 1.4 mm micro-implants placed in the self-tapping method with 0.9 or 1.1 mm pilot bur and without pre-drilling.[39] Statistically significant differences in success rates were noted: the highest in case of micro-screws placed without pre-drilling and the lowest in case of TISAD inserted in a hole drilled with 1.1 mm bur. The results of the cited studies indicate that micro-implant placement without pre-drilling promotes stability, however these outcomes should be interpreted with caution due to the limited number of micro-screws analyzed. It seems that in the maxilla, due to thin cortical and thick cancellous bone, skipping the drilling may enhance the bone-screw contact and improve stability. On the other hand, in the presence of very thick cortical bone in the mandible, micro-implantation without pre-drilling entails a high risk of inducing excessive pressure on the bone, likely resulting in ischemia and necrosis, which is why pre-drilling is necessary in the mandible. Miyawaki et al.[5] and Kuroda et al.[35] compared the surgical protocols with and without muco-periosteal flap elevation and found a higher survival rate of micro-implants inserted using the flapless procedure. Furthermore, postoperative pain and swelling were also significantly lower in patients who received the less invasive, flapless surgery.[35] Therefore, a small (2–3 mm) vertical stab incision of the mucosa, preceding TISAD insertion, which exposes the bone surface and prevents the soft tissues from winding around a pilot drill, seems to be the optimal soft tissue management, which is confirmed by Antoszewska et al., who utilized such protocol and obtained very high success rates, exceeding 93%.[4]

## Loading protocol

In contrast to prosthetic implants, requiring a healing period lasting several months and the necessity for osteointegration, orthodontic micro-implants may be loaded much earlier because their fixation relies mostly on primary, not on secondary stability. Some osteointegration indeed occurs in the case of TISAD, however it does not play a major role in their immovability.[40] The timing of the loading recommended in the literature ranges from immediate to 3 months post-operatively, although most of the authors deemed immediate loading possible and rational, provided a low force value is applied.[2,5,38–42] The meta-analysis by Crismani et al. made it possible to determine the optimal conditions of loading the micro-implants: several days after placement with a force up to 200 g.[10] Early loading is further validated by the meta-analysis of Dalessandri et al., who showed no difference in stability between micro-implants loaded within or over 4 weeks after insertion.[11] Nevertheless, it seems reasonable to postpone loading for 2 weeks after micro-implant placement, in order to allow uneventful healing of the mucosa around the TISAD heads, which is crucial to prevent inflammation: one of the major causes of micro-screw failures.

Table 3. Influence of micro-implant management on their stability

| Micro-implant management | Influence on the stability of the micro-implant |
|---|---|
| Self-drilling vs Self-tapping | in the maxilla: smaller or no pilot drilling promotes stability<br>in the mandible: pilot drilling with a bur-screw difference of 0.3–0.5 mm indicated |
| Flap preparation | flapless surgery ensures higher stability of the micro-implants |
| Loading protocol | allowed immediate loading with forces up to 200 g |

## Operator's experience

Lim et al. demonstrated that the experience of the operator has a significant impact on the stability of micro-implants.[37] The authors reported that clinicians who had inserted at least 20 micro-screws had a 3.6 times higher chance of achieving primary stability, compared to operators who had performed fewer procedures.[37] Jung et al. proved that the clinician's experience also plays a role in placing the TISAD on the palate.[43] What is more, Cho et al. found that the higher the number of performed micro-implantations, the lower the risk of damaging an adjacent root.[44] A comparison of the stability of micro-implants inserted by a maxillofacial surgeon and an orthodontist showed no significant differences, indicating that orthodontists are fully capable of performing successful micro-implantations after they have gained the necessary experience.[20]

# Summary

Temporary Intraoral Skeletal Anchorage Devices have gradually achieved widespread use in contemporary orthodontics; therefore awareness of the factors affecting the stability of the micro-implants is crucial for full utilization of the potential they offer. According to the most up-to-date research, bone quality and quantity, use of micro-screws of at least 1.2 × 8 mm dimensions and prophylaxis of inflammation are fundamental for micro-implant survival, whereas unadaptable factors such as age and sex do not have a significant impact on micro-screw loosening, which to this day occurs more frequently in the mandible. Greater experience in the surgical procedure improves the stability of inserted micro-implants; hence it is necessary to improve the learning curve in order to maximize the success rates of the micro-screws.

## References


1. Baek SH, Kim BM, Kyung SH, Lim JK, Kim YH. Success rate and risk factors associated with mini-implants reinstalled in the maxilla. *Angle Orthod.* 2008;78:895–901.
2. Luzi C, Verna C, Melsen B. A prospective clinical investigation of the failure rate of immediately loaded mini-implants used for orthodontic anchorage. *Prog Orthodont.* 2007;8:192–201.
3. Wiechmann D, Meyer U, Büchter A. Success rate of mini- and micro-implants used for orthodontic anchor age: a prospective clinical study. *Clin Oral Implan Res.* 2007;18:263–267.
4. Antoszewska J, Papadopoulos MA, Park HS, Ludwig B. Five-year experience with orthodontic miniscrew implants: A retrospective investigation of factors influencing success rates. *Am J Orthod Dentofacial Orthop.* 2009;136:158.e1–10.
5. Miyawaki S, Koyama I, Inoue M, Mishima K, Sugahara T, Takano-Yamamoto T. Factors associated with the stability of titanium screws placed in the posterior region for orthodontic anchorage. *Am J Orthod Dentofacial Orthop.* 2003;124:373–378.
6. Motoyoshi M. Clinical indices for orthodontic mini-implants. *J Oral Sci.* 2011;53:407–412.
7. Wilmes B, Rademacher C, Olthoff G, Drescher D. Parameters affecting primary stability of orthodontic mini-implants. *J Orofac Orthop.* 2006;67:162–174.
8. Chen CH, Chang CS, Hsieh CH, et al. The use of microimplants in orthodontic anchorage. *J Oral Maxillofac Surg.* 2006;64:1209–1213.
9. Sarul M, Minch L, Park HS, Antoszewska-Smith J. Effect of the length of orthodontic mini-screw implants on their long-term stability: A prospective study. *Angle Orthod.* 2015;85:33–38.
10. Crismani AG, Bertl MH, Celar AG, Bantleon HP, Burstone CJ. Miniscrews in orthodontic treatment: Review and analysis of published clinical trials. *Am J Orthod Dentofacial Orthop.* 2010;137:108–113.
11. Dalessandri D, Salgarello S, Dalessandri M, et al. Determinants for success rates of temporary anchorage devices in orthodontics: A meta-analysis (n > 50). *Eur J Orthod.* 2014;36:303–313.
12. Migliorati M, Benedicenti S, Signori A. Thread shape factor: evaluation of three different orthodontic miniscrews stability. *Eur J Orthod.* 2013;35:401–405.
13. Chaddad K, Ferreira AF, Geurs N, Reddy MS. Influence of surface characteristics on survival rates of mini-implants. *Angle Orthod.* 2008;78:107–113.
14. Moon CH, Park HK, Nam JS, Im JS, Baek SH. Relationship between vertical skeletal pattern and success rate of orthodontic mini-implants. *Am J Orthod Dentofacial Orthop.* 2010;138:51–57.
15. Cheng SJ, Tseng IY, Lee, JJ, Kok SH. A prospective study of the risk factors associated with failure of mini-implants used for orthodontic anchorage. *Int J Oral Maxillofac Implants.* 2004;19:100–106.
16. Chen YJ, Chang HH, Huang CY, et al. A retrospective analysis of the failure rate of three different orthodontic skeletal anchorage systems. *Clin Oral Implan Res.* 2007;18:768–775.
17. Lee SJ, Ahn SJ, Lee JW, Kim SH, Kim TW. Survival analysis of orthodontic mini-implants. *Am J Orthod Dentofacial Orthop.* 2010;137:194–199.
18. Lim HJ, Eun CS, Cho JH, Lee KH, Hwang HS. Factors associated with initial stability of miniscrews for orthodontic treatment. *Am J Orthod Dentofacial Orthop.* 2009;136:236–242.
19. Meredith N. Assessment of implant stability as a prognostic determinant. *Int J Prosthodont.* 1998;11:491–501.
20. Chen YJ, Chang HH, Lin HY, et al. Stability of miniplates and miniscrews used for orthodontic anchorage: Experience with 492 temporary anchorage devices. *Clin Oral Implan Res.* 2008;19:1188–1196.
21. Çehreli S, Arman-Özçırpıcı A. Primary stability and histomorphometric bone-implant contact of self-drilling and self-tapping orthodontic microimplants. *Am J Orthod Dentofacial Orthop.* 2012;142:187–195.
22. Migliorati M, Benedicenti S, Signori A, et al. Thread shape factor: Evaluation of three different orthodontic miniscrews stability. *Eur J Orthod.* 2012;35:401–405.
23. Wilmes B, Drescher D. Impact of bone quality, implant type, and implantation site preparation on insertion torques of mini-implants used for orthodontic anchorage. *Int J Oral Maxillofac Surg.* 2011;40:697–703.
24. Cha JY, Kil JK, Yoon TM, Hwang CJ. Miniscrew stability evaluated with computerized tomography scanning. *Am J Orthod Dentofacial Orthop.* 2010;137:73–79.
25. McManus MM, Qian F, Grosland NM, Marshall SD, Southard TE. Effect of miniscrew placement torque on resistance to miniscrew movement under load. *Am J Orthod Dentofacial Orthop.* 2011;140:93–98.
26. Motoyoshi M, Yoshida T, Ono A, Shimizu N. Effect of cortical bone thickness and implant placement torque on stability of orthodontic mini implants. *Int J Oral Maxillofac Implants.* 2007;22:779–784.
27. Marquezan M, Trindade Mattos C, Franzotti Sant'Anna E, de Souza MM, Cople Maia L. Does cortical thickness influence the primary stability of miniscrews? A systematic review and meta-analysis. *Angle Orthod.* 2014;84:1093–1103.
28. Motoyoshi M, Hirabayashi M, Uemura M, Shimizu N. Recommended placement torque when tightening an orthodontic mini-implant. *Clin Oral Implan Res.* 2006;17:109–114.
29. Meursinge Reynders RA, Ladu L, van Etten-Jamaludin F, Bipat S. Insertion torque and success of orthodontic mini-implants: A systematic review. *Am J Orthod Dentofacial Orthop.* 2012;142:596–614.
30. Park HS, Jeong SH, Kwon OW. Factors affecting the clinical success of screw implants used as orthodontic anchorage. *Am J Orthod Dentofacial Orthop.* 2008;130:18–25.
31. Viwattanatipa N, Thanakitcharu S, Uttaravichien A, Pitiphat W. Survival analyses of surgical miniscrews as orthodontic anchorage. *Am J Orthod Dentofacial Orthop.* 2009;136: 29–36.
32. Zitzmann NU, Berglundh T, Ericsson I, Lindhe J. Spontaneous progression of experimentally induced peri-implantitis. *J Clin Periodontol.* 2004;31:845–849.
33. Ericsson I, Berglundh T, Marinello C, Liljenberg B, Lindhe J. Long-standing plaque and gingivitis at implants and teeth in the dog. *Clin Oral Implan Res.* 1992;3:99–103.
34. Kuroda S, Yamada K, Deguchi T, Hashimoto T, Kyung HM, Takano-Yamamoto T. Root proximity is a major factor for screw failure in orthodontic anchorage *Am J Orthod Dentofacial Orthop.* 2007;131:Suppl 4:68–73.
35. Kuroda S, Sugawara Y, Deguchi T, Kyung HM, Takano-Yamamoto T. Clinical use of miniscrew implants as orthodontic anchorage: success rates and postoperative discomfort. *Am J Orthod Dentofacial Orthop.* 2007;131:9–15.
36. Bayat E, Bauss O. Effect of smoking on the failure rates of orthodonticminiscrews. *J Orofac Orthop.* 2010;71:117–124.
37. Lim HJ, Choi YJ, Evans CA, Hwang HS. Predictors of initial stability of orthodontic miniscrew implants. *Eur J Orthod.* 2011;33:528–532.
38. Chen Y, Shin HI, Kyung HM. Biomechanical and histological comparison of self-drilling and self-tapping orthodontic microimplants in dogs. *Am J Orthod Dentofacial Orthop.* 2008; 133:44–50.
39. Türköz C, Ataç MS, Tuncer C, Balos Tuncer B, Kaan E. The effect of drill-free and drilling methods on the stability of mini-implants under early orthodontic loading in adolescent patients. *Eur J Orthod.* 2011;33:533–536.
40. Melsen B, Costa A. Immediate loading of implants used for orthodontic anchorage. *Clin Orthod Res. 2000;3*:23–28.
41. Büchter A, Wiechmann D, Koerdt S, Wiesmann HP, Piffko J, Meyer U. Load-related implant reaction of mini-implants used for orthodontic anchorage. *Clin Oral Implan Res* 2005;16:473–479.
42. Motoyoshi M, Matsuoka M, Shimizu N. Application of orthodontic mini-implants in adolescents. *Int J Oral Maxillofac Surg.* 2007;36:695–699.
43. Jung BA, Kunkel M, Göllner P, Liechti T, Wagner W, Wehrbein H. Prognostic parameters contributing to palatal implant failures: A long-term survival analysis of 239 patients. *Clin Oral Implan Res.* 2012;23:746–750.
44. Cho UH, Yu W, Kyung HM. Root contact during drilling for microimplant placement. Affect of surgery site and operator expertise. *Angle Orthod.* 2010;80:130–136.

# Influence of antibiotic prophylaxis on the stability of orthodontic microimplants: A pilot randomized controlled trial

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**Introduction:** The aims of this 2-arm parallel pilot randomized controlled trial were to investigate the influence of antibiotic prophylaxis on the stability of orthodontic microimplants and to evaluate the efficacy of systemic inflammatory marker measurements in detecting infections in tissues surrounding microscrews. **Methods:** Orthodontic patients requiring en-masse distalization in the maxilla received antibiotics or a placebo before microimplant placement. Eligibility criteria included 13 years of age, and good general and oral health. Exclusion criteria comprised allergy to antibiotics, severe systemic allergy, heart and kidney diseases, and recent antibiotic treatment. Stability of the microimplants was the primary outcome; inflammation of the tissues surrounding the microscrews, pain related to the microimplantation, and serum levels of inflammatory markers were the secondary outcomes. Randomization in a 1:1 ratio was performed by auxilliary staff via a flip of a coin between 2 participants of the same sex and developmental stage, and the "winner" was allocated to the intervention group. Pharmaceutically prepared identical capsules with either amoxicillin (intervention) or glucose (control) given 1 hour before microimplant placement according to the allocation provided blinding of the participants. Subsequently, 1 clinician unaware of the allocation inserted the microimplants and assessed the outcomes, which simultaneously blinded the operator-assessor. Blood samples for laboratory analysis of inflammatory markers were collected a day before and 1, 3, and 7 days postoperatively. **Results:** Out of 80 participants initially assessed for eligibility, 41 received the randomized allocation. Three patients were lost to follow-up. Eventually, data of 18 and 20 participants (mean age, 20.4 $\pm$ 5.9 years) were available for analysis in the intervention and control groups, in which 1 and 2 patients lost a microimplant, respectively, resulting in odds ratio of 0.53 (95% confidence interval [CI], 0.0084-11.23; $P = 1.0$). The odds ratio for inflammation development was 1.22 (95% CI, 0.34-4.38), and the odds ratio for feeling milder pain was 1.174 (95% CI, 0.350-3.941) in the intervention compared with the control group, but the result was not statistically significant ($P = 0.758$; $P = 0.795$, respectively). The inflammatory marker levels did not increase due to either microimplantation (procalcitonin, $P = 0.445$; C-reactive protein, $P = 0.4$) or peri-implantitis. Antibiotic prophylaxis slightly decreased the levels of the biomarkers in the intervention group; however, the results were not statistically significant ($P = 0.68$; $P = 0.908$, respectively). No harms caused by the microimplantation procedure or drug intake were noted. **Conclusions:** Antibiotics provided no benefit in terms of microimplant stability, inflammation of soft tissues, or postoperative pain in our pilot sample. Measurements of serum levels of inflammatory markers were inefficient in detecting soft tissue inflammations. These initial results should be interpreted with caution until validated by a large multicenter definitive trial. **Registration:** This trial was not registered. **Protocol:** The protocol was not published before trial commencement. **Funding:** The trial was funded by Wroclaw Medical University; grant number pbmn91 and supported by Diagnostyka. (Am J Orthod Dentofacial Orthop 2018;153:621-31)

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All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none were reported.
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Submitted, February 2017; revised and accepted, November 2017.
0889-5406/$36.00

https://doi.org/10.1016/j.ajodo.2017.11.025

Temporary intraoral skeletal anchorage devices (TISADs) have become a vital tool in modern orthodontics due to their remarkable capabilities. Improvement of treatment efficiency, redundancy of the patient's compliance, and performance of complex tooth movements previously unobtainable without apparent side effects are some paramount advantages of TISAD use. However, we must recognize the most significant factor limiting their efficacy: premature loss of stability. The reported microscrew success rates

range from 75.4% to 94.4%, indicating that approximately 1 of 10 devices becomes mobile and cannot serve as the anchorage enabling achievement of the treatment goal.[1-4] Failure of a TISAD requires at best its reinsertion resulting in additional surgery and increases treatment cost and duration; in complex cases, microimplant instability may imply more severe consequences: eg, inability to intrude molars and need for referral for orthognathic surgery.

Investigation of both the patient's characteristics and the design and management of the microimplants in terms of their impact on TISAD stability showed various failure risk factors such as hyperdivergent skeletal relationship, small diameter or length of the screw, improper insertion torque, and placement in free mucosa or thin cortical bone.[5-9] Nevertheless, most researchers unanimously stated that inflammation of soft tissues surrounding the microimplant is the predominant factor jeopardizing TISAD stability,[5,10-13] which is fully confirmed by the most recent meta-analysis of the factors related to microimplant failures.[14] The authors concluded that variables such as age, sex, and type of loading of the screw have some mild impact on the stability of the microimplant, whereas inflammation of soft tissues results in as high as a 9-fold increase of the risk of microimplant failure. This conclusion corresponds well with the results of experimental studies showing that the inflammatory process spreading from the soft tissues causes degeneration of the bone surrounding the implant, which then loses stability and needs replacement.[15,16] Taking these phenomena into account, prevention of soft tissue inflammations seems to be a crucial measure for improvement of microimplant stability.

Infectious inflammation develops when oral bacteria penetrate the areas surrounding the TISAD; this is likely to happen at 2 times: (1) during and shortly after implantation, when tissue continuity is broken; and (2) during the whole period of microimplant loading, via the fissure between the microimplant head and the soft tissues. The reported microimplant survival analyses show that most failures take place within the first few weeks after TISAD insertion, indicating that factors acting during and immediately after implantation are crucial for stability: ie, host and operative factors.[3,10,17] On the other hand, considering the long-term issues, the meta-analysis by Papageorgiou et al[18] showed no influence of oral hygiene on the stability of microimplants; this significantly undermines the importance of long-term hygiene maintenance aspects. Thus, according to the evidence, operative-related factors and not maintenance ones should be screened for refinements to improve microscrew survival rates.

In general, development of infections in the surgical site depends on patient-host and surgery-related factors. Taking into account that most of a patient's characteristics (age and bone quality) cannot be modified, prevention of infections should focus on the surgical aspects of the insertion procedure, which include (1) localization and preparation of the operative area; (2) invasiveness, technique, and duration of the procedure; and (3) use of antimicrobial agents.[19] When performed properly, microimplantation is a quick and minimally invasive procedure leaving few possibilities for technical improvement. On the other hand, use of antimicrobial agents may exert a favorable effect on prevention of infections during microimplantation. The literature provides scarce data on the use of antimicrobials related to microimplants; a few authors have barely mentioned administration of antibiotics in their descriptions of the surgical protocol (Table I).[5,7,20,21] Various regimens ranging from 1 dose before implantation up to 7 days postoperatively were applied, but no author provided any rationale supporting use of the antibiotics in conjunction with the microimplants. Therefore, up to now, no studies have directly investigated the impact of antibiotics on the stability of orthodontic microimplants. However, taking into account a similar model, a meta-analysis evaluating the influence of antibiotic prophylaxis on the survival of dental implants showed that a single dose of preoperative prophylaxis improved the success rates from 92% to 96%, which was statistically and clinically significant.[22] Thus, the question arises whether a similar effect could be obtained for orthodontic microimplants. On the other hand, we must not forget that administration of antibiotics has some significant drawbacks: risk of adverse reactions and promotion of antibiotic-resistant species of bacteria that counterweigh the positive effects.

### Specific objectives of the pilot trial

The aim of this pilot trial was to investigate whether administration of antibiotic prophylaxis before the microimplantation procedure improves the stability of the microimplants, reduces the soft tissue inflammation rate, and alleves the pain after microimplant insertion. On the other hand, to evaluate the intensity of the general immunologic response to the tissue trauma from microimplantation and, in particular, to the inflammation of the tissues surrounding the microimplant, we included measurements of systemic inflammatory biomarker levels.

## MATERIAL AND METHODS

### Trial design and any changes after trial commencement

This was a parallel-group pilot randomized controlled trial with a 1:1 allocation ratio.

**Table I.** Baseline clinical and demographic characteristics of the participants

| *Group* | *Drug and timing of delivery* | *Type of microimplants* | *Location of microimplants* | *Number and average age (y) of male participants* | *Number and average age (y) of female participants* |
|---|---|---|---|---|---|
| Intervention | Amoxicillin with clavulanic acid 875 + 125 mg 1 hour preop | Absoanchor 13-12 08 SH (1.3 × 8 mm, self tapered) | Maxilla, buccally between first molar and second premolar, attached gingiva | n = 5 24.2 ± 6.5 | n = 13 20.8 ± 5.8 |
| Control | Glucose 1.0 g 1 hour preop | Absoanchor 13-12 08 SH (1.3 × 8 mm, self tapered) | Maxilla, buccally between first molar and second premolar, attached gingiva | n = 4 17.5 ± 5.8 | n = 16 19.7 ± 5.7 |

*SH*, small head.

### Participants, eligibility criteria, settings

This pilot randomized trial was conducted at the Department of Dentofacial Orthopedics and Orthodontics of the Wroclaw Medical University in Poland, and the participants were recruited from November 2013 to August 2015. The inclusion criteria comprised age, 13 years; good general, dental, and oral health; and malocclusion requiring en-masse distalization of the entire maxillary arch with absolute anchorage. The exclusion criteria were allergic reaction to penicillin or any other drug in the medical statement, severe systemic allergy, immune system disorders, endoprosthesis, heart defects, past incidents of endocarditis and glomerulonephritis, and antibiotic treatment in the 2 months before our study. The ethical committee of Wroclaw Medical University approved the study design (380/2012), and informed written consent was obtained from each participant. No changes to methods were introduced after commencement of the trial.

### Intervention

In orthodontic terms, the participants were planned for microimplant-supported distalization of the maxillary dental arch. From the methodologic perspective, the division of intervention and control groups relied on different pharmaceutical substances before microimplantation. In the intervention group, the subjects were given 1.0 g of amoxicillin with clavulanic acid (875 + 125 mg); the subjects in the control group received glucose (1.0 g) as a placebo. To prevent the patients from recognizing the type of drug they were given, identical antibiotic and placebo capsules were manufactured by a pharmacist. The capsules were taken by the subjects 1 hour before microimplantation.

### Microimplantation procedure

Two Absoanchor microimplants 1312-08 SH (tapered from 1.3 to 1.2 mm; 8 mm long; Dentos, Daegu, Korea) were placed buccally between the roots of the maxillary second premolar and first molar (1 on the left and 1 on the right sides) according to a previously described protocol.[11,23] The procedure started with local anesthesia followed by vertical indentation of the alveolar mucosa with a dental probe to mark the mesiodistal position of the microscrew. A limited 0.4 mL volume of anesthetic per side was used to preserve the periodontal ligament sensation and prevent potential implant-root contact or proximity. Subsequently, a small 2-to-3 mm vertical stab incision provided access to the surface of the alveolar bone, and the microimplant bed was performed with a 0.9-mm pilot drill at 500 rpm under ample saline solution irrigation. The microimplants were placed with a hand screwdriver by an experienced operator (J.A-S.) at an angle of 30° to 40° to the long axes of adjacent teeth. After a solid fixation of the microscrews was confirmed with cotton tweezers, the patient was given postoperative instructions. Low or medium locations were used to maintain the heads of the microscrews in the alveolar gingiva.

### Outcomes and any changes after trial commencement

The primary outcome was the stability of the microimplants. The assessment was performed 1 week postoperatively, after the healing of the soft tissue around the head of the microimplant. At first, the microscrews were checked for any clinical signs of mobility with cotton tweezers. Subsequently, they were loaded with nickel-titanium springs with a force of 200 g. If the screw remained steady after loading, the microimplant was considered successful. One millimeter of the microimplant head displacement was also considered to be stable if no pain was associated with the loading. The secondary outcomes were inflammation of the soft tissues around the head of a microimplant and postoperative pain. The inflammation of the soft tissues

was screened 1 week postoperatively on a scale: 0, no inflammation; 1, redness; 2, redness and swelling; and 3, redness, swelling, and exudate. Postoperative pain was measured by the patients 1 day after the microimplantation on a visual analog scale (VAS) ranging from 0 mm (no pain) to 100 mm (excruciating pain). To evaluate the general immunologic response to microimplantation and peri-implantitis, measurements of procalcitonin (PCT) and C-reactive protein (CRP) serum concentrations were also included. Consecutive blood samples for inflammatory marker measurements were collected and analyzed at the same laboratory (Diagnostyka, Opolska Str. 131A, 52-013, Wroclaw) before (control sample) and 1, 3, and 7 days after microimplantation. One diagnostic laboratory tested all blood samples. Highly sensitive electro-chemiluminescent method and the Elecsys Brahms PCT immunoassays and Cobas Integra 411 (assay reference 05056888 200; Roche, Basel, Switzerland) analyzes enabled assessment of the PCT with a detection threshold of 0.02 ng per milliliter. The CRP analysis involved the highly sensitivity immunoturbidimetric method with the use of Cobas CRPHS assay and analyzed with Cobas Integra 400 plus (assay ref 04628918 190; Roche), with a detection threshold of 0.1 mg per liter.

### Sample size estimation

Taking into account as high as 90% success rates of microimplants in the maxilla, we deemed that improvement up to 95% would be clinically significant.[18] The calculation of the sample size for the definitive trial with alfa = 0.05 and power of 0.85% yielded a result of 403 participants per group. Considering the preliminary character of our investigation and the significant invasiveness of quadruple blood testing, we decided to include 50 patients per group in this pilot trial. Because of the high number of participants needed to test the null hypothesis in the definitive trial, a multicenter one will probably be necessary to recruit enough patients.

### Interim analyses and stopping guidelines

To allow early discovery of any trends or aberrations in the levels of inflammatory markers, all data were evaluated after every 10 patients completed the trial. In case of adverse reactions from drug delivery, a patient would immediately be excluded from further participation in the trial. In case of severe or life-threatening adverse reactions from the pharmaceuticals, the entire trial would be terminated. The pilot trial would also be stopped if any significant problem with completion of the study occurred, especially in terms of participant recruitment.

### Randomization

Randomization stratified to skeletal maturity and sex was applied to ensure equal distribution of these characteristics in both groups and to prevent their influence on the results. The cutoff skeletal developmental stage was CS6 according to most recent modification of cervical vertebral assessment method.[24] Participants in CS1 to CS5 were considered growing patients, and those in CS6 were nongrowing patients. The allocation to groups was performed when 2 participants of the same sex and developmental stage were ready to enter the trial. Auxiliary staff unaware of the purpose of the study executed randomization between the patients with a flip of a coin in a separate room. The winning participant was admitted as number 1 and allocated to the intervention group, and the other one was number 2 and allocated to the control group. Before the trial, a pharmacist prepared 1.0 g of amoxicillin with clavulanic acid (875 + 125 mg) and glucose as the placebo in identical capsules and placed them in containers labeled 1 and 2, respectively. According to the allocations, the patients were given capsules from the respective containers and took them 1 hour before the microimplantation. This procedure ensured blinding of the patients from the administered drug. Thereafter, the 2 participants moved to the clinical room to undergo the microimplantation procedure carried out by a clinician (J.A-S.) who was unaware of the drugs taken by each patient. Since both the microimplantation and outcome assessment were performed by the same clinician, blinding of the operator and the assessor was instantly achieved.

### Statistical analysis

Data analysis started with assessment of the groups' homogeneity in terms of sex and developmental stage, followed by analysis of the outcome measures. A sum of the outcomes of the 2 evaluated microimplant sites was used to account for the clustering effect from insertion of 2 microimplants in 1 subject. In terms of microimplant failures, loss of at least 1 microscrew was regarded as a failure. Subsequently, the Fisher exact test and the odds ratio of microimplant failure between groups with 95% confidence intervals (CI) were calculated. The cumulative microimplant success rate reflecting overall survival of the microimplants was also calculated and compared between groups with the Fisher exact test. For the soft tissue conditions, the more intense inflammation noted on either the left or right side was taken into account, and the differences in the proportions of the subjects with specific levels of inflammation with 95% confidence intervals were estimated. Second, binary logistic regression analysis

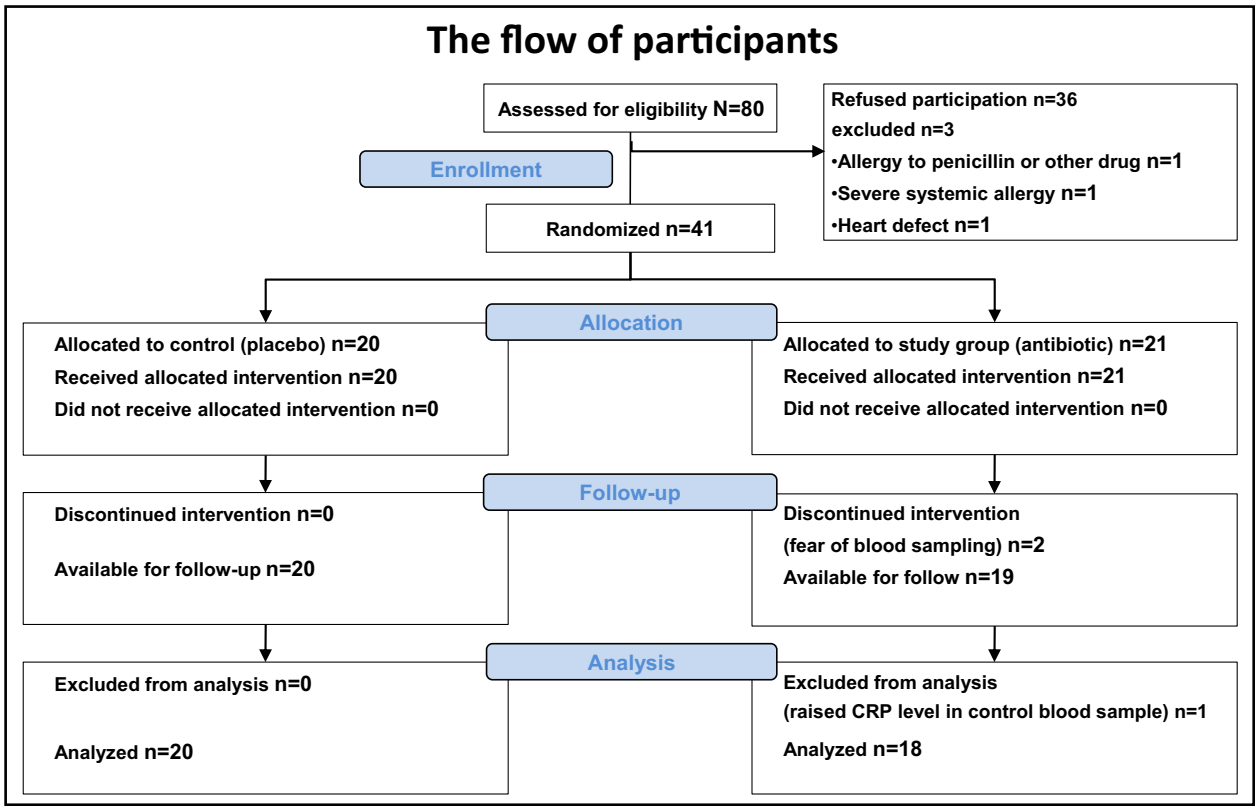


**Fig.** Flowchart of participants in the trial.

was used to estimate the odds ratio of developing any inflammation around either microimplant. Since The VAS is ordinal, an ordinal logistic regression under the assumption of a proportional odds model was used to determine the odds ratio for pain. The generalized estimating equation method was used for analysis of the influence of antibiotics on PCT and CRP serum concentrations in the blood samples. We used Statistica software (version 12 with medical bundle; StatSoft, Krakow, Poland) for all calculations, with the level of significance set at $P < 0.05$. General estimating equations analysis was performed with the Geepack:Generalized Estimating Equation Package, R Package (version 1.2-1).

## RESULTS

### Participant flow

The flow of participants is presented in the Figure. Out of 80 patients initially assessed for eligibility, 36 refused to participate in the study because of the multiple blood sampling; this resulted in 44 subjects available for actual eligibility assessment. Three patients could not enter the trial due to their health conditions listed in the exclusion criteria. Furthermore, 2 participants allocated to the antibiotic group discontinued participation in the study after collection of their first blood sample because they feared the following ones. Eventually, 19 and 20 subjects received the allocated intervention in the antibiotic and placebo groups, respectively. One patient from the antibiotic group was excluded from data analysis because of a raised CRP level in the control blood sample (6.5 mg/L). Eventually, data of 18 and 20 subjects in the antibiotic and placebo groups, respectively, were available for statistical analysis of all outcome measures. The patients were recruited from November 2012 to August 2015. We found that patients from our clinic were reluctant to participate in the trial because of the multiple blood sampling and drug administration. The interim analysis returned consistent results of primary and secondary outcome measures. Thus, a decision to terminate the trial was made, since it seemed evident that further continuation would not result in recruiting significant numbers of consecutive participants.

### Baseline sample characteristics

Baseline characteristics of the participants are presented in Table I. The sample comprised 29 women

**Table II.** Proportions of participants with failure in the groups

| *Group* | *Success* | *Failure* | *Odds ratio* | *Fisher exact test* P *value* |
|---|---|---|---|---|
| Intervention | 17 (94.4%) | 1 (5.6%) | OR 0.53%, 95% CI, 0.0084-11.23 | 1.0 |
| Control | 18 (88.9%) | 2 (11.1%) | | |
| Summary | 35 (92.1%) | 3 (7.9%) | | |

and 9 men, with mean ages of 20.2 ± 5.6 and 21.2 ± 6.8 years, respectively. The intervention and control groups proved to be homogenous in terms of age (19.2 ± 5.6 and 21.8 ± 6.0 years, respectively; $P = 0.26$) and sex distribution ($P = 0.709$).

### Microimplant survival analysis

The proportions of patients with stable and failed microimplants at the examination 1 week after insertion are presented in Table II. One of 18 and 2 of 20 participants lost 1 microimplant in the intervention and control groups, respectively. The Fisher exact test showed that the difference in the proportion of the subjects with stable and at least 1 failed microimplant between groups was not statistically significant ($P = 1.0$). The odds ratio for microimplant failure of at least 1 microimplant in the intervention group was 0.53 (95% CI, 0.0084-11.23). The cumulative success rates were 97.2% and 95% in the intervention and control groups, respectively, and the difference was not statistically significant (Table III; $P = 1.0$).

### Inflammation of the soft tissues surrounding the microimplant

Table IV presents the results of the soft tissue inflammation analysis. Ten and 11 subjects had both microimplants with no signs of inflammation in the intervention and control groups, respectively. There was no difference in the proportions of these participants between groups, with an OR of 0.00 (95% CI, −0.76-0.76). Redness was noted on at least 1 side in 7 participants in both groups, being frequent in the subjects from the intervention group, with an OR of 0.04 (95% CI, −0.25-0.29). Redness with swelling on at least 1 side was observed in 1 and 2 subjects in the intervention and control groups, respectively, with a higher frequency in the control group with an OR of 0.045 (95% CI, −0.30-0.39). All 95% confidence intervals contain 0, indicating that the differences in soft tissue conditions between the groups were not significant at $P = 0.05$. Table V presents the logistic regression analysis results; the odds ratio for developing

**Table III.** Overall microimplant success rates

| *Group* | *Success* | *Failure* | *Fisher exact test* P *value* |
|---|---|---|---|
| Intervention | 35 (97.2%) | 1 (2.8%) | 1.0 |
| Control | 38 (95.0%) | 2 (5.0%) | |
| Summary | 73 (96.0%) | 3 (4.0%) | |

inflammation around at least 1 microimplant was 1.22 (95% CI, 0,34-4,38) in the intervention to control group, but the result was not statistically significant ($P = 0.758$).

### Postoperative pain

The average pain levels measured on the VAS on the day after microimplantation are given in Table VI. In the entire sample, the mean pain level was 8.2 ± 0.69 mm, indicating only mild discomfort associated with insertion of the microimplants. In the control and intervention groups, the pain levels were 8.5 ± 0.75 mm and 7.8 ± 0.65 mm, respectively, and the difference was not statistically significant ($P = 0.798$). Table VII shows the proportions of subjects reporting pain. The results of the proportional odds model using the VAS as a response are given in Table VIII. The odds ratio of no pain or pain up to 10 instead of 20 on the VAS was 1.174 (95% CI, 0.350-3.941) in the intervention compared with the control group, but the result was not statistically significant ($P = 0.795$).

### PCT and CRP serum levels

The average PCT levels are presented in Table IX. The mean levels in both groups approximated 0.05 ng per milliliter in all sample series; this is well below the upper limit for a healthy person (0.1 ng/mL). There were no statistically significant differences in PCT levels in the groups in consecutive measurements. Generalized estimating equation analyses of PCT levels in the patients in the intervention and control groups are presented in Table X. Antibiotic prophylaxis decreased the level of PCT in participants in the intervention group by 0.001 ng per milliliter; however, the result was not statistically significant ($P = 0.68$). The average CRP levels shown in Table XI were also well below the limit for a healthy person (5 mg/L). There were no statistically significant differences in CRP levels within groups in consecutive measurements. Generalized estimating equation analysis of CRP levels in Table XII show that participants in the intervention group had lower CRP concentrations by 0.015 mg per liter; however, the result was not statistically significant ($P = 0.908$). The PCT and CRP levels in subjects with failed microimplants along with other outcomes are presented in the Supplementary Data. Despite the

**Table IV.** Inflammation of soft tissues surrounding the microimplants

| *Intensity of inflammation* | *Intervention n = 18* | *Control n = 20* | *Summary n = 38* | *95% CI* |
|---|---|---|---|---|
| 0, No inflammation | 10 (55.5%) | 11 (55.5%) | 21 (55.0%) | 0.00 (−0.76, 0.76) |
| 1, Redness | 7 (39%) | 7 (35.0%) | 14 (37.0%) | 0.04 (−0.25, 0.29) |
| 2, Redness and swelling | 1 (5,5%) | 2 (10.0%) | 3 (8.0%) | 0.045 (−0.30, 0.39) |
| 3, Redness, swelling, and exudate | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |

**Table V.** Odds ratios of inflammation development

| *Inflammation status* | *Intervention n = 18* | *Control n = 20* | *Total n = 38* | *OR (95% CI)* | P *value* |
|---|---|---|---|---|---|
| No inflammation | 9 (50%) | 11 (55%) | 20 (52.63%) | 1.22 (0.34-4.38) | 0.758 |
| Inflammation present | 9 (50%) | 9 (45%) | 18 (47.37%) | | |

**Table VI.** Pain levels 1 day after the microimplantation

| *Intensity of pain (0-100 mm VAS)* | *Intervention n = 18* | *Control n = 20* | *Summary n = 38* | *Intervention vs control* |
|---|---|---|---|---|
| Mean ± SD | 7.8 ± 0.65 | 8.5 ± 0.75 | 8.2 ± 0.69 | $P = 0.798$ |
| Minimum-maximum | 0-20.0 | 0-20.0 | 0-20.0 | |

inflammation, the levels of the markers remained within the norm of a healthy person.

### Harms

No adverse reactions from drug administration or complications related to microimplantation were noted during the study.

## DISCUSSION

### Main findings in the context of the existing evidence, interpretation

The failure of implants has been a major issue since the beginning of implantologic surgery, and postoperative infections are among the basic factors responsible for this complication. The oral cavity falls into the "clean-contaminated" category in terms of surgical site classification, due to the presence of residual microflora bacteria, which can invade the surgical wound and cause infection. In such operative fields, where risk of infection is 10% to 15 %, antibiotic prophylaxis is generally advised.[19] Unfortunately, up to date, no studies have investigated the influence of antibiotics on orthodontic microimplant stability and survival. However, the issue of antibiotic prophylaxis in oral surgery has been well investigated in regard to third molar extraction and dental implant placement. The meta-analysis by Ren and Malmstrom[25] showed a positive impact of antibiotic prophylaxis on the clinical outcome of third molar removal expressed by reduction of postoperative infection and alveolar osteitis incidence. They stated that there is solid evidence for administration of a single dose of penicillin 1 hour before surgery in generally healthy subjects to prevent these complications. For dental implants, the most recent meta-analysis by Esposito et al[22] proved that 2 g of amoxicillin given 1 hour before implant placement allowed a significant increase of the success rates from 92% to 96%. Therefore, there is significant evidence of the beneficial impact of antibiotic prophylaxis on oral surgery outcomes, and our study was the first one addressing this issue in respect to orthodontic microimplants.

To determine the sole effects of antibiotic intake and reduce the influence of other factors, we restricted the locations of the microimplants to 1 only, ie in the maxilla buccally between the second premolar and first molar. This location has high success rates that ensured consistency of the study model and enabled clear evaluation of the impact of antibiotics as the only significant variable.[11] In our sample, 1 and 2 subjects lost 1 microimplant during the first week after placement in the intervention and control groups, respectively, resulting in a statistically insignificant difference in microscrew survival between participants. All 3 failed microscrews were surrounded by inflamed and swollen soft tissues, whereas no failures were noted with absent or mild inflammation-only reddening of the mucosa. It seems plausible that swelling of the soft tissues indicates a cutoff intensity of the inflammatory process that is prognostic of microimplant loss. Therefore, our results support the major role of inflammation in the premature

**Table VII.** Proportions of the subjects reporting pain

| *Pain intensity (VAS 0-100 mm)* | *Intervention n = 18* | *Control n = 20* | *Summary n = 38* | *95% CI* |
|---|---|---|---|---|
| 0 | 6 (33.3%) | 7 (35.0%) | 13 (34.2%) | 0.02 (−0.27, 0.31) |
| 10 | 10 (55.5%) | 9 (45.0%) | 19 (50.0%) | 0.1 (−0.21, 0.41) |
| 20 | 2 (11.2%) | 4 (20.0%) | 6 (15.8%) | 0.09 (−0.38, 0.56) |

**Table VIII.** Proportional odds model pain odds ratio in intervention vs control groups

| | *Coefficient β (95% CI)* | P *value* | *OR (95% CI)* |
|---|---|---|---|
| Intercept 1 | −0.734 (−1.624, 0.156) | 0.106 | 0.480 (0.197, 1.169) |
| Intercept 2 | 1.597 (0.567, 2.627) | 0.002 | 4.939 (1.763, 13.831) |
| Drug | 0.16 (−1.051, 1.371) | 0.795 | 1.174 (0.350, 3.941) |

**Table IX.** Procalcitonin serum levels in 4 consecutive measurements

| | *Group* | |
|---|---|---|
| *PCT (ng/ml)* | *Intervention n = 18* | *Control n = 20* |
| Before procedure (control) | | |
| Mean ± SD | 0.044 ± 0.056 | 0.042 ± 0.023 |
| Minimum-maximum | 0.020-0.080 | 0.000-0.090 |
| 1 day after procedure | | |
| Mean ± SD | 0.038 ± 0.021 | 0.040 ± 0.016 |
| Minimum-maximum | 0.020-0.091 | 0.020-0.082 |
| 3 days after procedure | | |
| Mean ± SD | 0.043 ± 0.036 | 0.039 ± 0.014 |
| Minimum-maximum | 0.020-0.178 | 0.020-0.060 |
| 7 days after procedure | | |
| Mean ± SD | 0.061 ± 0.068 | 0.068 ± 0.109 |
| Minimum-maximum | 0.020-0.293 | 0.020-0.500 |
| Friedman test | $P = 0.335$ | $P = 0.445$ |

loss of stability of microimplants. In our sample, all microscrews that were stable at the initial examination retained their stability until the end of treatment; this is in line with the reports of survival of microscrews showing that failures occur predominantly in the first weeks after placement.[3,10,17] The joint interpretation of these findings may be the following: in case of no or only mild inflammation of the soft tissues in the first weeks after placement, the microimplant has a high probability for survival in the long term. On the other hand, significant inflammation including swelling of the soft tissues soon after implantation prejudges early failure of the microscrew.

Administration of antibiotics did not provide significant improvement of the analyzed variables in our sample. Despite slightly higher success rates and lower odds for microimplant loss in the antibiotic group, the differences were not statistically significant. Therefore, no positive impact of antibiotic prophylaxis on the survival of orthodontic microscrews was observed in this preliminary study. Similar findings pertain to the other clinical outcomes, since antibiotics did not reduce soft tissue inflammations or pain in our sample. About half of the subjects in the intervention and control groups had perfect soft tissue conditions on both microimplant sites, and the other half had mild to moderate inflammation; these frequencies are consistent with previous reports of inflammation incidence,[5,11] and there was no significant difference between the groups in this respect. A slightly lower mean pain level was noted in the patients who received antibiotics; however, again the differences were statistically insignificant. The reported pain levels after microimplant placement assessed in a 100-mm VAS ranged from 12.3 to 36.6 mm, indicating that moderate pain and discomfort are associated with this procedure.[26,27] The somewhat lower mean pain level of 8.2 mm found in our sample most likely resulted from performance of all procedures by an experienced clinician and the small size of the microimplants; both ensured microinvasiveness of the surgery. Therefore, the results of this preliminary study do not support administration of antibiotic prophylaxis before microimplant placement, although they must be interpreted as preliminary results. The final evaluation of the influence of antibiotics on the measured outcomes will be possible after recruiting more subjects in a definitive trial to ensure adequate power of the results. The small number of participants in our sample resulted from their reluctance to undergo quadruple blood testing; as many as 36 initially eligible patients refused participation for this reason. Administration of improper antibiotics could potentially explain the apparent inefficiency of the prophylaxis in our sample; however, the relevance of the selected antibiotic is unquestionable, since amoxicillin with clavulanic acid covers the spectrum of both oral residual flora and bacteria specifically associated with soft tissue inflammation and TISAD failures.[28,29] The combined dosage of 1 g (875 mg of amoxicillin, 125 mg of clavulanic acid) was different from the American Heart Association's Guidelines for infective endocarditis

**Table X.** Generalized estimating equation analysis of PCT levels

| | *Coefficient β (95% CI)* | P *value* |
|---|---|---|
| Intercept | 0.030 (0.022, 0.038) | 1.50E-12 |
| Drug | −0.001 (−0.007, 0.005) | 0.68 |
| Time | 0.007 (0.004, 0.010) | 7.10E-07 |

*E*, Euler's number.

**Table XI.** CRP serum levels in 4 consecutive measurements

| | *Group* | |
|---|---|---|
| *CRP (mg/L)* | *Intervention n = 18* | *Control n = 20* |
| Before procedure (control) | | |
| Mean ± SD | 0.54 ± 0.53 | 0.41 ± 0.41 |
| Minimum-maximum | 0.00-2.20 | 0.00-1.34 |
| 1 day after procedure | | |
| Mean ± SD | 0.81 ± 1.01 | 0.50 ± 0.44 |
| Minimum-maximum | 0.10-4.60 | 0.00-1.65 |
| 3 days after procedure | | |
| Mean ± SD | 0.78 ± 0.89 | 0.60 ± 0.42 |
| Minimum-maximum | 0.08-4.00 | 0.00-1.50 |
| 7 days after procedure | | |
| Mean ± SD | 0.68 ± 0.44 | 1.40 ± 2.38 |
| Minimum-maximum | 0.07-1.80 | 0.00-6.94 |
| Friedman test | $P = 0.211$ | $P = 0.400$ |

prevention of 2 g of amoxicillin.[30] However, the dose of prophylactic antibiotic depends directly on the intended outcome. Therefore, taking into account that the pathophysiologies of bacterial invasion resulting in endocardiac thrombotic clots and microimplant surgical site infection are significantly different, and that 875 mg of amoxicillin with 125 mg of clavulanic acid ensures serum concentrations well exceeding the minimal inhibitory concentration of potentially virulent species, we believed that it was justified to lower the dose of the drug to reduce the risk of adverse reactions, especially in the gastrointestinal tract (after consultation with a professor of pharmacology).[31,32] Along with the amount of delivered antibiotics, the issue of 1 dose might have played a role, since the antibiotic was active for only a few hours after delivery, leaving the possibility of bacteria invading the soft tissues later. Contrary to dental implant surgery, the mucous membrane is left unsutured after microscrew placement; this allows reopening of the crevice between the head of the microimplant and the soft tissues after insertion: eg, by irritation from a toothbrush. We cannot prevent that, and a full course of antibiotics after microimplantation counteracting this possibility would no longer be a prophylaxis, but an ethically and medically questionable treatment. As health care providers, we must remember that every use of antibiotics has the risk of adverse drug reactions and promotion of antibiotic-resistant species. Considering these negative aspects, we think that full antibiotic treatment is not justified as a mean of microimplant stability improvement, even if it is proved effective, since the drawbacks outweigh the benefits of this practice.

**Table XII.** Generalized estimating equation analysis of CRP levels

| | *Coefficient β (95% CI)* | P *value* |
|---|---|---|
| Intercept | 0.288 (0.068, 0.507) | 0.0103 |
| Drug | −0.015 (−0.274, 0.243) | 0.9084 |
| Time | 0.172 (0.046, 0.298) | 0.0760 |

Acute phase proteins, such as CRP or PCT, are commonly used for identification and monitoring of bacterial infections, in both general medicine and periodontology and oral surgery.[33-36] The measurements of their serum levels were included to this study for 2 purposes: (1) CRP, to elucidate whether tissue trauma during microimplantation is expressed in the general immune system by an increase of this marker level, and (2) CRP and PCT, to check whether clinically observed inflammation has an infectious origin confirmed by elevation of the marker level. In general, the CRP serum level increases in response to tissue trauma and returns to normal within a week or two.[37] In our sample, no significant alternations of CRP level were noted because of microimplantation in either group, indicating that the procedure is truly microinvasive and does not affect the general immune system; this was a positive finding. It is also compatible with a report showing that orthodontic movement of teeth during alignment does not elevate systemic CRP levels.[38] Thus, it may be stated that orthodontic treatment itself combined with microimplant use does not affect the general immune system in terms of inflammatory processes. On the other hand, we expected elevation of PCT and CRP levels in the 3 participants with significantly inflamed soft tissues and failed microimplants, but again they were not elevated and remained well below the norm for a healthy person. Possibly, the inflammatory processes in the microimplant sites are not robust enough to produce systemically detectable alterations of the inflammatory marker levels, which is the case in periodontitis and postsurgical infections.[35,36] Therefore, we concluded that PCT and CRP measurements do not provide valuable information about the condition of tissues surrounding the microscrew and are not an efficient tool for screening microimplant-related inflammations. The generalized

estimating equation analysis showed that antibiotic prophylaxis somewhat decreased the levels of PCT and CRP in the participants in the intervention group; however, the results were statistically not significant. Thus, antibiotic intake does not improve the inflammatory biomarkers profile after microimplantation, which as reported above is not required, since the levels of PCT and CRP after the procedure do not exceed the norms for a healthy person.

### Limitations and generalizability of the trial

The major limitation of this pilot trial was the small sample size because of reasons discussed above: reluctance of the eligible subjects to have quadruple blood testing and their refusal to participate. Another limitation was restriction of the location to the maxilla, which provided a predictable study model for a preliminary investigation; however, the results do not apply to the mandible. The generalizability of the trial is reduced by the fact that all microimplantations and clinical assessments were performed by 1 experienced clinician; this in turn ensured a high consistency of the procedures.

### Indications for the definitive trial

In terms of sample size, it seems that a multicenter trial could enroll the 800 participants necessary to analyze the influence of antibiotic prophylaxis on the stability of microimplants with adequate power. Future trials should include mandibular locations of the microscrews, since the survival rates of TISADs are generally lower in the mandible, leaving theoretically more room for improvement from antibiotic intake. The analysis of inflammatory markers provided little information about the condition of the soft tissues surrounding the microimplants in the maxilla; thus it could in our opinion be discarded from the protocol of future trials. However, it may prove more useful in the mandible, where more robust inflammations occur. The combined dose of 1.0 g of amoxicillin with clavulanic acid caused no adverse reactions in our sample and can be used in future trials.

## CONCLUSIONS

The results of this pilot trial do not support administration of a single dose antibiotic prophylaxis before orthodontic microimplant placement, since no positive influence on the analyzed variables was observed in our sample. However, because of the small sample size, the results should be interpreted as preliminary until validated by a definitive, most possibly, multicenter trial including mandibular locations of the microimplants. What is more, we concluded that PCT and CRP measurements do not provide valuable information about the condition of the tissues surrounding the microscrew and are not an efficient tool for screening microimplant-related inflammations in the maxilla. Eventually, in our opinion, a full course of antibiotic treatment with microimplant application should be avoided, because the improvement of microscrew survival does not balance the profound negative effects of antibiotic use: ie, adverse reactions and antibiotic resistance.

## SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.ajodo.2017.11.025.

## REFERENCES

1. Baek SH, Kim BM, Kyung SH, Lim JK, Kim YH. Success rate and risk factors associated with mini-implants reinstalled in the maxilla. Angle Orthod 2008;78:895-901.
2. Luzi C, Verna C, Melsen B. A prospective clinical investigation of the failure rate of immediately loaded mini-implants used for orthodontic anchorage. Prog Orthod 2007;8:192-201.
3. Wiechmann D, Meyer U, Büchter A. Success rate of mini- and micro-implants used for orthodontic anchorage: a prospective clinical study. Clin Oral Implants Res 2007;18:263-7.
4. Sarul M, Antoszewska J. Absoanchor miniscrews in non-extraction treatment of class II malocclusion in adult—case report. Dent Med Probl 2009;46:513-8.
5. Miyawaki S, Koyama I, Inoue M, Mishima K, Sugahara T, Takano-Yamamoto T. Factors associated with the stability of titanium screws placed in the posterior region for orthodontic anchorage. Am J Orthod Dentofacial Orthop 2003;124:373-8.
6. Sarul M, Minch L, Park HS, Antoszewska-Smith J. Effect of the length of orthodontic mini-screw implants on their long-term stability: a prospective study. Angle Orthod 2015;85:33-8.
7. Motoyoshi M, Hirabayashi M, Uemura M, Shimizu N. Recommended placement torque when tightening an orthodontic mini-implant. Clin Oral Implants Res 2006;17:109-14.
8. Antoszewska J, Papadopoulos MA, Park HS, Ludwig B. Five-year experience with orthodontic miniscrew implants: a retrospective investigation of factors influencing success rates. Am J Orthod Dentofacial Orthop 2009;136:158.e1-10.
9. Motoyoshi M, Matsuoka M, Shimizu N. Application of orthodontic mini-implants in adolescents. Int J Oral Maxillofac Surg 2007;3:695-9.
10. Cheng SJ, Tseng IY, Lee JJ, Kok SH. A prospective study of the risk factors associated with failure of mini-implants used for orthodontic anchorage. Int J Oral Maxillofac Implants 2004;19:100-6.
11. Park HS, Jeong SW, Kwon OW. Factors affecting the clinical success of screw implants used as orthodontic anchorage. Am J Orthod Dentofacial Orthop 2006;130:18-25.
12. Chen YJ, Chang HH, Lin HY, Lai EH, Hung HC, Yao CC. Stability of miniplates and miniscrews used for orthodontic anchorage: experience with 492 temporary anchorage devices. Clin Oral Implants Res 2008;19:1188-96.
13. Viwattanatipa N, Thanakitcharu S, Uttraravichien A, Pitiphat W. Survival analyses of surgical miniscrews as orthodontic anchorage. Am J Orthod Dentofacial Orthop 2009;136:29-36.

14. Dalessandri D, Salgarello S, Dalessandri M, Lazzaroni E, Piancino M, Paganelli C, et al. Determinants for success rates of temporary anchorage devices in orthodontics: a meta-analysis (n >50). Eur J Orthod 2014;36:303-13.
15. Zitzmann NU, Berglundh T, Ericsson I, Lindhe J. Spontaneous progression of experimentally induced peri-implantitis. J Clin Periodontol 2004;31:845-9.
16. Ericsson I, Berglundh T, Marinello C, Liljenberg B, Lindhe J. Long-standing plaque and gingivitis at implants and teeth in the dog. Clin Oral Implants Res 1992;3:99-103.
17. Lee SJ, Ahn SJ, Lee JW, Kim SH, Kim TW. Survival analysis of orthodontic mini-implants. Am J Orthod Dentofacial Orthop 2010;137:194-9.
18. Papageorgiou SN, Zogakis IP, Papadopoulos MA. Failure rates and associated risk factors of orthodontic miniscrew implants: a meta-analysis. Am J Orthod Dentofacial Orthop 2012;142:577-95.
19. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection. Infect Control Hosp Epidemiol 1999;20:250-78.
20. Liou EJ, Pai BC, Lin JC. Do miniscrews remain stationary under orthodontic forces? Am J Orthod Dentofacial Orthop 2004;126:42-7.
21. Hedayati Z, Hashemi SM, Zamiri B, Fattahi HR. Anchorage value of surgical titanium screws in orthodontic tooth movement. Int J Oral Maxillofac Surg 2007;36:588-92.
22. Esposito M, Worthington HV, Loli V, Coulthard P, Grusovin MG. Interventions for replacing missing teeth: antibiotics at dental implant placement to prevent complications. Cochrane Database Syst Rev 2010;(7):CD004152: Update in Cochrane Database Syst Rev 2013;7:CD004152.
23. Antoszewska J, Kawala B, Sarul M. Czynniki wpływające na stabilność implantów ortodontycznych. Metoda wrocławska—factors affecting stability of orthodontic implants. Orthod For 2010; 6:5-14.
24. Baccetti T, Franchi L, McNamara JA Jr. The cervical vertebral maturation (CVM) method for the assessment of optimal treatment timing in dentofacial orthopedics. Semin Orthod 2005;11:119-29.
25. Ren YF, Malmstrom HS. Effectiveness of antibiotic prophylaxis in third molar surgery: a meta-analysis of randomized controlled clinical trials. J Oral Maxillofac Surg 2007;65:1909-21.
26. Lee TC, McGrath CP, Wong RW, Rabie AB. Patients' perceptions regarding microimplant as anchorage in orthodontics. Angle Orthod 2008;78:228-33.
27. Chen CM, Chang CS, Tseng YC, Hsu KR, Lee KT, Lee HE. The perception of pain following interdental microimplant treatment for skeletal anchorage: a retrospective study. Odontology 2011; 99:88-91.
28. Sato R, Sato T, Takahashi I, Sugawara J, Takahashi N. Profiling of bacterial flora in crevices around titanium orthodontic anchor plates. Clin Oral Implants Res 2007;18:21-6.
29. Apel S, Apel C, Morea C, Tortamano A, Dominguez GC, Conrads G. Microflora associated with successful and failed orthodontic mini-implants. Clin Oral Implants Res 2009;11:1186-90.
30. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 2007;116:1736-54.
31. Jacobs MR, Spangler SK, Appelbaum PC. Susceptibility of bacteroides non-fragilis and fusobacteria to amoxicillin, amoxicillin/clavulanate, ticarcillin, ticarcillin/clavulanate, cefoxitin, imipenem and metronidazole. Eur J Clin Microbiol Infect Dis 1990;9:417-21.
32. Brook I, Wexler HM, Goldstein EJ. Antianaerobic antimicrobials: spectrum and susceptibility testing. Clin Microbiol Rev 2013;26: 526-46.
33. Wang T, Wang H, Yang DL, Jiang LQ, Zhang LJ, Ding WY. Factors predicting surgical site infection after posterior lumbar surgery: multicenter retrospective study. Medicine (Baltimore) 2017;96: e6042.
34. Salzberg TN, Overstreet BT, Rogers JD, Califano JV, Best AM, Schenkein HA. C-reactive protein levels in patients with aggressive periodontitis. J Periodontol 2006;77:933-9.
35. Redman RS, Kerr GS, Payne JB, Mikuls TR, Huang J, Sayles HR, et al. Salivary and serum procalcitonin and C-reactive protein as biomarkers of periodontitis in United States veterans with osteoarthritis or rheumatoid arthritis. Biotech Histochem 2016;91:77-85.
36. Chander PM, Ali FM, Aher V. C-reactive protein a better indicator of inflammation after third molar extraction. Niger J Clin Pract 2013;16:297-301.
37. Pritchett JW. C-reactive protein levels determine the severity of soft-tissue injuries. Am J Orthop (Belle Mead NJ) 1996;25:759-61.
38. MacLaine JK, Rabie AB, Wong R. Does orthodontic tooth movement cause an elevation in systemic inflammatory markers? Eur J Orthod 2010;32:435-40.