REVIEW PAPER

# THE EFFECTS OF DIFFERENT DRUGS WITH ANTI-INFLAMATORY POTENTIAL IN PREVENTION OF PULP DAMAGE DURING THE TEETH BLEACHING

Miona Glisic[1], Andjela Milojevic[1], Milica Milinkovic[2] and Marina Rankovic[3]

[1]*Department of Dentistry, Faculty of Medical Sciences, University of Kragujevac*
[2]*Department of Physiology, Faculty of Medical Sciences, University of Kragujevac*
[3]*Department of Pharmacy, Faculty of Medical Sciences, University of Kragujevac*

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**Corresponding author:**

**Miona Glisic**

Institute for Cardiovascular Diseases Dedinje, Serbia

Phone: +381 63 75-818-75
E-mail: mionagrujovic@yahoo.com

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## ABSTRACT

*This paper aims to collect all the necessary information and conclusions which deal with the anti-inflammatory drugs within the scope of teeth bleaching, and which are rooted in scientific research. It is a well-known fact that the teeth whiteners / bleachers are at the same time a very aggressive agents, which opened up the question of the safety of their application. The most frequently applied bleaching agents are the hydrogen-peroxide ($H_2O_2$) and carbim peroxide ($CH_6N_2O_3$), therefore this paper will be based on the research which included these two agents. The first studies were directed towards investigating the outcome / impact on the enamel, i.e. if there is direct surface damage of the enamel layer after the use of such agents. However, bearing in mind that the clinical practice has shown that in a number of cases there arises the sensitivity of teeth in the form of painful sensation after the bleaching treatment, some researches were directed towards the estimation of the permeability of the enamel and dentin for the bleaching agent, and later the effect on the pulp tissue. Along with the existing proof about the irritability of these agents to the pulp tissue, the modern research have the idea of looking into the effects of the anti-inflamatory drugs as the accompanying and prevention therapy of any of the irreversible damage of the pulp. On one hand the application of these drugs can reduce the sensitivity and painfulness of the teeth, which makes the intervention pleasant for the patient, but on the other hand the intervention becomes completely justifiable from the aspect of safety and the basic principle primum non nocere. The anti-inflammatory drugs which will be the topic of this study are H hydrocortisone, acetaminophen, ipobruphen and etodolac. Taking into consideration the vasoconstrictive and anti-oxidative effect, the anti-inflammatory effect of the carvedilol will be looked into, which belongs to the group of beta blockers. Based on available informations it can be noticed that the most efficient anti-inflammatory effect in teeth whitening is achived by hydrocortisone.*

***Keywords***: *Teeth bleaching, anti-inflammatory drugs, the pulp inflammation, hydrogen-peroxide.*

## INTRODUCTION

The demand for the aesthetic procedures has increased in the modern dentistry. Teeth bleaching has taken a place of one of the most commonly requested aesthetic interventions in the dentistry. It is a well -known that bleaching can be carried out in strictly controlled conditions , by applying the highly concentrated agents for whitening, or by applying agents with low concentration over a period of few days (1-8). The third option for teeth bleaching, which is based on the use of the commercial, untestified agents and mechanisms was discarded by all the dentist specialists and is strongly advised against (9-11).

Although teeth bleaching is considered to be a conservative technique connected with the simple application and highly effective performances, there is concern about the biological safety of the procedure. Based on the unselective effect of the highly concentrated peroxide products this attitude of precaution is justified. The studies have proven that the hydrogen-peroxide diffusion through the teeth tissue can cause the damage to the pulp and greater post-operational sensitivity. Although the success of the teeth whitening treatement is in the direct connection with the diffusing capacity of the peroxide through the enamel and dentine, it is believed that a more intensive penetration entails a bigger risk and the danger of the arise of the undesired effects (12-14).

It has been proven on the rats species that the concentration of $H_2O_2$ influences the effects which will manifest themselves on the pulp tissue, in such a way that the higher concentration of $H_2O_2$ can cause the pulp necrosis and / or lead to the apoptyc processes. On the other hand the lower concentrations of $H_2O_2$ cause the medium inflammation of the pulp tissue, the cell polipheration and to a smaller extent the apopotasis of the cell elements with the tendency of these processes reducing over time (15). Thus, teeth whitening / bleaching should be couterindicated in all the clinical cases in which there is a direct exposure of the dentine or any other change in the build of the enamel tissue and which is potentially connected with the pulp permeability (16-17).

As can be noticed from the previously stated the teeth sensitivity can be expected as a rule after the treatment with the highly concentrated agents for teeth bleaching. As the teeth sensitivity can vary, i.e. as the level of inflammation of the pulp tissue can vary from very weak to highly evident, it makes sense to take into consideration the options of the accompanying anti-inflammatory therapy which aims at preventing of the abovementioned inflammation processes. Simultaneously with the easing of the symptoms which are unpleasant for the patient, these drugs will act as a protection to the pulp tissue, preventing extensive inflammatory processes (pulpitises) which can lead to the necrosis of the pulp tissues (18-19).

Modern scientific-research works deal with the estimation of the efficiency of the hydrocortisone and acetamynophene on the animal models, on the rats. The main problem which is a part of these studies is the subjective character of pain as a symptom, thus the impossibility of the precise marking and following. The problem stems from experiencing differently the pain sensation, where every individual has his / her specific kind of perception and interpretation of the pain impulse. Thus the visual-analogue scale (VAS) is not sufficiently precise. Scientists have come up with the solution of this problem by measuring and following the level of specific protein molecules which are released during the inflammatory process and are in the direct connection with the promotion of the pain sensation. These are the substance P and the calcitonin related peptide (*CGRP - calcitonin gene-related peptide) (20-21).*

The aim of this paper is to establish which anti-inflammatory drug or a combination of drugs can show the best effect on the inflammatory pulp after the teeth whitening treatment by reviewing the existing data in scientific papers.

## THE TEETH BLEACHING EFFECTS AND THE BIOLOGICAL RESPONSE OF THE PULP

The hydrogen-peroxide ($H_2O_2$), the active ingredient of the teeth whitening / bleaching agent, reacts with the teeth enamel in the contact dots and produces oxygen ( in the form of the free radicals) and water. The teeth bleaching effect can be achieved by the oxidative reactions of the organic structures , with the help of the molecules from the group of the reactive oxygen species. The use of the $H_2O_2$ in high concentrations (25-40%) lead to the more effective teeth whitening (22).

We should point out that higher concentrations and the time of application, i.e the exposure of the teeth to the hydrogen-peroxide ar in proportion to the greater ROS, as are superoxidic anyons ($O_2^-$), hydroxyl radicals ($^-OH$) and $O_2$ and $H_2O_2$. Due to the small molecular weight of the free radicals, as well as the porose nature and permeability of the enamel, the free radicals enter dentine and through the dentine tubuli reach the pulp tissue of the tooth. ROS induces the oxidative stress, which is dependent by the time and concentration because the endogens and exogenes tend to inhibit the effect of the ROS. The oxidative stress is capable of causing the mutation and inactivity of the enzyme, the protein fragmentation and the degradation of the pulp cells (23).

As the response to all these stimuli, the defence cells in the pulp tissue contribute to the release of the inflammatory mediators, which results in the short-term teeth sensitivity which can be perceived as acute pain at arousal. The pulp cell damage caused by the penetration of the hydrogen-peroxide induces the synthesis and release of the biochemical mediators of the inflammation, such as postagladines, hystamine and bradikinine, which are included in this process. These intermediaries cause the vasodilatation and the growth in the vascular permeability of the pulp calve. As the pulp tissue is

located in the pulp chamber , i.e. strictly defined space, any state which is accompanied by the edema causes the rise in the intra-pulp pressure (24-26). The rise of the pressure makes additional burden and the reaction on the nociceptors which at the slightest stimulation generate painful impulses and then transmit it through the nerval fibres to the zones of the brain when we become aware of the painful sensation. The intrapulpic pressure stimulates mechanically the peripheral neural fibres which react by producing and releasing the peptidic neuro transmitters, including the P substance and the calcitonine similar to peptide (CGRP). These neuropeptides arouse the birth and conduction of the painful impulses, by which the emission of the pain signal is promoted from the area of the damaged tissue (27). This is the cause of the frequent informing about the unease and pains with the patients which undergo the bleaching treatment. However, an important problem arises when this inflammatory state is prolonged, and the inflammatory response gets stronger and becomes autodestructive. To be precisem the inflammatory response as a defence reaction, if comprehensive, becomes a local damage, i.e. on the spot / area where all the aggregated proinflammatory factors operate. In this case, the reversible state of the inflammated pulp, will progregate into a more complicated form of the pus (purulent) or the necrosis will be developed when we talk about the irreversible diseases of the pulp tissue (28).

The characteristic of the pulp pathology which arises due to the teeth whitening means that there are no microorganisms, but the ethiology is of the physical-chemical nature. Therefore, the complete inflammatory process is activated by the physical-chemical factors, making sterile characteristics of the inflammation. The pulp necrosis caused in this way is the state of dying cell elements of the pulp due to the ichemy, and should be differentiatd from the pup gangrene which is dominantely accompanied by the direct toxic and necrotic effect of the microorganism. It follows from this that anti-inflammatory therapy is completely sufficient and even causal in this case.That is, by stopping the inflammation, the whole cascade of unwanted events which can potentially be caused by the teeth bleaching (20-21).

## PERIOPERATIVE APPLICATION OF THE ANTI-INFLAMMATRY DRUGS IN PREVENTION OF THE PULP DAMAGE DURING THE TEETH BLEACHING

As can be clearly seen from the above mentioned there is a clear justifyability of finding the adequate way of preventing the inflammation of the pulpe tissue within the teeth whitening treatment. As the clinical practice shows the systematic and locally applicable drugs are used in order to reduce the clinical effect of the pro-inflammatory mediators. The locally applied agents can go under one mutual name as the de-sensibilization agents and can be used prior to or after the whitening / bleaching treatment. The effect of the agents for the desensibilization can be directed towards the sealing of the dentine tubuli and preventing the penetration towards the pulp (physical effect) and / or by blocking the neural stimulus (the chemical effect). The anti-inflammatory drugs applied systematically can reduce the inflammatory response of the complete organism, and also the pulpe tissue (29-30).

The drugs which are included in this research are the drugs from the corticosteoryd, non-steoryd and anti-inflammatory group of drugs as well as beta-blockers. The corticosteroid which is applicable is the hydrocortisone, whereas the Ibuprofen is one of the drug from the NSAID group and acetaminophen (paracetamol) belongs to a class of drugs called analgesics (pain relievers) and antipyretics (fever reducers), and the applicable beta-blocker is carvedilol. There is also a difference in the application way, where the hydrocortisone and carvedol are applied locally, whereas NSAID is applied systmematically. Although the effects of the hydrocortisone are more potent if they are applied systematically, due to the potential unwanted reactios such way of application is not justified within the scope of teeth sensitivity when it comes to the whitening (29-31). Carvedilol was applied in the form of gel by which teeth are covered after the bleaching treatment (32-35)

The effect mechanism depends on type and group to which the drug belongs. Corticosteroids and glycocorticoids represent the group of drugs which possess extremey potent anti-inflammatory effect, and are chemically extremely liposoluble drugs, which as such can unhindered penetrate to the cell membrane and reach the cytoplasmosis, and even penetrate the cell nucleus. The mechanism of the anti-inflammatory effect can primarily be noticed in the inhibition of the degranulation of the mastocite and the reduction of the hystamine release and other pre-formed inflammatory mediators (36). They also stimulate the gene`s transcription to the anexine (lipocortine), the protein which inhibits the phospholipoic activity. The increased lypocortine leads to a greater inhibition of the phospholiopasis A, thus the smaller quantities of the phospholipde will be metabolized. Therefore smaller quantities of the archahydonic acids arise, which in turn is the substrate for the effect of the cyclooxigenesis (COX), from which reaction there arise prostaglandins and leukonutrients (37). The third effect on the factors of the early inflammation is reflected in the stabilization of the lisososome membranes, and making more difficult the release of theof vasoactive quinines and destructive enzymes (38).

The anti-inflammatory effect of NSAID is directed towards the inhibition of COX enzyme and the blockage of the sequence of the cascade of reactions which would result in the inflammatory factors (39). In particular, NSAID unselectively inhibits COX-1 and COX-2 and thus form postglandine and thromboxane from the arachidonic acid. Within the intreleukine group IL 6 especially stands out as the most potent proinflammatory molecule. At the same time IL 6 has the capability of interreacting with the talamus and raising the body temperature (40-41). Carvedilol is primarily a beta blocker (β1, β2), i.e. bocks the the bonding of these receptors , which slows down the heart rate and reduces the force by which the heart pumps the blood. In that way it also reduces the blood pressure. Carvedilol was applied because of its

effect of constriction which it causes on the small blood vessels, with the idea to prevent the excudation and subsequent edema the rise in the blood pressure (42).

In following parts of the text the anti-inflamatory effect of the most frequently used agents will be further discussed. Summary of their effect are presented in Table 1.

**Table 1.** Summary of the anti-inflamatory effect of different NSAID during the bleaching

| Medicament | Effect | Reference |
|---|---|---|
| Hydrocortisone (Otosporin®) | The prevention of the occurrence of the necrosis in the top of the pulp and the reduction of the inflammation of the pulp tissue. | Gallinari et al. 2019. |
| | The penetration through the dentine to the pulp tissue and the achievement of the anti-inflammatory effect. | Benneti et al. 2018. |
| Acetaminofen (Paracetamol®) | Expression of the neuropeptides and the control of the teeth sensitivity (COX-3 inhibition). | Gallinari et al. 2019. |
| Acetaminogen + codein | The prevention of the teeth sensitivity. | Oliveira 2018. |
| Ibuprofen | The prevention of the immediate sensitivity of the teeth. | Charakorn et al. 2009. |
| | The prevention of the sensitivity 1 hour after the application. | Paule 2013 i<br>Gessica de Souza 2014. |
| | The regression of the inflammatory process during the first 24h from the teeth whitening treatment. | Silva et al. 2020. |
| Carvedilol | The reduction of the pulp inflammation. | Louzada et al. 2019. |
| Etodolac | The inflammation control. The achievement of the analgetic effect in the repeated dosages. | Vaez et al. 2018. |
| | The inhibition of the effect of the bradiquinine. | Inoue et al. 1994. |

## HYDROCORTISONE

There has been a recent research which dealt with the estimation of the effectiveness of the metamisole-sodium has not discovered any reduction of sensitivity of teeth which was the result of the dentistry office bleaching (43). However, Otosporin® is a drug with different anti-inflamatory effect due to the powerful penetrating power which leads to the conclusion that the effect should be better and faster. This drug consists of the combinationt of the antibiotic polymixine B sulphate and neomycin sulphate and hydrocortisone, which have an anti-inflammatory, immune-suppressive and vosonstconstrictive properties. It is used in different endodontic procedures with predictions that it is local use can minimize the damage caused by teeth whitening. The corticosteroid effect of Otosporin® is what makes this drug stand out to be used as the inflammatory agent for the inflammation of the inflammation of the pupl tissue (44- 49).

It has been shown that hydrocortisone has the ability of penetrating into the dentine and to reduce the sensitivitu of teeth after the preparation of the deep cavities. In terms of enamel the micro cracks present in its surfaces can also be beneficial to the penetration of Otostoporin through this tissue and the access of the drug to the pulp-dentine complex. Penetration of this drug can be increased after the use of the $H_2O_2$, due the porosity of the enamel. The greater access is undoubtedly followed by the more potent effect (46-48).

The study which was carried out *in vivo* on the animal model estimated the efficiency of the hydrocortisone. During the whitening, as during the time of the application of Otosporin, the parodontal tissues were protected with the gingiva-protector, resinous barrier, which prevents the absorbtion of the drug by the paradoncium. Hydrocortisone is a drug for which it was expected to reduce the inflammatory inphiltrate and promote the vasoconstriction of the inflammatory area, by reducing edema and unease and by stabilizings the nervous cell membranes. Taking into consideration this study, it can be concluded that the results achieved in the group which is treated by otosporin showed the efficiency of this drug with the reduction of the inflammation. There has been noticed a great difference in the group treated by

otosporin where the areas of necroses are much smaller or do not occur (49).

A special attention was directed towards the fact that the recuperation of the pulp tissue of the experimental model happens much faster and stronger than with people. However, it is noticeable that this experimental model can imitate the conditions of the human pulp tissue, with the existence of all the cells as well as the pressure in this tissue (20-21).

The another study dealt with the histological analysis, and has shown that the inflammation of the pulp tissue, occlusive and medium thirds was to a great extent bigger in the group treated by the whitener only as compared with the group which apart from the whitener was treated also by otosporine. On the other hand differences have not been noticed when it comes to the extent of inflammation of the cervical third (48).

## ACETAMINOPHEN (PARACETAMOL)

Paracetamol was implemented per os due to its slight side effects to the experimental models. As the drug was systematically distributed the inividual differences in the thickness, structure and permeability of the enamel are irrelevant and more uniform results are expected. The effects of the paracetamol drug were the strongest concerning the expression of the neuropeptide, thanks to its prevailing analgetic effect, i.e. the inhibition COX-3. The indirect effect of this drug in controlling the production and release of these neuropeptides as well as the pro-inflammatory factors was the result of the reduced inflammatory response. It has been noted that after teeth whitening there has been the development of the necroses in the top part of the pulp both in the control (placebo) as well as in the group treated with paracetamol. The observations after 24h and 48h show that the disorganization of the cell elements in all groups, with the tendency of inflammation calming after 24h. It has been noted that the coronary and medium third of the pulp becomes inflammated from the medium to the very high level whereas the cervical third becomes weak or remains uninflammated (20-21). These results are explained by the distance of the pulp of this teeth segment from the area where the teeth bleaching agent was applied, i.e. the incapability of the bleaching agent to penetrate to this pulp segment and to cause changes. (50-51)

A special research investigated the efficiency of the paracetamol in the combination with the codien. Codein is a drug from the opioid group, i.e. the member of the group of narcotic analgetics. Obtained the results indicated high efficiency of this drug combination in preventing the immediate sensitivity of teeth after their whitening (46). The caution and additional research are recommended in order to establish if the prevention of sensitivity was caused by anti-inflammatory effect or the analgetic effect of both these drugs. The very analgesis is the palliative solution of the state, i.e. it covers up the inflammation which as a fact exists in the pulp tissue.

The opposing results are provided by the study carried out by Coppla et al. They stated that the use of the combination acetaminofen – codein before teeth whitening at the dentistry office does not reduce the risk and the intensity of the teeth caused by whitening (46). As the measurement methodology of the painful sensation was based on the quantitative scale, from 1 to 10, it is possible that the subjectivity of the pain led to the opposing results.

## IBUPROFEN

Ibuprofen was also applied *per os*, immediately before the treatment of whitening. The study which was carried out by Charakorn P. et al. suggested undoubted efficiency of ipobruphen in reducing the painful sensations and teeth sensitivity immediately after the bleaching. On the other hand the efficiency of ibuprophena drops in time and the sensitivity of the teeth can be established again after 1 hour of the treatment and remains the same or similar up to 24 hours after the treatment (47). Such result pointed out benefit of the isolated analgetic effect, without the sufficient effect on the prevention of the pulp tissue inflammation, i.e. without causal effect in the problem of the teeth sensitivity. The other two studies testify the reduction of the sensitivity of the teeth dentine one hour after the application of the Ibuprofen (48-52). The study included a few anti-inflammatory drugs but from all the tested ones, only Ibuprofen shows the positive impact in the reduction of the dentine sensitivity. It is necessary to obtain more studies in order to suggest a method or drugs which could efficiently reduce the oversensitivity of the dentine which is connected to the teeth bleaching (48-54).

The hystological analysis by Gallinari et al. showed that the use of Ibuprofena with the aim of preventing the teeth sensitivity after teeth whitening is much more efficient if the drug is applied systematically rather than locally. The conclusion has been drawn from the observation that Ibuprofen is more efficient on the systematic level than on the local level (5). In groups which underwent teeth whitening / bleaching with the treatment by Ibuprofen, the inflammatory process and the expression of the neuropeptides were reduced over time. The results emphasized fact that the use of Ibuprofena leads to the regression of the inflammatory process during the first 24h after the teeth whitening / bleaching treatment. Also, the use of agents for desensibilation showed the positive effects on calming the inflammation and the expression of the neuropeptides connected to pain, the reduction of the painful effects of the teeth whitening / bleaching treatment (55).

The results of research conducted by Charakorn et al. and Silva et al. say the opposite, that is, the first study refutes the anti-inflammatory effect of Ibuprofen while Silva et al. emphasize the high efficacy of Ibuprofen and advocate for additional trials and introduction into regular use in clinical practice (50-55).

## CARVEDILOL

Carvedilol was applied locally in the form of gel, with the idea to show the effects of vasoconstriction and as a result prevent the pulp edema and the increase in the pulp pressure. Additionally, carvedilol is an antioxidant agent, thus the effects in the prevention of the free radicals were also observed (56).

The study on the rat model showed impressive results which vouch for the efficiency of the carvedilol in the intended indication. 48 hours after teeth bleaching the group underwent just teeth whitening experienced necrosis in the occusal third of the coronary pulp, whereas the group which additionally received carvedilol had a very high inflammation marked without the existence of the necrosis of the pulp tissue. In the medium third of the pulp, the whitened group showed very high inflammation, and the group which used carvedilol after teeth whitening possessed a moderate inflammation. In the cervical third the trend continues, i.e. the whitened, group showed medium inflammation, whereas the group in which carvedilol was applied had a mild inflammation. Therefore it can be concluded that carvedilol gel has a potential to minimize the damage of the hydrogen-peroxide, especially in the deep parts of the teeth pulp of rats after the bleaching (47).

## ETODOLAC

In the research which was carried out by Vaez et al. etodolac was applied systematically in the form of the capsule, immediately before the teeth whitening treatment (57-58). The previous study had shown that etodolac possess a greater efficiency of inhibiting the effect of bradicanine from other drugs in its group, which are usually used for the control of the inflammatory process (43). In terms of pharmocynetics, etodolac reaches the maximum concentration in the plasma about 1 to 2 hours after the application. Thus it was expected that during the procedure of teeth bleaqching the maximum concentration in the plasma will be achieved. Unfortunately, the analgetic effect of the preventive application of etodolac on the reported teeth sensitivity. Despite the proven efficiency in the inflammation control, the analgetic effect of etodolac can be increased only when its application is repeated, whereas it seems that one dosage before the whitening treatment is not enough to prevent the teeth sensitivity (57-59).

The preventive application of the etodolac has not influenced the risk of teeth sensitivity undependently of the estimation and the use of the scale were. The order of treatments did not have any impact on the teeth whitening, whereas the other session resulted in the additional modification of the colour. The preventive application of etodolac in one dosage hour before the teeth whitening did not change the colour of the teeth and the risk and intensity of the teeth sensitivity which were reported by the patients (60).

## CONCLUSIONS

The teeth bleaching represents the aesthetic intervention which is accompanied by a high risk from the undesired reactions. The teeth whitening in the dentistry office is almost always followed by the pulp tissue inflammation, and not infrequently by the pulp necrosis in the most coronary segment (the top part of the pulp). However, the most researches of the effect of the anti-inflammatory therapy in preventing the teeth sensitivity is followed as a part of the dentistry office teeth bleaching.

According to literature data presented in this review it seems that the teeth whitening in the dentistry office must be accompanied by some sort of the anti-inflammatory therapy and agents for the desensibilization, although the results are not convincing. In certain extent these drugs contribute to the reduction of the inflammation which is necessary part of this highly aggressive treatment. Based on avaliable informations it can be noticed that the most efficient anti-inflammatory effect in teeth whitening is achieved by hydrocortisone.

If the future researches refute the efficiency or contraindicate the use of the anti-inflammatory therapy, the teeth whitening in the dentistry office must be revised towards the reduction of the concentration of the agents for whitening or the possible application of the agents which is safer.

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