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## **Topical Drugs for Pain Relief** Ağrı Kesici Olarak Topikal İlaçlar

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### **ABSTRACT**

Topical therapy helps patients with oral and perioral pain problems such as ulcers, burning mouth syndrome, temporomandibular disorders, neuromas, neuropathies and neuralgias. Topical drugs used in the field of dentistry are topical anaesthetics, topical analgesics, topical antibiotics and topical corticosteroids. It provides symptomatic/curative effect. Topical drugs are easy to apply, avoids hepatic first pass metabolism and more sites specific. But it can only be used for medications that require low plasma concentrations to achieve a therapeutic effect.

**Key words:** Topical therapy, topical analgesics, topical antibiotics, topical anesthetics, topical corticosteroids, drugs.

### **ÖZET**

Topikal terapi ülser, yanan ağız sendromu, temporomandibular bozukluklar, nöromalar ve nöraljiler gibi oral ya da perioral ağrı sorunu olan hastalara yardımcı olur. Diş hekimliği alanında kullanılan topikal ilaçlar topikal anestezipler, topikal analjezikler, topikal antibiyotikler ve topikal kortikosteroidlerdir. Semptomatik ya da tedavi edici etki sağlarlar. Topikal ilaçların uygulaması kolaydır, karaciğerin ilk geçiş metabolizmasından etkilenmezler ve uygulandığı alanlara daha özgüdürler. Ancak terapötik etki gösterirken daha düşük plazma konsantrasyonu gerektiren durumlarda kullanılan ilaçlardır.

**Anahtar Kelimeler:** Topikal terapi, topikal analjezikler, diş hekimliği, ilaçlar



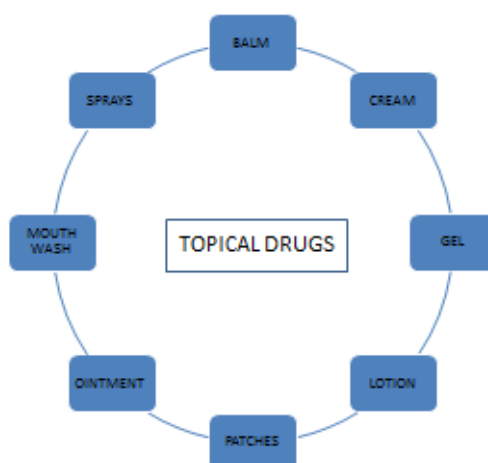
## Introduction

Pain is perhaps the most common reason for an unscheduled visit to a dentist and most general dentists would probably see at least one or two patients with pain almost every working day<sup>1</sup>. International association for the study of pain (1994) defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage<sup>2</sup>. Pain is not a single entity; it is part of the entire inflammatory process and one of the clinical signs of inflammation. Oral pain is associated with pulpitis, periodontitis, pericoronitis, abscesses (periapical/periodontal), trauma, and other conditions including temporomandibular disorders (TMDs) and masticatory muscle disorders. Pain can also be manifested as burning sensation in the oral cavity. Management of pain is by the administration of various drugs based on the severity and chronicity of pain. The main routes of drug administration are topical, parenteral and enteral routes, in which dentists most commonly prefer topical administration rather than systemic route. Topical administration involves local application of a drug to the site of action. This is the most direct and easiest mode of drug administration.

Topical drugs avoid hepatic first pass metabolism, avoids gastrointestinal incompatibility, suitable for self-medication, shows less fluctuation in drug levels, achieves efficacy with a lower total daily dose, more site-specific with drug delivery and improved patient compliance. It is easy for the patients to terminate medication when needed<sup>3</sup>. Significant risks associated with oral or intravenous administration is avoided in topical application. But it can cause skin irritation, and allergic reactions. Topical administration cannot replace systemic therapy in all cases. It can be used for medications that require low plasma concentrations to achieve a therapeutic effect<sup>4</sup>.

Topical therapy helps patients with oral and perioral pain problems such as ulcers, burning mouth syndrome, temporomandibular disorders, neuromas, neuropathies and neuralgias. Vehicle-carrier agents and bases developed can penetrate the mucosa and cutaneous tissues and transport the active medication to the treatment site. Several topical intraoral medications are used in the treatment of oral ulcerations and infections, including antifungals; non-steroidal anti-inflammatory drugs (NSAIDs); and corticosteroids. Because of their rapid onset and low side-effect profile, topical medications offer a distinct advantage over systemic administration for orofacial disorders.

Topical drugs used in the field of dentistry are topical anaesthetics, topical analgesics, topical antibiotics and topical corticosteroids. It is available as balm, cream, gel, lotion, patches, ointment, mouth wash and spray [Figure 1]. It provides symptomatic/curative effect. Pharmaceutical drugs are not the only path for pain relief. Natural pain treatments like herbal medicine, in which parts of a plant are used medicinally to treat health problems is an increasingly popular way to manage pain as well. Many herbs are thought to provide pain management and decrease inflammation<sup>5</sup>.



**Figure 1. Types of topical drugs**

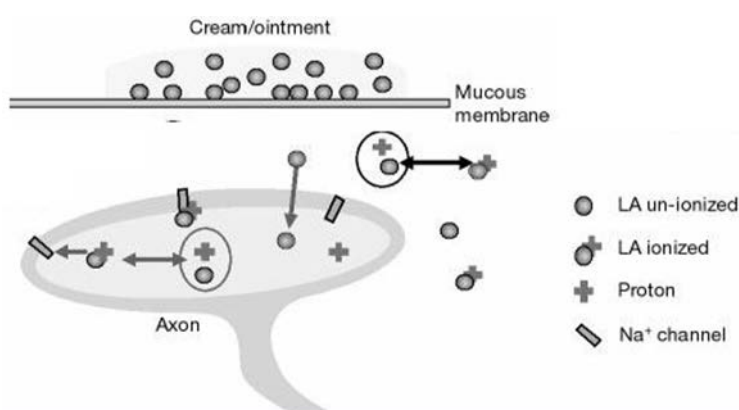
### **Topical Anaesthetics**

Topical anaesthetics are routinely used in dentistry to attenuate the pain associated with local anaesthetic injections. It is also used for the topical treatment of mouth ulcers and erosive conditions of the oral mucosa. Other indications are to prevent gag reflex of the patient while placing X-ray film in the oral cavity, or when a tray is placed in the mouth to take an impression or give a fluoride treatment. It decreases discomfort during scaling and root planning or during the removal of suture. When topical anaesthetics are applied to the mucous membrane, only the superficial layer is anaesthetised and there is no loss of motor function. Topical anaesthetics only provide short term pain relief. The duration of relief is dependent on

the resistance of the carrier to the effects of mechanical movement and saliva. The various topical anaesthetic agents used in dentistry include lidocaine, benzocaine, tetracaine etc.

### Benzocaine

Benzocaine is the most popular topical anaesthetic agent. It is an ester of aminobenzoic acid and is poorly soluble in water. The low water solubility and consequently slow absorption from the area of topical application not only prolongs the anesthesia but also reduces its toxicity. Benzocaine blocks the initiation and conduction of nerve impulses by decreasing the neuronal membrane permeability to sodium ions, which increases the pain threshold<sup>6</sup> [Figure 2]. It is contraindicated in hypersensitivity, complete heart block, and low plasma-cholinesterase concentrations. Adverse reactions include hypersensitivity reactions; vertigo, nystagmus, sensitization, CNS excitation, tinnitus, blurred vision, nausea and vomiting, muscle twitching and tremors. Methemoglobinemia is an uncommon adverse reaction known to be associated with benzocaine. This condition reduces the ability of red blood cells to deliver oxygen throughout the body, which can lead to bluish discoloration of the skin, nausea and fatigue. It can progress to stupor, coma and death. Almost all reported cases of benzocaine-induced Methemoglobinemia were associated with high-concentration preparations (14 percent to 20 percent benzocaine). Compounding pharmacies can formulate low concentration or benzocaine-free topical anesthetics, including combinations of other topical anesthetics such as lidocaine and tetracaine or prilocaine.



**Figure 2. Mechanism of action of topical anesthetics**

Benzocaine belongs to pregnancy category C. Mucopain® penetrates the oral mucosa and offer local anesthetic activity that lasts for 10-20 minutes. Its active ingredient is Benzocaine USP-20% w/w in a water miscible base and inactive ingredients include PEG, Fumed Silica, Sodium Saccharin, Sodium Propyl Paraben, Sodium Methyl Paraben, Viscarin, and Flavour.

### **Lignocaine**

Lignocaine is an amide type local anesthetic and class 1b antiarrhythmic drug. It stabilises the neuronal membrane and inhibits sodium ion movements, which are necessary for conduction of impulses. Lidocaine is available in two forms for the production of topical anesthesia: Lidocaine base and lidocaine hydrochloride. Lidocaine base is insoluble in water and used in a 5 % concentration. It is incorporated into a variety of flavoured gels and ointments for the use in the oral cavity. It produces excellent surface anesthesia within 15 seconds of application. Lidocaine hydrochloride is used in a 2% or 4% concentration. It tends to penetrate tissue better than lidocaine base due to its water solubility<sup>7</sup>.

Lidocaine use may obtund or diminish taste and the gag reflex and/or result in a burning sensation, in addition to possible cardiovascular and central nervous system effects<sup>8</sup>. Viscous lidocaine is a thick liquid that can be used to relive pain from dry socket or alveolar osteitis, a complication from tooth extraction. Absolute contraindications for the use of lidocaine include: Heart block, second or third degree (without pacemaker), severe sinoatrial block (without pacemaker), or serious adverse drug reaction to lidocaine or amide local anesthetics. It belongs to pregnancy category B. Adverse drug reactions are rare when lidocaine is used as a local anesthetic and is administered correctly. Most adverse drug reactions associated with lidocaine for anesthesia relate to administration technique (resulting in systemic exposure) or pharmacological effects of anesthesia, and allergic reactions only rarely occur.

Xylocaine Viscous® is available as a 2% aqueous solution adjusted to a pH of 6.0-7.0. It is indicated for use of inflamed and denuded mucus membranes. Generally for an adult an amount of less than 1 ounce, usually 1/2 ounce, is administered at intervals of not less than 3 hours with no more than 8 doses being administered in a 24 hour period. When applied by means of cotton applicators or packs, the suggested maximum dose is 1 to 5 ml(40 to 200mg) or 0.6 to 3.0mg/kg (0.3 to 1.5 mg/lb) not to exceed 300 mg or 4.5 mg/kg(2 mg/lb)<sup>7</sup>. The peak effect on the mucus membrane appears in 2-5 minutes and the duration of the effect is 30-60 minutes.

Eutectic mixture of lignocaine/prilocaine proved to be beneficial for pain relief in dental field. Eutectic mixture refers to lowering of melting point of two solids when they are mixed. This happens when lignocaine and prilocaine are mixed in equal proportion at 25degree celcius. In dentistry it has been tried for obtunding pain of intrapalatal injection. A study showed that application of topical anesthesia before needle prick using a combination of 2.5% lidocaine and 2.5% prilocaine (L/P) as either a creamy mixture (EMLA) or a gel (Oraqix<sup>®</sup>) was significantly ( $P < .05$ ) more effective than 20% benzocaine gel in reducing pain. This significant reduction of pain from needle prick suggests that these lignocaine /prilocaine combinations are more effective and may replace the commonly used 20% benzocaine in dental practice<sup>9</sup>.

Lidocaine patch [Figure 3] is a small adhesive strip that contains lidocaine. It is placed in the mouth for up to 15 minutes. The effect starts with in 2 to 5 minutes and can last for about 30 minutes after the patch is removed. Lidocaine patch is safer because less of the anesthetic enters the bloodstream.

### **Tetracaine**

Tetracaine is a powerful topical anesthetic. It is a highly lipid soluble Para amino benzoic acid ester, more potent and more toxic due to slow hydrolysis by plasma pseudocholinesterase. It spreads through the body faster than other anesthetics do due to its high water solubility. Tetracaine is used with benzocaine to reduce the gag reflex before taking impressions or X-rays. Because of rapid mucosal absorption and high systemic toxicity, its use for surface anaesthesia in the mouth is restricted. The maximum recommended dose of topically applied tetracaine is 20 mg or 1 ml of a 2 % solution<sup>7</sup>.

Pain relief in recurrent aphthous stomatitis can be attained using topical lidocaine 2% gel or spray, or benzocaine lozenges. Oral lidocaine has been used topically for relieving the burning sensation in burning mouth syndrome. However, topical anaesthetics for the treatment of BMS are not as useful as the unpredictable effect; the pain can either increase or decrease. A three-drug mouthwash (lidocaine, diphenhydramine and sodium bicarbonate in normal saline) can provide effective symptomatic relief in patients with chemotherapy-induced mucositis<sup>10</sup>.



**Figure 3. Anaesthetic patch**

While prescribing oral topical anesthetics the patient is asked to avoid food and beverages for one hour after application since the production of topical anesthesia may impair swallowing and thus enhance the danger of aspiration. There is increased chance of biting trauma due to numbness of the tongue or buccal mucosa.

### **Topical Analgesics**

Analgesic is a drug that selectively relieves pain by acting in the central nervous system or on peripheral pain mechanisms, without significantly altering consciousness. Analgesics are classified into opioid /narcotic/morphine like analgesics and non-opioid/non-narcotic/non-steroidal anti-inflammatory drugs<sup>11</sup>.

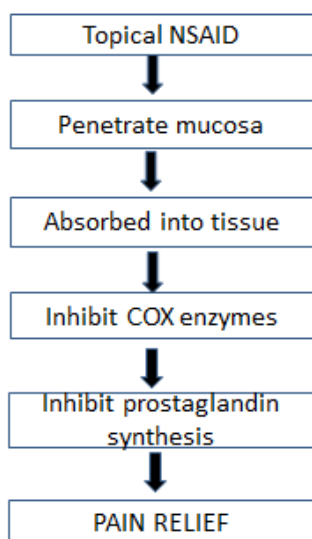
#### **Morphine**

Morphine and other opioids exert their actions by interacting with specific receptors present on neurons in the central nervous system and in peripheral tissues. Randomized double-blinded crossover study conducted in patients suffering from radiotherapy- and/or chemotherapy-induced oral mucositis showed a possible analgesic effect of topical morphine<sup>12</sup>.

#### **Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)**

The NSAIDs are a class of drugs that have analgesics, antipyretic and anti-inflammatory actions in different measures. In contrast to morphine, they do not depress central nervous system; has no abuse liability or physical dependence. NSAIDs reduce the production of

prostaglandins [Table 1] that sensitize nerve endings at the site of injury. Clinical trials have shown that NSAIDs are effective in the management of any level of dental pain, whether mild, moderate or severe<sup>13</sup>. The most commonly used topical analgesics in oral mucosal pain are choline salicylate, benzydamine, benzalkonium chloride and diclofenac sodium.



**Figure.4. Mechanism of action of NSAIDS**

Choline salicylate has analgesic and anti-inflammatory action. It acts by inhibition of Prostaglandin (PGs) synthesis by blocking the activity of the precursor enzyme cyclooxygenase. It is contraindicated in haemophilia, haemorrhagic disorders, gout, and patients with history of hypersensitivity to salicylates, severe renal or hepatic impairment, pregnancy and lactation. Topical oral salicylate gels are no longer indicated in those younger than age 16 years for pain associated with infant teething, orthodontic devices, cold sores, or mouth ulcers<sup>14</sup>. Salicylate use in children was implicated in the development of Reye's syndrome<sup>15</sup>. Benzalkonium Chloride is a mixture of alkylbenzyltrimethyl ammonium chlorides which has broad spectrum antimicrobial activity. Benzydamine is a short-acting, nonsteroidal anti-inflammatory agent and may be useful in treating painful ulcers. It helps to reduce swelling and discomfort.



Diclofenac is a powerful anti-inflammatory and analgesic drug that is well suited for local use in the oral cavity, which belong to aryl acetic acid derivative. It is among the most extensively used NSAID, employed in rheumatoid and osteoarthritis, toothache, post- traumatic and postoperative inflammatory conditions<sup>11</sup>. 3% diclofenac in 2.5% hyaluronan was an effective treatment for common, painful disorder Recurrent aphthous stomatitis according to Iraj et al<sup>16</sup>. Sangita et al showed that 0.074% diclofenac mouthwash is an effective and tolerable medicinal product for post-surgical symptomatic relief<sup>13</sup>. VOLINI GEL<sup>®</sup> (Diclofenac Diethylamine BP 1.16% w/w) is indicated for relief from pain, swelling and inflammation due to joint pain, low back pain, neck pain & shoulder pain, minor sports injury, sprains & sprains. In dentistry it is used to relieve pain caused by temporomandibular disorders.

### Topical Antibiotics

It helps prevent infections caused by bacteria. Certain topical antibiotics are proved to be useful for pain relief. Topical antibiotics are available in many forms, including creams, ointments, powders, and sprays. . In a clinical randomized study conducted on seventeen patients showed that minocycline rinses are significantly more effective than tetracycline for management of RAS as assessed by pain report<sup>17</sup>. Antibiotic mouthwash can be prepared by the patient by dissolving the contents of 250 mg tetracycline capsule in 10 ml of water to give a 2% solution.

### Topical Corticosteroids

Corticosteroids are a class of chemicals that includes the steroid hormones that are produced in the adrenal cortex of vertebrates, and synthetic analogues of these hormones. Corticosteroids are used for the management of many oral inflammatory conditions. Topical corticosteroids reduce pain and inflammation in vesiculo-erosive diseases of the oral mucosa. There are various treatment modalities are oral submucous fibrosis but topical steroid ointment helps in cases with ulcers and painful oral mucosa. Topical steroid such as mometasone furoate microemulsion shows a significant reduction in pain in erosive-ulcerative oral lichen planus<sup>18</sup>. The treatment of choice for mild mucous membrane pemphigoid appearing in the mouth include corticosteroid mouthwashes and ointments.



**Figure 4. Anabel protective mouth ulcer film**

Various studies showed the efficacy of topical corticosteroids for symptomatic relief in recurrent aphthous stomatitis, oral lichen planus, erythema multiforme, pemphigus, mucous membrane pemphigoid, bullous pemphigoid, systemic lupus erythematosus, post herpetic neuralgia, facial pain and temporomandibular joint disorders<sup>19</sup>. Hydrocortisone hemisuccinate (as pellets of 2.5 mg) and triamcinolone acetonide (in an adhesive paste containing 0.1% of the steroid) are the drugs most commonly adopted for local oral application in RAS. An aqueous suspension of triamcinolone acetonide 0.1% was used as an oral rinse in the treatment of 46 patients with symptomatic oral lichen planus (Vincent 1990)<sup>19</sup>. A high-potency topical corticosteroid (0.05% clobetasol propionate in Orabase; Colgate, New York, NY) was used for controlling the symptomatology of mucocoeles<sup>20</sup>. Topical corticosteroids prescription includes triamcinolone acetonide 0.1%, Kenalog in Orabase; hydrocortisone acetate 1% ointment; and betamethasone dipropionate 0.05% ointment.

## Natural Herbs

### Capsaicin

Capsaicin is a natural constituent in pungent red chilli peppers. It can selectively activate, desensitize, or exert a neurotoxic effect on small diameter sensory afferent nerves while leaving larger diameter afferents unaffected; depending on the concentration used and the mode of application<sup>21</sup>. It demonstrated positive effects on BMS pain intensity. It induces desensitization to thermal, chemical and mechanical stimuli by inducing selective and reversible desensitization of the afferent sensory C fiber endings. It is used as mouth rinse one teaspoon of a 1:2 dilution or higher of hot pepper and water. Capsaicin itself can cause burning sensation, thus limiting its use in BMS<sup>22</sup>.

Topical capsaicin produces benefit in postherpetic neuralgia<sup>23,24</sup>, oral neuropathic pain, trigeminal neuralgia, temporomandibular joint disorders<sup>25,26</sup>. Recently Capsaicin has been used to treat atypical odontalgia<sup>27</sup>, especially when a specific pain "trigger point" is involved. Capsaicin is applied directly to this "trigger point" several times a day. Topical capsaicin is often considered an adjuvantive therapy to other approaches and not considered as a sole therapy.

### **Turmeric**

Rinsing the mouth with turmeric water (boil 5 g of turmeric powder, two cloves, and two dried leaves of guava in 200 g water) gives instant relief. Massaging the aching teeth with roasted, ground turmeric eliminates pain and swelling. Applying the powder of burnt turmeric pieces and bishop's weed seed on teeth and cleaning them makes the gums and teeth strong. Applying a paste made from 1 tsp of turmeric with ½ tsp of salt and ½ tsp of mustard oil provides relief from gingivitis and periodontitis. This paste can be used to rub the teeth and gums twice daily.

### **Aloe Vera**

Aloe vera (*Aloe barbadensis*) commonly called as "babosa". "Curacao aloe" is a succulent plant belonging to the Liliacea family. It has been used initially in wound healing and was found to be beneficial as radiation protectors, immune stimulant, chemopreventive etc. It has been proved to relieve pain in radiation induced mucositis, oral lichen planus, recurrent aphthous ulcer minor. It also reduced burning sensation in oral submucous fibrosis<sup>28</sup>. SaliCept patches placed immediately after extraction reduced alveolar osteitis significantly<sup>29</sup>.

### **Conclusion**

The two main complaints a dentist come across are pain and burning sensation associated with intra oral lesions. Topical drugs can relieve these complaints to a greater extent thereby improving the patients comfort level. Because of these benefits and less side effects, dentists prefer using topical drugs for symptomatic relief.

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