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Review Article

DENTAL USE OF KETOROLAC TROMETHAMINE: STATUS AND FUTURE PERSPECTIVES

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ABSTRACT

The history of evidence-based use of non-steroidal anti-inflammatory drugs (NSAIDs) goes back at least two hundred and fifty years. Over the past period, the path has been passed from the use of willow bark decoctions to the synthesis and introduction of selective cyclooxygenase inhibitors into clinical practice. To date, the research direction has shifted from the search for new substances to the search for new routes of administration. The wide range of existing drug substances, however, has only in a few dosage forms. Thus, ketorolac tromethamine is known only as a solution for parenteral and intranasal administration, as well as oral tablets. This drug belongs to NSAIDs, particularly non-selective cyclooxygenase inhibitors, and shows a pronounced analgesic activity. Due to this property, ketorolac can serve as an alternative to opioid analgesics or can reduce the dosage of the latter when used in combination. However, a number of systemic side effects (ulcerogenic properties, negative effect on the blood), unfortunately, impose their limitations. A possible solution to this situation may be the creation of local delivery systems, in particular, *in situ* implants. This review highlights the problem of developing local systems for the delivery of ketorolac tromethamine for the relief of acute pain. Special attention is paid to *in situ* implants based on bioadhesive polymers.

Keywords: Nonsteroidal anti-inflammatory drug, Dentistry, *In situ* implant, Postoperative analgesia, Ketorolac

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INTRODUCTION

Oral cavity diseases are among the most acute healthcare problems of the present time. It is known that 3.5 billion people worldwide suffer from caries, severe periodontal disease, and partial or complete loss of teeth [1].

Often, a toothache is associated with significant discomfort when eating as well as when performing hygiene procedures. In this regard, the idea of relieving the patient's condition by using drugs encourages researchers to return to this problem repeatedly.

It is generally accepted that the first successful public outpatient operation using ether anesthesia in European history was performed on October 16, 1846 [2]. However, the presence of serious side effects and the complexity of the procedure prompted researchers to look for other substances that relieve pain. In addition to local anesthesia, the idea of scientifically based use of opioids was being developed.

At the same time, anti-inflammatory drugs were studied. Thus, according to Pao and Knaus [3], the medicinal substances of this group have experienced development from extracts of plant raw materials (cinchona tree, willow) to synthesized selective cyclooxygenase (COX) inhibitors.

It is interesting to note that opioids are still used in clinical practice. According to Kakariqi *et al.* [4], opioids have become the basic treatment of moderate to severe pain in high -income countries. To date, there is no consensus on which treatment regimen (with the use of opioids or NSAIDs) is considered the most optimal. Recently, however, there have been increasing publications about a combination therapy to reduce the dose of an opioid analgesic as much as possible [5, 6].

The widespread use of NSAIDs makes them convenient objects for research and development, but it is also fraught with dangers: the introduction of a new drug to clinical practice can provoke a wave of side effects. This fate affected, for example, selective cyclooxygenase-2 (COX-2)–called "coxibs": these drugs were found to increase the risk of severe side effects [7]. This fact has actually led to a loosing of interest in selective COX-2 blockers and the complete abandonment of drugs such as valdecoxib [8] and lumiracoxib [3].

However, non-selective NSAIDs do not weaken their positions. Moreover, the ADA Delegation House [9] encourages dentists to use this group of drugs as a first-line treatment for acute pain.

The current situation arouses curiosity and encourages the search for new dosage forms of NSAIDs to reduce the frequency of adverse drug reactions.

Ketorolac tromethamine, a non–selective NSAID known for its pronounced analgesic activity comparable to that of morphine sulfate, was chosen as the object of the study. The objectives included an analysis of the safety problem of ketorolac use, as well as coverage of the problem of developing new dosage forms. Articles included in the Scopus and Web of Science databases were used as source data. Meta-analyses and randomized controlled trials were taken into account to study the safety of ketorolac use. The existing prototypes of local delivery systems were also studied. The PubMed service was the main search tool. The starting keywords were "ketorolac tromethamine", and "dental dosage forms", followed by narrowing to "dental use of ketorolac". Particular attention was paid to articles published between 2005 and 2021.

Since the issue of the safety of the use of ketorolac trometamine was well studied earlier, the authors of this study could be guided by sources of a high degree of reliability: meta-analyses and review articles. However, as the field of study narrowed from general to particular, the number of publications also fell. Therefore, the review also included research articles that require discussion and greater caution in evaluating the results.

The collected and analyzed data allows to speak with a certain degree of confidence about the prospects of developing new systems for the delivery of ketorolac tromethamine, preferably local, which would help to circumvent a number of side effects.

Ketorolac safety–pros and cons

The first mention of ketorolac tromethamine dates back to the 80's of the 20th century. Thus, in 1984, it was reported about the pharmacological activity of a new analgesic (+/-)-5-benzoyl-1,2-dihydro-3h-pyrrolo [1,2a] pyrrole-1-carboxylic acid, which was not inferior to sodium naproxen and morphine sulfate [10]. Later, Gillies *et al.* [11] reported that patients who took ketorolac in the postoperative period required less morphine to relieve pain compared to the control group.

In parallel with the research on the effectiveness of the new drug and the expansion of its application areas, the safety of ketorolac was considered in detail. In almost every publication devoted to

NSAIDs, from year to year, the authors noted that drugs of this group could cause ulceration of the gastrointestinal tract [6, 12].

The mechanism of the side effects is explained by the principle of action: ketorolac and other non-selective COX inhibitors also inhibit the production of prostaglandins and thromboxanes, since they block COX-1 [13]. Lack of prostaglandins, in turn, negatively affects the resistance of the mucous membrane to the action of gastric acid and other aggressive factors. Due to the negative effect on the production of thromboxanes, it is considered that therapy with ketorolac can provoke a violation of blood clotting.

In the meantime, the data is contradictory. A meta-analysis by Phillips-Reed *et al.* [14] highlighted the intense debate among researchers about the safety of systemic use of ketorolac in pediatrics during tonsillectomy. Of the five studies reviewed, only three indicate the dangers of the drug–either for adults or for children. The remaining ones represent the full range of opinions, from recognizing ketorolac as safe to call for additional study of this issue.

However, the overall picture is even more complicated. Maslin *et al.* [15] concluded that the relationship between the systemic use of ketorolac and the occurrence of postoperative bleeding could not be identified. The authors recognize the importance of threatening side effects reports during a tonsillectomy, but when analyzing data on other operations in patients with healthy kidneys and liver, the differences are decreasing. The idea of using ketorolac as an opioid-saving agent in the treatment of vulnerable groups of patients is suggested. Gobble *et al*. [16], based on the results of a meta-analysis of 27 studies, concludes that postoperative bleeding is not associated with ketorolac trometamine. It is important to note that the results of this study show that the analgesic activity of ketorolac tromethamine either exceeded or was comparable to that of opioids. The authors also recommend ketorolac trometamine for postoperative pain control.

Currently, ketorolac tromethamine is used only in the form of solutions for parenteral or intranasal administration, as well as in the form of oral tablets. Toothache is pronounced and has a local character, which suggests the idea of creating a dosage form for topical use. This route of administration may avoid the occurrence of systemic side effects since the absorption into the bloodstream will be minimal.

Ketorolac in dentistry

The pronounced pharmacological activity of ketorolac makes this drug very attractive for use in dental practice. The idea of fast and powerful analgesia encourages experiments with different routes of administration, combinations of formulations, as well as the creation of novel dosage forms.

Currently, a solution for intramuscular, subcutaneous, and intravenous administration, oral tablets, and intranasal spray are used in clinical practice [17].

Ketorolac has been shown to be effective: discussions are more likely about the severity of its action or effect in combination compared to betamethasone [18], dexamethasone [19, 20] and prednisolone [21]. The data indicate the advantage of glucocorticoids or a slight difference in the effect, as shown in table 1.

Table 1: Comparison of therapeutic effect of glucocorticoids and ketorolac trometamine: dental practice

Type of study	Treatment	Comparison objects	Conclusions	Reference
Double-blind, randomized controlled trial (n=30*)	Implantation	Ketorolac trometamine+ Amoxicillin Ketorolac trometamine+ Amoxicillin+ Betamethasone	There is no difference between ketorolac and betamethasone in combination with ketorolac	Meta *et al.* [18]
Triple-blind randomized controlled trial (n=50)	Mandibular third molar removal	Dexamethasone Ketorolac trometamine	The clinical performance of dexamethasone is superior to ketorolac trometamine	Martins-de-Barros *et al.* [19]
Randomized controlled trial (n=42)	Single-visit root canal treatment	Saline Sodium hypochlorite Ketorolac trometamine Dexamethasone	Dexamethasone irrigation is more effective in controlling post-operative pain.	Evangelin *et al.* [20]
Double-blind, randomized controlled trial (n=92)	Single-visit root canal treatment	Ketorolac Prednisolone Placebo	Single treatment dose of prednisolone has a more sustained effect compared with placebo or ketorolac	Praveen *et al.* [21]

*One patient was excluded from control group

It should be noted that steroid drugs are also not devoid of a whole complex of serious side effects. Their improper use can significantly affect the health of the patient, and therefore the dosages are usually selected individually. In this regard, it is reasonable to assume that, when choosing between NSAIDs and glucocorticoids, attention should be paid not only to the actual therapeutic effect but also to the adverse effects.

However, narcotic analgesics are also considered as an alternative. A randomized comparative study of the use of ketorolac and tramadol in the treatment of patients with maxillofacial injuries revealed the benefits of the latter: analgesic activity with intravenous administration is observed longer [22]. On the other hand, the difference in the severity of analgesia is close to insignificant in operations for the removal of the third molar [23]. It is important to note that in the study mentioned above ketorolac was used orally.

The complex picture of the clinical effects of both the first and second groups explains the fierce "competition" between opioids and NSAIDs. Morphine derivatives are characterized by the ability to cause addiction and drug dependence, a number of them have a powerful depressing effect on the respiratory center. At the same time, cyclooxygenase inhibitors, especially non-selective ones, provoke ulceration of the stomach and duodenum, which can lead to internal bleeding. This issue still is not resolved [5, 6].

The Hersh *et al.* [6] revealed a curious and disturbing picture. The authors express concern about the widespread use of opioids for the relief of toothache and show alarming statistics on the abuse of drugs in this group by high school students.

One solution to this problem may be a combination of local anesthetics and NSAIDs, as well as the creation of a different dosage form that would not affect the gastrointestinal tract directly. This idea is supported by data from clinical studies [24-26], as well as reviews [27, 28], indicating the potential benefits of using ketorolac and the like during the alveolar nerve block (table 2).

At the same time, there are also nuances associated with the route of administration. In one of the research that considered the possibility of buccal infiltration with ketorolac, 2 out of 26 patients in the ketorolac group experienced such severe pain after injection that they had to be removed from the experiment [25].

Table 2: NSAID*s in premedication before IANB

Authors	Type of study	Comparison objects	Results	Comments	Reference
Hungund *et al.*	Clinical study (placebo-control, randomized, double-blind)	Placebo Ketorolac	Ketorolac taken at least 30 min before local anesthesia effectively relieves operative pain during periodontal surgery	Oral premedication	[24]
Aggarwal *et al.*	Clinical study (randomized, double-blind)	Articaine Articaine+ketorolac Dexamethasone	Articaine and ketorolac infiltration can increase the success rate of anesthesia after IANB	Buccal infiltration of articaine+ketorolac	[25]
Akhlaghi *et al.*	Clinical study (randomized, double-blind, placebo-controlled)	Placebo Ketorolac	Buccal infiltration of ketorolac can increase the success rate of anesthesia after IANB	Buccal infiltration of ketorolac	[26]
Nagendrababu *et al.*	Review	NSAID Placebo	NSAIDs and ibuprofen taken orally before surgery increased the anesthetic success of IANB	Oral premedication	[27]
Sivaramakrishnan *et al.*	Review	Ketorolac Placebo or other drugs	Oral ketorolac can be successful as a premedication before IANB	Oral premedication	[28]

*IANB–inferior alveolar nerve block, **NSAID-Non-steroidal anti-inflammatory drug

In the described cases, the quality of anesthesia improved, although recent research notes that ketorolac should be used to relieve postoperative pain since the oral drug taken in advance (45 min before the intervention) did not have the desired effect during the operation [29]. On the other hand, the authors did not conduct control: all patients took ketorolac and rather compared its effectiveness in combination with a local anesthetic.

The use of an intranasal ketorolac spray was also studied. An analysis of three randomized, placebo-controlled, double-blind trials shows that the analgesic activity of this NSAID is superior to or comparable to opioids [30].

Thus, the analysis of publications showed the practical applicability of the idea of using ketorolac in dentistry. Rather, the problem is to create the most efficient delivery system for this drug.

Dental dosage forms: difficulties of development and research directions

The physiological features of the oral cavity complicate the problem of local delivery systems development [31]. Periodic meals, voluntary and involuntary movements of the tongue, constant production of saliva, and the absence of untouched zones due to make additional requirements for local dosage forms. The latter includes mucoadhesion (not too weak, but not too strong) to avoid discomfort and irritation of the mucous membrane. It is also worth mentioning the need for taste correction since unpleasant sensations can significantly reduce compliance or even encourage the patient to abandon the drug.

The described problems are solved in different ways. For example, there are several types of delayed-release systems used for the treatment of periodontal diseases: fibers, gels, microspheres, as well as strips and films [32]. Exclusively medical personnel administer them since, with severe periodontitis, access to the subgingival space with minor surgical operations or injection is required. However, with moderate and mild severity of the disease, direct application of the drug to the gum is possible. The use of local delivery systems allows to minimize system effects, in some cases to lower the dosage of the active substance. In the case of using biodegradable polymers, there is no need to a second visit to extract the matrix.

Most of the studies relate more to antibacterial therapy at present (table 3).

Table 3: Local dosage forms for dental use

Therapeutic class	Drug	Dosage form	Reference
Antiseptic	Chlorhexidine	*In situ* gel	[33]
	Silver nitrate nanoparticles	Gel	[34]
	Benzoyl peroxide	*In situ* gel	[35]
Antimicrobial drug	Ornidazole	*In situ* gel	[36]
	Metronidazole	Fiber	[37]
		Cross-linked chitosan microparticles	[38]
		Thiolated chitosan-poly (methacrylic acid) nanoparticles	[39]
	Tetracyclines	*In situ* gel	[35, 40]
		Nanocomposite film	[41]

The problem of choosing the optimal dosage form

Despite the promise of using ketorolac in dentistry, most studies are currently focused on ophthalmic dosage forms [42-44].

However, there have been previous attempts to develop local delivery systems for use orally. For example, Yang *et al.* [45] considered the possibility of creating a ketorolac tromethamine gel in combination with genpin. Carbopol was used as a base and bioadhesive component. Even though the permeability was measured *in vitro*, the authors tried to approach the physiological conditions and used freshly obtained mouse skin. The regenerative properties of the pharmaceutical composition were studied by evaluating the strength of the skin samples treated with experimental formulations after three days of treatment. Clinical trials were conducted with the participation of female volunteers aged 28 to 59 y to study the degree of reduction in the periodontal pocket depth. All of the patients had gingival bleeding, as well as gingival redness and gingival swelling. The number of volunteers is unknown. The authors report that double-blindness was used, and a placebo was used for control.

The results showed that the combination of "ketorolac-genpin" significantly reduces the periodontal pocket depth, increases the strength of the epithelium, and can be considered as an effective treatment for gingivitis.

Alsarra *et al.* [46] described a mucoadhesive film with ketorolac based on hydroxypropylmethylcellulose and carbopol 934. The physical and mechanical properties of the samples, as well as the ability to swell and bioadhesion *in vitro*, were studied. *In vitro*, *in situ*, and *in vivo* releases were also evaluated. Preclinical studies showed the anti-inflammatory and analgesic activity of the film. During the clinical studies, it was no

reports about side effects affecting the gastrointestinal tract. Data were obtained indicating that the maximum concentration of ketorolac (130.6±22.2 μg/ml) was reached in 1.5 h.

The authors suggested that the developed dosage form can be used as an effective local analgesic after dental surgery.

Admittedly, the existing approaches to drug relief of pain have a number of disadvantages. Therefore, solutions for rinsing do not have the proper effect (strength and duration) due to short contact with the damaged mucous membrane. The disadvantages of injecting can be attributed to the pronounced painfulness of the procedure, the necessity of the involvement of medical personnel as well as low compliance. In this regard, the use of oral NSAIDs is still the solution, despite the risk of systemic side effects [6]. In turn, the polymer film as well as fibers, can be inconvenient to use. It should also be noted that difficulties arise when introducing the active substance into the dosage form, as well as restrictions in the amount of the actuve substance to be loaded.

The solution to the described problem may be the development of *in situ* delivery systems, in particular, *in situ* implants. This dosage form is a rigid elastic system that is formed directly in contact with the tissues because of a phase transition in response to changes in environmental factors [47]. The basis of the implant is generally a polymer matrix containing an active pharmaceutical ingredient that can be gradually released during the biodegradation of the polymer *in vivo* [48]. A characteristic and important feature of this system is its high mucoadhesive ability, which prevents premature evacuation of the implant from the application site. In addition, the formation of the gel causes the protection of the damaged mucous membrane from mechanical influences [49]. The advantages of this delivery system include a prolonged stay at the application site and a modified release, determined by the properties and composition of the gel-forming polymers [47]. Thus, having the advantages of classical methods of treatment, like using soaked tampons, *in situ* implantation, can increase bioavailability and patient compliance.

Currently, *in situ* implants have been developed and described for various routes of administration, both parenteral and non-invasive. Barbara Vigani *et al.* [47] provided information on *in situ* delivery systems developed over the past ten years. Of particular interest are buccal systems for treating diseases such as oral mucositis and periodontitis. Among their advantages, the authors referred to the provision of a stable and, importantly, long-term release of the active substance due to the increased time spent at the application site.

Polymers for *in situ* delivery systems can be divided according to the mechanism of *in situ* gelation system into ion-sensitive [49], pH-dependent [50, 51], thermoreversible [48, 52], etc.

Rossi *et al.* [48] described a thermosensitive mucoadhesive gel for the treatment of oral mucositis. It was based on a mixture of the polymer trimethyl chitosan and glycerol-2-phosphate. The active substance was benzydamine hydrochloride. This system turns into a gel after being injected into the oral cavity. According to the authors, it is able to control drug release and resist the physiological mechanisms of erosion from the application site.

Another publication concerns the platelet lysate delivery system [52]. The key feature of the described dosage form is its response to different temperatures. The base is a mixture of poloxamer 407 and sodium alginate. This composition had a low viscosity at 8 °C and quickly turned into a gel at 34-35 °C; that is, it had thermoreversible properties.

Vigani *et al.* [49] developed an in situ gel-forming system for application to the oral mucosa consisting of κ-carrageenan (κ-CG) and hydroxypropyl cellulose (HPC). The described dosage form had a low viscosity at room temperature, a protective effect at the site of application, and showed mucoadhesive properties. The gel was forming due to interactions between κ-carrageenan and saliva ions. The authors used k-CG as a gel-forming ion-sensitive polymer, HPC as a mucoadhesive agent, and $CaCl_2$ as a salt capable of enhancing the interaction between k–CG and saliva ions.

Kassem *et al.* [53] described a system containing either meloxicam (NSAID) or minocycline hydrochloride (antimicrobial agent). The high concentration of poloxamer provided a large number of polymer micelles, which increased the rigidity and tortuosity of the gel structure, resulting in a prolonged release of the active substance. Clinical evaluation of the drug with minocycline hydrochloride showed better results, reducing the periodontal pocket depth and the severity of gum inflammation. *In vitro*, this system released 85% of the active substance within three days.

Do *et al.* [54] described an *in situ* implant with doxycycline hyclate based on a biodegradable polymer poly (lactic-co-glycolic acid) (PLGA) dissolved in a biocompatible solvent–N-methyl-pyrrolidone. The dosage form was intended for administration into the periodontal pocket. Mechanical and adhesive properties were evaluated, and antibacterial activity was determined *in vitro*. To increase the adhesive ability of the implant, plasticizers–acetyl tributyl citrate and dibutyl citrate–were added.

Main aspects of in situ development of the ketorolac tromethamine system

Based on the scientific search, a group of polymers was selected that is potentially promising for the development of an *in situ* implant containing ketorolac tromethamine. Due to the pathological conditions of the area formed after the resection of the tooth, it is possible to identify thermosensitive *in situ* polymers as optimal for creating a new delivery system. Such polymers primarily include poloxamer 407 and its combinations with other excipients to achieve the desired parameters (gelation temperature, gel strength, biodegradability time, mucoadhesion, etc.) [55]. The advantage of these excipients is their commercial availability for research and further potential production.

An alternative to poloxamers can be PLGA copolymers with various additives that provide the desired thermoreversible properties. However, the need for directed synthesis of polymer compositions may make it difficult to scale and distribute the technology.

In addition to the main thermoreversible ingredient, additional plasticizers can be included in the composition, if necessary, in a concentration that does not affect the phase transition and the viscosity of the initial solution. It is also permissible to use antioxidants, pH stabilizers, and others.

During the process of pharmaceutical development of *in situ* implants (not only with ketorolac), but the following parameters of the dosage form can be recommended for determination: gelation temperature [33], rheological behavior [33, 35, 48], drug release kinetics [54], as well as mucoadhesion [48] and syringe ability [33, 35].

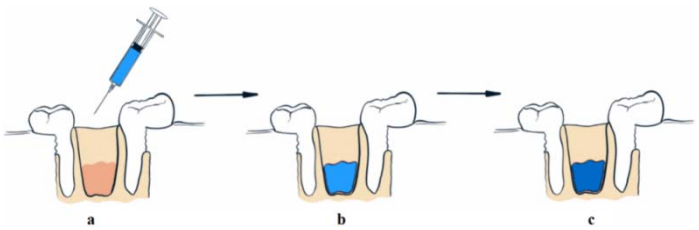

Fig. 1: The scheme of the *in situ* implant application, a–Implantation with a pre-filled syringe, b-The implant fills the alveolar socket, c-Sol-gel transition

As a package for the developed dosage form, it can be recommended to use prefilled syringes containing a strictly defined dose intended for the formation of an implant in the tooth socket, as shown in fig. 1. The use of this type of packaging will reduce the risks of incorrect dosing by medical personnel, as well as ensure the sterility of the dose and the absence of microbial contamination during administration.

CONCLUSION

The problem of using NSAIDs in dentistry has not been sufficiently studied. It is necessary to develop dosage forms for topical use, mainly because it would allow circumventing the problem of the occurrence of systemic side effects.

The study showed the comparative effectiveness and safety of the dental use of ketorolac. The next step could be the identification of the stability of pharmaceutical compositions based on cellulose derivatives, thermosensitive types of poloxamers, PLGA, as well as carbopol.

The creation of a thermoreversible or (and) pH-sensitive system can increase the effectiveness and safety of treatment. Bioadhesive properties of the base can provide a prolonged effect by increasing the time witch the dosage form is located at the application site.

Besides, ketorolac has a bitter taste, which can seriously worsen the organoleptic characteristics of the dosage form and negate all its benefits. Therefore, it is necessary to take into account the need to introduce taste correctors or consider the possibility of masking bitterness.

The authors conclude that the development of a local bioadhesive delivery system with ketorolac is promising. Of particular interest is the creation of *in situ* implants.

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AUTHORS CONTRIBUTIONS

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Design: Bakhrushina EO, Demina NB.

Data Collection or Processing: Kashperko AS, Bakhrushina EO, Sakharova PS.

Analysis or Interpretation: all authors.

Literature Search: Kashperko AS, Bakhrushina EO, Sakharova PS.

Writing: all authors.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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