Orthodontics

Аналитично определяне на оптималния период на използване на никел-титанови ортодонтски дъги.

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An analytical determination of the optimal usage duration for nickel-titanium orthodontic wires.

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Summary

Rationale*: The main goal of the present study is to evaluate the optimal duration for the use of three types of Ni contained orthodontic wires, analysing the dynamics of Nickel Content (NC) as a function of intraoral usage duration, and minimising the Nickel Release (NR). Our core hypothesis is that the NC change during the period of use of orthodontic wires might follow the same common pattern/model, with different parameters, for different types of wires.*

Materials and Methods*: The analysed dataset contains several wires of each type sorted in three states, according to the period of use. The NC is assessed via Energy-dispersive X-ray Spectroscopy (EDS) in several visually different areas along each wire. For statistical analysis, we have defined a global and a local measure of NC. We have constructed a two-parametrical analytical model of NC dynamics under the assumption that the rate of change of NC is proportional to the product of Nickel-potent and Nickel-free compounds quantities.*

Results*: Statistical analysis performed on the global measure has not shown significant changes between considered states. In contrast, the local measure analysis has revealed statistically significant changes between states. To quantify the NC dynamics, the analytical model's solution is fitted to the local statistical results. Then, the model parameters for each group of wires are reconstructed, and group-level optimal duration of use is proposed.*

Conclusions*: If further extended, the obtained model may become a tool in the orthodontists' hands to decide about the wire's optimal duration of use on a patient-specific level.*

Keywords*: NiTi orthodontic wires, Nickel release hypothesis, Analytical models.*

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Резюме

Обосновка*: Основната цел на настоящото изследване е да се оцени оптималната продължителност на употреба за три типа Ni-съдържащи ортодонтски дъги, като се анализира динамиката на Никеловото Съдържание (NC) като функция от продължителността на интраорална употреба и се минимизира Освобождаването на Никел (NR). Нашата основна хипотеза е, че промяната в NC през периода на използване на ортодонтски дъги може да следва един и същ общ шаблон / модел, с различни параметри, за различни видове дъги.*

Материали и методи*: Анализираните данни съдържат няколко екземпляра от всеки тип изследвани дъги, сортирани в три състояния, според периода на употреба. NC е оценено чрез Енерго-Дисперсионна рентгенова Спектроскопия (EDS) в няколко визуално различни области по протежение на всяка дъга. За целите на статистическия анализ са дефинирани глобална и локална мерки за NC. Създаден е дву-параметричен аналитичен модел на динамиката на NC съгласно допускането, че скоростта на промяна на NC е пропорционална на произведението от количества на никел-съдържащите и никел-свободните съединения.*

Резултати*: Проведеният статистически анализ по глобалната мярка не показа значителни промени между разглежданите състояния. За разлика от това, анализът на локалната мярка разкри статистически значими промени. За да се квантифицира динамиката на NC, решението на аналитичния модел е използвано за апроксимация на статистическите резултати. След това параметрите на модела за всяка група дъги са реконструирани и е предложена оптимална продължителност на използване на дъгите на ниво група.*

Заключение*: Ако бъде разширен, полученият модел може да се превърне в инструмент, за определяне на оптималната продължителност на употреба на ортодонтските дъги на ниво специфичен пациент.*

Ключови думи*: NiTi ортодонтски дъги, Хипотезата за освобождаване на никел, Аналитични модели.*

Introduction

Nickel-containing alloys nowadays have become an integral part of almost every routine orthodontic treatment [1]. The *Nickel* (*Ni*) allergies in patients motivate the attention devoted to the *Nickel-Release (NR)* hypothesis [2]. During intraoral use, the orthodontic wires are subjected to chemical and electrochemical reactions, which causes corrosion and leads to the release of metal ions including Nickel [3]. It is estimated that 4.5–28.5% of the population have hyper-sensitivity to *Ni*, with a higher prevalence in females. It has been shown that the level of *Nickel* in saliva and serum increases significantly after the insertion of fixed orthodontic appliances [4]. On the other hand, the surface corrosion of *NiTi* arch wires may increase the friction that appears at the interface between the archwire and bracket, reducing the free sliding action during orthodontic treatment [5]. Classical allergic responses are characterized by dose-independence, i.e., low doses would not cause inflammation through toxicity but would activate immune cells. Additionally, mutagenicity and carcinogenic effects are not related to the dose of the toxicant [6]. Observations indicate that early contact with potential allergens may actually lead to a diminished probability for allergic reactions later in life [5]. That motivates our interest to the main topic and future researches.

Aim

The aim of the present study is to evaluate the optimal period of use for three types of commonly used *Nickel* contained *(Ni-contained*) orthodontic wires, through the analysis of the dynamics of *Nickel content* (*NC)* as a function of intraoral usage duration. Our main hypothesis in this study is that the *NC* change during the period of use of orthodontic wires might follow the same common model, with different parameters, for different types of wires.

Materials and Methods

Examined wires. In the present study 29 *Ni* contained orthodontic wires from the following three types have been used: 1. Austenitic nickel-titanium (*NiTi*), 2. Heat-activated nickel-titanium without copper content (*NiTi Heat*), 3. Heat-activated nickel-titanium with copper content (*CuNiTi Heat*). The examined wires are brand and composition matched and are of the same cross-section (0.016 x 0.022 inches).

To account for the *NR* dynamics, i.e Nickel release (NR) during orthodontic treatment we have divided wires into three groups by duration of intraoral usage: 1. *AR* - as received; 2. *R6* - retrieved after intraoral use for less than six weeks; 3. *R8* - retrieved after intraoral use for more than eight weeks. The examined *R_* wires were retrieved during the routine visits of orthodontic patients. After retrieval, the wires were placed in a disinfectant bath for 30 minutes, and then cleaned with a cotton swab moistened with a 95% alcoholic solution to remove any deposits and food. Further, each wire was placed in a resealable plastic bag, together with the wire's data sheet, ready for analysis.

The number of examined wires in stages AR/R6/R8 are respectively shown in tabl.1. In total 145 samples are analysed.

The chemical composition of the wire for global quantification measure has been determined by the *X-ray* microanalysis using the ***Energy dispersive X-ray Spectroscopy Analysis(*** *EDS)* method, *Oxford Instruments INCA Energy* system. This made it possible to not only compare received and retrieved arch-wires, but also several groups of wires of the same type, with different duration of use.

Local Nickel content (NC) for every wire, was measured by *EDS* again, but in five visually different areas along the wire. As a reference, we have used the *EDS* values of *NC*, measured on the unused wires. Thus, a relative *NC* measure for each wire in the analysed locations have been obtained. The relative error of the analysis in mass percentage is 0.5 to 1%.

Nickel content quantification measures for a wire. To quantify the *NC* for a wire, we have used *global* and *local* quantification measures.

The ***Global Quantification Measure* (*GM*)** is defined for each of the examined wires as the average of the measured *NC* values over all the samples: all of the analysed locations.

The ***Local Quantification Measure* (*LM*)**, is defined as follows: For each wire at stage *AR*, *LM* is defined as equal to the corresponding *GM*. The mean of the *LM* values at stage *AR* over all wires for each type is called "reference". Then, for all other stages, we have defined *LM* as the measurement value at the position where the absolute difference to the "reference" is maximal or in other words the *Ni* quantitative composition changes most. **Therefore, the *LM* has been associated with the analysis of wire's areas, which represent the potential foci of corrosion processes.**

Dynamic modelling. It observes the change in chemical composition during intraoral usage as sigmoid functions (logistic regression) over time. We have introduced a two-parametrical analytical model of *NC* dynamics under the assumption that the rate of change of *NC* is proportional to the product of *Nickel*-potent and *Nickel*-free compounds quantities. The motivation behind the choice of this model is in accordance with the general assumption that *"the rate of change of NC is proportional to the product of Nickel-potent and Nickel-free compounds quantities"*. Studying the behaviour of the resulting curves, which model the *NR* dynamics, one may predict the trends of change of the *NC* over time, thus to account

Table 1*. Distribution of the studied arch-wires by groups.*

Ni - Ti			Heat activated Ni - Ti			Heat activated Cu -Ni-Ti			**Total**
AR	R6	R8	AR	R6	R8	AR	R6	R8	
2	10	4	2	2	2	2	3	2	29

for the optimal period of intraoral use for the considered types of wires.

Because of the use of the mass percentages, it is convenient to use the relative concentration $S(t) \equiv NC(t)/100$, which is normalized between zero and one. The dynamics of $S(t)$ according to the above assumption might be written as a dynamic model: $d/_{dt}[S(t)] = kS(t)(1 - S(t))$. A sigmoid function $S(t)$ is defined for a time interval. The definition of $S(t)$ represents a family of sigmoid curves with centre and slope parameters $\{t_0, k\}$. It measures the **amount of nickel at the three points**, respectively, for the three types of arch-wires at the three time intervals. The modelling task is then performed by fitting the curves $S(t)$ to the averaged data in three time points, corresponding to stages *AR, R6, R8*, and the sigmoid parameters are reconstructed. The data processing and methods implemented in this study has been performed on Matlab® (Math Works Inc. Natic, USA, 2019a) through custom and system functions.

The statistical analysis, used for processing the results are : the non-parametric *Kruskal-Wallis* one-way *ANOVA* test has been used to study the statistical distributions of the values obtained from the quantitative measures. The level of significance of the differences between the groups have been determined by performing multi-variance comparison based on the *ANOVA* test statistics, using *Mann-Whitney* multiple comparative tests, *Bonferroni* corrected for group comparison. The results are considered statistically significant if they have reached a confidence level higher than 95% (p <0.05)

Results

The results obtained in the statistical processing of data on the effect of duration of intraoral use on NC are:

Global quantification measure (*GM*) does not show statistically significant differences between the groups. Therefore, the averaged *NC* of the wire does not change significantly as a function of the treatment duration.

Local quantification measure (*LM)*

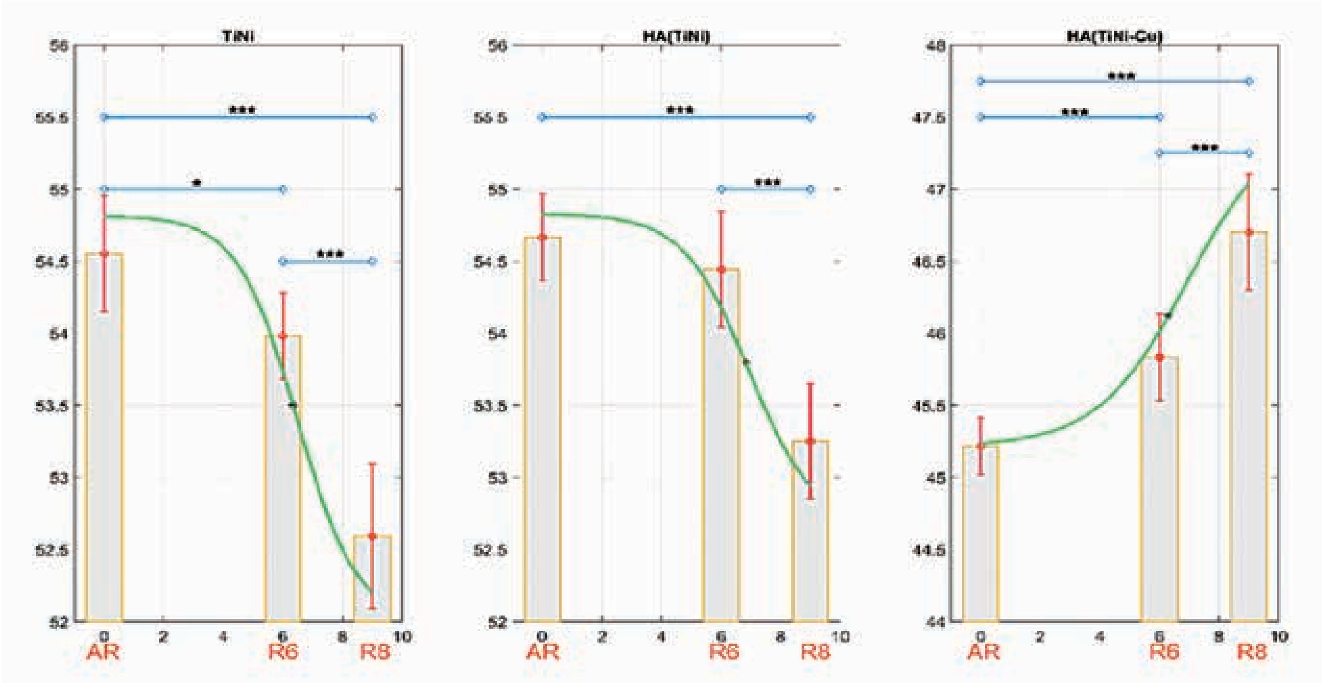
Orthodontic arch-wires were examined in a "pure" section of the arch-wire as well as in a section with visible changes (corrosive fields) in order to be compared by local properties. Table. 2 shows the results obtained by LM, with corrosion sections denoted as $T_{1,}$ $T_{2,}$ $T_{3,}$ $T_{4.}$

This approach helps avoiding averaging across different areas with essential differences in chemical composition, which would inevitably lead to an unrealistic outcome, while compromising overall research.

As can be seen from the table. 2, local measurements have shown statistically significant differences at a group level. Statistical analysis of *AR* vs *R6* vs *R8* stages for *LM* is shown on *figure № 1*, which gave us the information about NC dynamics.

Table 2. *Results of EDS for Local quantification measure.*

Type of wire	NiTi			Heat activated NiTi			Heat activated Cu-NiTi		
Points	AR	R6	R8	AR	R6	R8	AR	R6	R8
T1	54.66	53.77	49.53	54.76	54.75	54.65	45.12	46.34	46.45
T2	54.53	54.64	51.52	54.49	54.74	54.18	45.51	45.86	47.28
T3	54.94	62.45	54.61	54.74	53.93	54.29	45.58	45.52	46.83
T4	54.55	62.42	54.57				45.59		
Mean value	54.67	58.32	54.59	54.66	54.47	54.38	45.45	45.91	46.85
Maximum	54.94	62.45	54.61	54.76	54.75	54.65	45.59	46.34	47.28
Minimum	54.53	53.77	49.53	54.49	53.93	54.18	45.12	45.52	46.45



Panel **A** Panel **B** Panel **C**

Fig. 1. *Statistical analysis applied to the Local Measure of NC and of the NC Dynamics continues Approximation.*

The figure contains three big panels, one for each type of the examined wires (NiTi, Heat NiTi, Heat CuNiTi). Each panel contains:

- The x-axis shows the duration of intraoral use in weeks. On the x-axis of each panel are marked the wire's group stages *AR*, *R6*, and *R8*.
- The y-axis shows the Nickel mass percentages.
- The vertical gray bars show the averaged *NC* (y-axis in percentage) with the standard error inserted as vertical red lines.
- The number of stars on the horizontal lines indicate the level of statistical significance of the differences between each two stages ($p<0.05$, $p<0.01$ and $p<0.001$ for one, two or three stars correspondingly).
- The green curve shows the approximated *NC* dynamics.
- The center of each curve is marked with a black circle, showing extreme values or optimal stay of the orthodontic arch-wire

The results might be interpreted as: the group-level NC, after different periods of intraoral use of a wire, measured in locations of very likely corrosion processes shows statistically significant differences. In short:

- For NiTi wires (panel A in Fig. 1): In the R6 stage, the NC is significantly lower than in stage AR, and the NC in stage R8 is significantly lower than in stages AR, and R6.
- For NiTi Heat (panel B in Fig. 1) wires: There are no statistically significant differences in NC between stage AR and stage R6. The NC in stage R8 is again significantly lower than in stages AR, and R6.
- For CuNiTi Heat wires (panel C in Fig.1): The NC increases from stage AR to stage R6, and then to R8.

The relation between dynamics of *NC* and duration of clinical usage of Nickel-containing orthodontic arch-wire, is illustrated by sigmoid functions (green curves) in the three panels on Fig.1.

In the figure 1 we can see the point for the maximum time to which there is no change in NR, which is the optimum for clinical use of the arch-wires.

- For the *NiTi* wires (panel A in Fig. 1), the centre (point of maximum velocity) is after 6 weeks (6.2), and the slope value is -0.5.
- For the *NiTi* Heat wires (panel B), $t_0 = 7$ weeks (6.8) with slope value of -0.45.
- For the *CuNiTi Heat* wires (panel C) $t_0 = 6\ (6.2), k = 0.33$.

By establishing these values, we have completed our aim of obtaining the optimal usage duration for Nickel-containing orthodontic arch-wires.

Therefore, the *NR* has been described as a *Dynamical System*, allowing the application of the *Maximum Principle of Pontryagin* from control theory, according to which the control is applied in the extreme points. The only extremes in our model solution are the centres of the obtained curves, and therefore they define the optimal periods of use for the considered types of wires. However, the steepness of the slope gives a possibility for about a week of time variation.

An important inferral from the obtained dynamics is that the heat-activated wires *NiTi Heat* have longer time of seven weeks to reach the maximum release velocity point, while for the austenitic *NiTi* wires and the *CuNiTi Heat* wires this time is **one week shorter**. On the other hand the slope is steeper for the austenitic *NiTi* wires following by *NiTi Heat* wires and the *CuNiTi Heat* wires.

The dynamics results for the first two: NiTi and *NiTi Heat* types of wires show similar behavior: After the first six/seven weeks of use, the *NC* significantly decreases. In contrast, the dynamics of *CuNiTi Heat* wires follow different behavior- during the examined period the *NC* either stays steady or increases. The explanation of the result is that the Nickel-free compound decays faster than the Nickel-potent compound ($k > 0$ in rate equation for $d/_{dt}[S(t)]$) and therefore the relative *NC* increases in time. This result is connected to the fact that the incorporation of copper into nickel-titanium alloys has led to the increased system complexity.

Discussion

It has been shown that the mean values of NC do not change significantly as a function of the duration of treatment, which confirms and extends the results of the study of T. Eliades et al. [7]

Given the fact that the analysis has been performed on a group level, it does not account for the patient specifics. Therefore, we explain the obtained dynamic results not as a set of recipes, but rather as a tool for assessment of the optimal period of treatment, aiming to improve patient's life quality and the quality of dental services. The main problem, not solved explicitly in the present study, is related to the *NC* safety threshold. It may depend on many factors as age, sex, duration of absorption, etc. Therefore, it is patient-specific and case-specific, which makes the prediction of the optimal period of use of a *Ni* contained orthodontic wire on the individual level, an *ill-posed* problem.

Another limitation is that the *NR* dynamics may depend on many factors affecting metal corrosion. For example, the level of alloy's defects during the production process [7] as well as many environmental, climate, urbanisation and cultural factors [1], [9] can accelerate the corrosion.

Previous research results on the increase of nickel concentration in the saliva comparing stages before and after placement of *Ni-Ti* arch-wires and bands showed that immediately after placement of the bands and brackets, the median nickel concentration increases in statistical significance. [8] In the four- and eight-week's measurements, after the placement the *Ni* concentrations differed no longer statistically from those before placement of the arch-wires. Our study confirms the results published in [8], with decreasing *NC* in *Ni-Ti* arch-wires and increasing in the saliva. Even after four weeks when nickel ion levels drop to their original levels, the Nickel ions in the saliva are still present.

Unfortunately, the present study leaves the consideration of all these factors in the orthodontist's hands. The experienced orthodontist is the only person who can decide how to stretch or shrink the dynamic models to different time intervals, considering the specific influence of the above-listed factors. Following the obtained results, one may extend the created methodology framework for studying dynamic mechanisms behind the safe use of orthodontic materials. Firstly, it is important to make the right diagnosis and to know all the symptoms of nickel allergy. In hypersensitive patients, it is better to avoid the general use of *Ni*-containing arch-wires. Alternatives include twist-flex stainless steel, TMA, ion-implanted with nitrogen *Ni-Ti*, Timolium arch-wires, etc.

A major outcome of all of *NR* was that the transport and distribution of nickel in the body depends on the site of absorption, the rate, and concentration of nickel exposure, the solubility of the nickel compound, and the physiological status of the body. The nickel ion can also bind with body proteins to form a nickel-rich metalloproteinase. After all, still it is not possible to predict how much nickel ions the body will absorb and whether it will have a long-term effect on health.

This study at the present stage was not intended as a clinical trial but as a “proof of principle” on applying quantitative dynamics to the processes related to *NR* hypothesis. Its feasibility warns further prospective investigation and clinical validation.

Last but not least, our work concerns primarily the quantification of *Ni* release and was intended to assess how and to what extent it would affect human condition and health. This last question is still difficult to address, as no systematic data are available.

Conclusions

As the main result of this study, we consider the obtained model of *NR* dynamics during the use of the investigated three types of orthodontic wires. The novelty in the approach is based on the simple idea to account for the differences in the lengths of the intraoral use. In addition to the main result, the present study has three essential contributions to the methodology of *NR* analysis. The **first contribution** is the announcement of the *LM* as an important *NC* measure. The use of *LM* is motivated by the hypothesis that local absorption of *Ni* in the tissue (*LM*) is the relevant clinical factor for the potential side effects rather than the overall *Ni* release (*GM*). As a **second contribution**, we consider the way of interpolation of statistical results to obtain an *NR* dynamics approximation and the proof of our core hypothesis that *the NC change during the period of use of orthodontic wires might follow the same common pattern/model, with different parameters, for different types of wires*. The **third contribution** is the model itself and the parameters’ reconstruction for the considered type of wires.

The established methodological framework can be expanded to study the dynamic mechanisms responsible for the safe use of orthodontic materials.

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