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Review Article

Contemporary Topical Therapeutics for Temporomandibular Joint Pain; A Review of the Literature

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Abstract

Pain is the main reason for patients with temporomandibular joint disorders to attend dental clinics seeking for treatment. As for the most common musculoskeletal conditions, pharmacotherapy can be used in temporomandibular disorders (TMDs). However, there has been a shift in public and medical opinion away from systemic analgesics once medical and dental profession became concerned about the use of such medications with adverse events. Topical analgesics may potentially achieve similar effects to oral formulations without their systemic drawbacks. This review focuses on the contemporary topical agents used in the treatment of TMD. An advanced search of publications from 1980 to 2016 was made in ScienceDirect, PubMed, Medline, and Google Scholar databases.

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Context

The issue of pharmacotherapy safety in treating musculoskeletal pain, has brought attention to topical application, a safe and still effective route of drug delivery.

Evidence Acquisition

This review focuses on the topical agents used in temporomandibular disorders (TMDs). An advanced search of publications starting from 1980 through 2016 was made in ScienceDirect, PubMed, Medline, and Google Scholar databases using different combinations of keywords ("topical medication" OR "topical therapeutic" OR "topical pharmacotherapeutic agent" OR "topical analgesic") AND ("temporomandibular joint" OR "temporomandibular disorder" OR "temporomandibular joint dysfunction" OR "temporomandibular joint pain").

The relevance of searched articles to topical pharmacotherapy of temporomandibular joint disorders was considered and the following eligibility criteria were implied: 1) original articles; 2) English-language articles; and 3) full-text articles.

TMDs are recently classified as muscle disorders, disc displacements, arthralgia, osteoarthritis and osteoarthrosis (1). TMDs are the most common musculoskeletal condition after chronic low back pain (2). The TMJ pain may be resulted from sensitization of trigeminal sensory neurons innervating the TMJ region (3). A patient with TMD may also have a pain complaint in the neck, shoulder or upper neck region (4). As for other musculoskeletal disorders, pharmacotherapy may be applied in TMD. Commonly used pharmacotherapeutics in TMD are analgesics, myorelaxants, corticosteroids, anti-convulsants and anti-depressants. Analgesics can be divided into two groups: 1. Narcotics (opioids), and 2. Non-narcotics including salicylates, para-amino-phenol derivatives (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) (5).

Highlights

- Pain is the main reason for patients with TMJ disorders to seek for treatment.
- Topical application of TMD medication is a safe and still effective route of delivery.
- Topical NSAIDs, counterirritants, dexamethasone iontophoresis, balms and creams of herbal origin are the most common topical medication for TMD.

Topical Agents

The persistent concern over the use of narcotics (opioids) in addition to the public awareness of the cardiovascular risk of traditional NSAIDs and cyclooxygenase-2 (COX-2) inhibitors, has brought attention to a non-systemic approach-topical analgesics. The sites of action for topical analgesic, are soft tissue and peripheral nerves underlying the application site. In this regard, topical agents use the cutaneous delivery to specifically target the site of application. In contrast, transdermal drugs are administered distal to the site of application (6). A topical agent must have a low molecular weight less than

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500 Da (7), in association with hydrophobic/ hydrophilic characters in order to penetrate stratum corneum and epidermis, respectively (8).

Dexamethasone Iontophoresis

The terms topical and transdermal are alternatively used for such methods of drug delivery. Both delivery methods should pass the stratum corneum – barrier to topical treatment. Once passed this layer, topical analgesics may have access to the unmyelinated C-fibers and encounter the epidermal cells. Below this layer, the dermis contains nociceptive fibers, connective tissue and blood vessels. Transdermal method deliver medication via percutaneous absorption with the aim of gaining systemic levels of drugs in comparison to oral rout of delivery (9,10). Such delivery of ionized drugs can be enhanced by iontophoresis (11). The concept of iontophoresis dates back to 1908, when it was demonstrated that ions could be driven across the skin by means of an electrical current (12).

Dexamethasone sodium phosphate is the most commonly used medication with iontophoresis (13). Traditional administration of the medication directly into painful TMJ without the discomfort of intra-articular injection has popularized the iontophoresis (14). Dexamethasone Iontophoresis (DIP) has not been effective in reducing pain in TMJ disorders such as concurrent TMJ capsulitis and disc displacement without reduction (15). However, it appeared to be an effective initial treatment for TMJ involvement in juvenile idiopathic arthritis (16).

Topical NSAIDs

Till 2000, extensively prescribed NSAIDs had been responsible for approximately one-quarter of all adverse drug reactions. NSAIDs were widely prescribed for patients with rheumatic disease, prone to gastrointestinal complications (17). Topical NSAIDs penetrate slowly into systemic circulation. Following topical application, peak plasma levels are less than 10% of the concentrations obtained from oral dosing. Polyethylene glycol and limonene – as topical penetration enhancers- increase the absorption rate of NSAIDs by up to 75 fold (17). In a rheumatologic knee arthroscopy, the topically applied ketoprofen levels were 30-fold greater in cartilage than in plasma. Systemic toxicity or local skin reactions are rarely induced by NSAIDs (18).

Topically applied diclofenac and oral formulation of such medication have shown to be equally effective when treating TMJ dysfunction syndrome (19). Topical NSAIDs can be found in the forms of plaster, gel, or cream (20).

Potassium/Dmi/HEC gel

A new topical gel and method for rapidly relieving TMJ, muscles of mastication, and myofacial pain was developed in 2007. The gel composed of 72% aqueous hydroxyethyl cellulose, 18% potassium complex, and 10% dimethyl isorbide. Potassium alters the electrical potential of the nerves of the central nervous system (CNS) and the autonomic nervous system (ANS). Its mode of action is based on sound physiologic science. The potassium/Dmi/ aqueous HEC gel can directly target the affected tissues without being involved in the regular pharmacological activities (21). The gel would not enter any of the usual pharmacokinetic pathways that use intramuscular, intravenous, or subcutaneous injections of corticosteroids, sedatives, local anesthetics, muscle relaxants, NSAIDs, narcotics, and other medications given via oral, rectal, or vaginal routes of drug delivery (22).

Aqua Titan

Recently, there is an interest in the athletic field for the garments treated with titanium microparticles (Aqua Titan) used during recovery from fatiguing sports (23). Aqua Titan is a material consisting of microscopic titanium particles dispersed in water. Aqua Titan has been reported to have positive influence on muscle tissue, thereby, may have a supplementary role in treating TMD patients with muscular origin (24). Water-soluble titanium microparticle-permeated "tape" seems to have beneficial influence on TMD pain and limitation of daily functions (25).

Topical Counterirritants

Counterirritants in particular capsaicin, menthol, camphor, and garlic are analgesics that act on nociceptive neurons through excitation and desensitization. These plant formulas act on structurally similar ion channels, called transient receptor potential (TRP) superfamily (26,27).

Thermosensitive receptor counterirritants detect a wide range of temperatures ranging from harmful heat to extreme cold, also extracellular osmolarity variations, lipids, pressure and/or acidic pH and depletion of Ca^{+2} deposits (9,28). Other type of counterirritant is topical rubefacients containing salicylates. Few data describes the efficacy of salicylates for the treatment of acute musculoskeletal pain (6). Another counterirritant, often found in over-the-counter analgesic preparation include peppermint oil, marsh tea, and poison ivy (29).

Topical Capsaicin

Capsaicin, is a safe and efficient topical agent for the treatment of neuralgia and arthritic pain. This topical analgesic is marketed as 0.025%, 0.075% and 0.1% creams and was approved by the United States Food and Drug Administration (FDA) in early 1990's (30,31).

Adverse effects of Capsaicin may be observed mainly at the site of application and include burning and erythema (32). Capsaicin (trans-8-methyl-*N*-vanillyl-6-nonenamide) is a compound of chilli pepper which acts on impaired nerve endings and blocks CNS impulses. It depresses the function of type-C nociceptive fibers

by depleting substance P (SP), the principal neurotransmitter of pain from synaptic terminals. Those fibers had been found in the TMJ structures of monkey (33). Since SP and prostaglandin E2 are elevated in the TMJ synovial fluid, in inflammatory TMJ arthropathy, topical capsaicin may be effective in such cases. Effects of SP on inflammatory responses are modulated by neuro-peptides including SP-like immunoreactivity, calcitonin gene-related peptide, and neuropeptide Y (34,35). However, in a randomized, double blind study, capsaicin cream produced no statistically significant influence on TMJ measured variables compared to placebo (36).

Theraflex-TMJ

Complied with the FDA regulations, Theraflex is used to manage osteoarthritis and muscle disorders. Later, a drug with less potency was derived from the original formula and was called Theraflex-TMJ. Theraflex-TMJ cream, contains methyl salicylate, copper pyrocarboxylate and zinc pyrocarboxylate. Methyl salicylate is an ingredient that is required for incorporating into a counterirritant. Copper and zinc are essential elements for controlling inflammation. The anti-inflammatory action of copper includes the direct inhibitory effect of prostaglandin synthesis. It was proposed that zinc plays an important role in human health because of its participation in multiple enzymatic reactions and its involvement in the immune system (37).

Ping On

Ping On ointment has been registered in Hong Kong since 1965. Ever since, it has been has been used extensively as a soothing massage balm for muscular aches, strain and sprain. The main ingredient of Ping On ointment (according to manufacturer) consist of peppermint oil 18%; menthol 20%; natural camphor 6%; birch oil 6%; sandalwood oil 1%; eucalyptus oil 4%; bee wax 8%; and aromatic oil 3%. It does not contain antibiotics, steroids, or preservatives (38). The essential oils of eucalyptus induce analgesia through peripheral and central actions (39). Menthol has been used since antiquity for medicinal purposes. It is a plant alcohol called terpene alcohol. Applied topically, menthol causes tingling sensation and a feeling of coolness due to stimulation of cold receptors by inhibiting Ca^{+2} currents of neuronal membranes. Menthol is endowed with analgesic properties through a selective activation of k-opioid receptors (40). Despite its wide-spread use, mechanism by which menthol elicits the same cool sensation as low temperature was almost recently elucidated (41). Menthol's ability as a penetration enhancer makes it an ideal vehicle for topical formulation (42).

Bee Venom

Apitherapy is the use of honey bee products including honey, pollen, and bee venom to treat pain, arthritis, rheumatism, tumors, and skin diseases. The practice of apitherapy dates back to medicine in ancient Egypt, 6000 years ago. The use of bee products in modern medicine is confined to treat wounds and burns. Bee products, including bee venom, may also be used as an appealing start in arthritis (43,44).

The prime elements of bee venom (mellitin and phospholipase A_2) are responsible for development of local inflammation and pain. Mellitin's inhibitory action on nuclear factor kappa β can be crucial for the effects of bee venom (45-47).

Anti-inflammatory and analgesic effects of bee venom may increase pain threshold as a result of counter-irritation process (48).

Results

NSAIDS

In an absorption study in the articular tissues, when applied topically, the ketoprofen levels were 30-fold greater in the cartilage than in plasma (18). Topically applied diclofenac and oral diclofenac were equally effective in the treatment for TMJ dysfunction syndrome (19).

Dexamethasone Iontophoresis

Dexamethasone combined with lidocaine could be an effective mode of delivering ionized anti-inflammatory drugs to inflamed tissues (12). The same combination improved mandibular function but did not reduce pain in disc displacement without reduction (15). TMJ-related symptoms (a heterogeneous sample) did not respond positively to iontophoretically applied dexamethasone (14).

Theraflex-TMJ

Theraflex-TMJ formulated to treat signs and symptoms of TMJ disorders. The data suggests that topical cream is safe and effective for reducing pain in masseter muscle and TMJ pain (37).

Capsaicin

According to global evaluations, 80% of the capsaicin-treated patients experienced a reduction of pain after 2 weeks of treatment (30). Capsaicin has been effective in some patients with peri-ocular and facial pain (32). A randomized clinical trial has revealed that capsaicin produces not statistically significant effect on TMJ variables in comparison to placebo (36).

Potassium/Dmi/HEC gel

The gel routinely provides rapid pain relief within minutes after it is applied. The author believes that such pain relief minimizes patient anxiety prior to a definite diagnosis and treatment (21).

Aqua Titan

Water soluble titanium tape seems to have beneficial

effects on TMD-related pain and limitation of daily functions (25). Aqua Titan patch help treat patients with TMJ muscle disorders (24). Altered neuromuscular stiffness through dermal use of microtitanium particles can help muscle function after fatiguing exercises (23).

Menthol

Menthol is attributed to the analgesic properties via a selective activation of k-opioid receptor system as well as binding to TRPM8 (6,40).

Camphor

Over-the-counter camphor-containing balms have been used to provide analgesia. Recently, TRPV1 the capsaicin receptor, TRPA1 the garlic receptor and TRPV3 have been recognized from camphor's mechanism of action (27).

Essentials oils of Eucalyptus

A recent investigation into the analgesic and anti-inflammatory effects of essential oils of eucalyptus concluded with both central and peripheral actions of the induced analgesia (39).

Bee Venom

Anti-inflammatory and analgesic effects of bee venom may increase pain threshold due to counter-irritation effect (43). Accelerated wound healing, anti-arthritis, and anti-cancer effects of bee venom have been recently discovered (44-47) without any adverse effects (48).

Discussion

Persistent pain is the main reason for patients with TMJ disorders to look for treatment by physicians or dentists. Inflammation of TMJ can produce pain and can also induce sensitization of trigeminal neurons, in experimental animals. Trigeminal afferent nerves spread over the structures in the head, including the TMJ. Most information about noxious stimuli is relayed to CNS by nociceptive neurons (8,49). Pain and spasms frequently overlap and hide the cause of the TMJ disorder. For better diagnosis of such disorder, it is recommended to initially relieve the patient's pain. Once pain has been removed, it will be easier to diagnose and treat the dysfunctional phase of TMJ disorder. For this purpose, some topical agents – as mentioned in this review – are to relieve pain as a first measure and non-invasive approach (21).

Following topical application of NSAIDs, peak plasma levels were less than ten percent of the concentrations obtained from oral dosing. Systemic absorption from such topical application is merely 3-5 percent of the oral route. Hence systemic toxicity from topical NSAIDs are rare. The length of time before Cmax (peak plasma level) is gained following topical application, ranged from 2.2 hours to 23 hours – nearly ten times longer than the time needed for equivalent oral dose. Topically applied NSAIDs reach a steady level during 2 to 5 days of repeated application (17). Penetration studies also describe the achievement of therapeutic concentrations of topical NSAIDs below the application site (6).

Ernest A. Jennings and his team of anatomy and cell biology at the University of Melbourne have almost recently commented on neurobiology of TMJ pain. These authors have stressed on the voltage – gated Na^+ channels (VGSCs) as logical targets for blocking sensory neuronal activity. Activation of VGSCs are critical for the generation and propagation of neuronal action potentials. Critical role of Na^+ in neuronal excitability has led to a series of studies in the field. According to a distinctive study, Na^+ channels were selectively blocked on primary afferent fibers with TRPV1 receptors, as they were activated by capsaicin (8).

Capsaicin, the spicy active ingredient in chilli pepper has been frequently used to relieve neuropathic pain. A meta-analysis has already reported that capsaicin cream provided better pain relief for osteoarthritis than placebo (9,50). Topically applied capsaicin demonstrated a biphasic pharmaceutical effect. The first phase involves the activation of TRPV1 and the second phase induces analgesia through the depletion of neurotransmitters (SP) (51). The first phase is followed by vasodilation in response to initial application (of topical agent) and sensitization of A delta and C nociceptive fibers. The second phase, in turn, leads to persistent desensitization of nociceptors. This way, the relief of musculoskeletal pain may result (52).

Conclusions

In order to find an evidence-based topical analgesic, physicians or dentists should be acquainted with over-the-counter topical preparations – as diverse as those in the present review. Contemporary topical analgesics are branded as potential topical agents although they may not be fully documented or supported by randomized clinical trials. The primary afferent neurons to TMJ region as well as receptors and channels, may be considered for further studies in search of targets for peripherally acting medications for TMJ pain.

Authors' Contribution

All authors contributed equally to this work.

Ethical Statement

Not applicable.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interests.

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