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The Treatment of Complications of Impacted Wisdom Teeth

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Abstract

The extraction of impacted lower third molar teeth is one of the most common oral surgical procedures. Often, complications which cause discomfort for patients occur with these operations. Many treatment modalities are being used and investigated for the treatment of complications of impacted wisdom teeth. In this review, treatment options used for complications are mentioned.

Introduction

Of all other teeth, wisdom teeth are the ones with the highest rate of remaining impacted [1,2]. The extraction of impacted lower third molar teeth is one of the most common oral surgical procedures [3]. Often, complications which cause discomfort for patients occur with these operations [4]. Wisdom teeth that remain impacted in the jaw can cause complications such as pericoronitis, root resorption, tooth decay, periodontitis, infections (local and facial), cysts, tumors, and mandibular fractures [5].

Complications such as alveolitis, infection, pain, swelling, trismus, hemorrhage, nerve damage, mandibular/tuberosity fracture, escape of the tooth or the root of the tooth to an anatomical site, adjacent tooth damage, or temporomandibular joint damage may occur after the surgery of impacted wisdom teeth [6].

All oral surgical procedures result in varying degrees of pain, swelling, and trismus [7-9]. Swelling and trismus usually reach their maximum level 1-2 days after a surgical procedure, begin to decrease on the 3rd or 4th day, and are usually resolved towards the end of the first week [7]. The pain reaches its maximum intensity 6-8 hours following surgery, continues for 2-3 days, and decreases towards the seventh day [10,11].

Postoperative trismus, swelling, and pain levels have been reported to differ based on the age and sex of patients and the operation time and difficulty of the wisdom tooth procedure [10,12]. Age, sex, medical history, oral contraceptive use, presence of pericoronitis, poor oral hygiene, smoking, the position of the impacted tooth, the relationship of wisdom teeth with the inferior alveolar nerve, operation time, operative technique, the surgeon's experience, perioperative antibiotic use, topical antiseptic use, intra-socket drug delivery, and anesthetic technique are among factors that affect postoperative complications [6,13]. Pain may be associated with the healing process in general and healing depends on different parameters such as the patient's age, the amount of bone removed, the surgeon's experience, and operation time [14]. The amount of pain felt after an operation is lower in younger individuals [15].

It is recommended that the operation of impacted wisdom teeth be done before the age of 24 in both genders, but especially in females [16]. Carrying out surgical operations at 24 years of age or older constitutes a risk factor in terms of complications [17]. The risk of mandibular fracture after an operation exists, even if it is low. Male patients aged over 25 years, in particular, should be warned against this risk [18]. Coronectomy can also be performed to prevent nerve damage in teeth associated with the inferior alveolar nerve in impacted wisdom tooth operations [19].

Materials and Methods

Many treatment modalities are being used and investigated for the treatment of complications of impacted wisdom teeth. These include methods such as the use of medications like analgesics, steroids, muscle relaxants, vitamins, and antibiotics, ice application, low dose laser therapy, different flap techniques, different closure techniques, drainage, and prp-prf procedures [20-28].

Nonsteroidal Anti-inflammatory Drugs (NSAIDS)

Analgesics are used to control pain after a surgical operation. Postoperative pain is usually short or moderate lasting, and analgesics are often necessary for the first 24-48 hours [20]. The most commonly used analgesics after an impacted wisdom tooth operation are paracetamol, NSAIDs, or combinations of these with opioids or steroids [20-22,29].

Preoperative use of NSAIDs, which are used often for postoperative pain management, is more preferred. There are 2 possible mechanisms for the efficacy of NSAIDs administered prior to surgical trauma. The first is simply a pharmacokinetic advantage, by administering NSAIDs before the onset of pain, initiating drug absorption and reaching the therapeutic blood level at the onset of pain. The second is the limitation of the production of prostaglandins and prostacyclins associated with hyperalgesia and edema with the presence of a cyclooxygenase inhibitor in the surgical site [30,31].Suppression of the inflammatory response when NSAIDs are administered preoperatively may reduce sequelae caused by tissue trauma and the accompanying pain [31].

Ibuprofen is one of the anti-inflammatory drugs commonly used in impacted wisdom tooth surgery [32-35]. Preoperative ibuprofen 400 mg (3x1 for 5 days) and 800mg (two doses 1 hour before surgery) are effective in preventing postoperative pain and swelling at a daily dose of 1200-1600 mg [32,36].

Premedication with ibuprofen ensures that postoperative pain begins 100 minutes later [37].

Diclofenac potassium is known to have both analgesic and anti-inflammatory properties [38,39]. The preoperative use of a single dose of diclofenac sodium 75 mg is effective in preventing postoperative pain [38]. Following a surgical procedure, diclofenac potassium (preop and postop oral 50 mg) may also be given in combination with dexamethasone (prophylactic 8 mg and postop 4 mg IV) to control edema and trismus [40].

The effects of 20 mg of tenoxicam, 200 mg of flurbiprofen and 100 mg of diclofenac sodium are similar in the prevention of edema and trismus after third molar surgery. Tenoxicam is more effective in pain relief on the second postoperative day [21].

Aspirin is an effective analgesic for moderate-severe acute pain. It is more effective at higher doses, but with increased side effects such as drowsiness and gastric irritation. When aspirin is given preoperatively, the bleeding time increases [41], the platelet aggregation response declines significantly, hemorrhage increases significantly during and after the surgery, the incidence of hematoma and ecchymosis increases, and subjective swelling increases [42].

Ketoprofen is a propionic acid derivative with analgesic, anti-inflammatory, and antipyretic properties. The drug is widely used for the treatment of musculoskeletal disorders and evidence from clinical trials suggests that ketoprofen is as effective in reducing pain and discomfort associated with these disorders as other nonsteroidal anti-inflammatory drugs [43,44]. 25, 50, and 100 mg doses of ketoprofen can be used to control postoperative pain (the daily dose should not exceed 300 mg) [45,46]. The postoperative single dose use of ketoprofen 25 mg and ibuprofen 400 mg following wisdom tooth surgeries have been shown to result in similar dose effect curves in patients with pain [46].

COX-2 inhibitors (celecoxib, daily dose max. 200 mg; rofecoxib daily dose max. 25 mg) quickly reach therapeutic levels with one or two doses daily and maintain this level for a long time. COX-2 inhibitors are effective at controlling postoperative pain [47].

Most nonsteroidal anti-inflammatory drugs have a low risk during short term use. Many of the serious side effects occur after long term use. However, there are three classes of antihypertensive agents that may interact with NSAIDs:

angiotensin converting enzyme inhibitors, beta blockers, and diuretics. The effect of all these drugs is supported by renal prostaglandins. Since the main effect of NSAIDs is the inhibition of prostaglandin, it may diminish the efficacy of these agents. This effect usually lasts for about 7 or 8 days. For this reason, the use of NSAIDs in a hypertensive patient should be limited to 4-6 days [48].

NSAIDs have an effect on gastric mucosa and platelet aggregation, especially with long term use and in elderly patients. When taken with oral anticoagulants, NSAIDs may significantly increase the likelihood of gastric bleeding. This is especially true for aspirin. NSAIDs may suppress renal function and increase digoxin, methotrexate, and lithium concentrations, all of which are destroyed by the kidneys and which have low therapeutic indices. NSAIDs should be avoided in patients who use these drugs and who have decreased renal function [49].

Paracetamol

Another analgesic used commonly after an impacted wisdom tooth surgery is paracetamol [20,50,51]. Paracetamol, also called acetaminophen, is a para-aminophenol derived nonopioid medication with central analgesic and antipyretic effects [52]. It is a weakinhibitor of cyclooxygenases in surrounding tissues [53,54].

Paracetamol reaches its peak concentration in 30-60 minutes, is absorbed with oral administration, and has a half life of 2-3 hours. It is well tolerated by adults without sacrificing safety risk [55,56]. 500 mg can be used as needed in 4-6 hours intervals for adults. Raising the dose of paracetamol over 4000mg/day increases the risk of hepatic damage [50].

The fixed dose combination of paracetamol (500 mg) and ibuprofen (150 mg) has been developed to provide more analgesia than their own components alone, without getting into the safety risks that exist when either drug is used at high doses. This combination provides better analgesia than paracetamol or ibuprofen alone [57].

Opioids

Most opioids used in clinical practice provide an analgesic effect by activating opioid receptors in neurons in the pain conduction pathway [58]. Opioids have a depressive effect on the cardiovascular and respiratory systems [59-61]. Their main side effects are nausea, vomiting, drowsiness, and dizziness [58].

Tramadol is a synthetic analog of codeine, is a centrally effective analgesic, and has a low affinity for opioid receptors. The main effect of tramadol arises from the inhibition of the neuronal involvement of norepinephrine and serotonin in synapses on the descending inhibitory pain pathways [62]. However, although tramadol is an opioid, it causes few side effects. For this reason, it can be used for both acute and chronic pain (with a daily maximum dose of 400 mg, at doses of 50-100 mg in adults) [59-61].

The combination of tramadol and ibuprofen, with its supra-additive anti-inflammatory effect, is safe and effective for the treatment of postoperative pain [63].

Submucous local tramadol increases the anesthetic efficacy of epinephrine and mepivacaine in inferior alveolar nerve blockage but does not extend the duration of soft tissue anesthesia [64].

Codeine + naproxen sodium combination (30 mg + 550 mg, 2x1 daily) is effective in preventing pain, edema and trismus after lower third molar surgery [22].

Antibiotics

Postoperative use of antibiotics in impacted wisdom tooth surgeries results in less surgical site infection, pain, swelling, and trismus [65-67]. Antibiotic use as a prophylactic treatment against potential infections caused by susceptible microorganisms is a common practice [68]. The timing and protocols of this practice vary [69]. Although mouthwashes and placing an antibiotic in the extraction hole are partially effective at preventing postoperative infections, the most common form of antibiotic prophylaxis still in use is the systemic approach [70]. Antibiotics administered for dry sockets and/or infection after a wisdom tooth extraction reduce the risk of infection by 57% [71].At the same time, prophylactic antibiotics

reduce the risk of infection by about 70% [72]. In addition to preventing infections and reducing the incidence of dry sockets, antibiotic prophylaxis also decreases general postoperative morbidity [66].

Amoxicillin/clavulanic acid 1000/62.5 mg (preop single dose or postop 2x1 5 days) is effective at preventing the development of infective or inflammatory conditions after wisdom tooth surgeries [73]. It is useful for reducing the incidences of alveolar osteitis (AO) and infections [74]. Its combined use with 0.2% chlorhexidinegluconate mouthwash is also effective for the prevention of AO [75].

Recently, there has been a gravitation towards the use of narrow spectrum drugs that are only effective against the relevant pathogens. For example, metronidazole (400 mg, 2x1), a specific anaerobic agent, is effective at preventing complications after wisdom tooth surgeries [76,77].

The use of prophylactic IV antibiotics allows for a lower rate of surgical site infection. Postoperative pain is reduced in patients who use intravenous penicillin (15000IU x kg) or clindamycin (600mg) - for those with a penicillin allergy - an hour before surgery [78].

In the past decade, the use of macrolide antibiotics in dentistry has been encouraged because of the therapeutic advantages of newer derivatives, such as a broader antibacterial spectrum, improved tissue distribution, and low incidence of side effects [79]. Azithromycin is preferred because it is broad spectrum, effective on periodontal tissues, and effective in odontogenic infection [80-85].

Corticosteroids

Corticosteroids have benefits such as reducing inflammation, ensuring that less swelling, edema, and trismus occur, as well as reducing postoperative nausea and vomiting [86-91]. In the initial phase, they suppress the production of prostaglandins and leukotrienes, thus inhibiting inflammation. Perioperative steroid injection is believed to provide adequate plasma concentration and effectively control postoperative edema through an anti-inflammatory effect [92]. Postoperative use of corticosteroids has also been found to be reliable. Its routine use for the prevention of inflammatory complications is not appropriate [90].

Researchers report that in order to derive the most benefit from corticosteroids, they should be used at a dose equivalent to 300 mg cortisol (e.g. 60 mg prednisone) and continued for at least 3-5 days. This is because swelling is at its maximum 48-72 hours after an operation and the effects of steroids last 24 at most when they are administered as a single dose [90].

Methylprednisolone (32 mg, 12 hours before and 12 hours after surgery) prevents the growth of the macrophages in the inflammation zone, the increase of the number of fibroblasts in connective tissue, and the suppression of the immune system. Methylprednisolone reduces the formation of quinine and bradykinin by stabilizing cellular and organelle membranes and blocks histamine and histamine-like substances between cells [91].

The use of dexamethasone after a wisdom tooth extraction operation reduces trismus and swelling. It can be used at 4 mg or 8 mg doses preoperatively or postoperatively [8,92]. The masseter is the muscle that is most affected by postoperative edema after a wisdom tooth surgery. An intra-oral masseteric injection of dexamethasone is easily tolerated and is an effective way to reduce postoperative edema with both local and systemic diffusion [93].

Corticosteroids can cause possible side effects such as adrenal suppression, gastrointestinal disorders, psychosis exacerbation, infection, delayed wound healing, and interaction with the immune system. For these reasons, they should only be used on suitable patients [90,94,95]. Corticosteroids are useful in cases where serious surgical trauma is predicted or the patient is at risk for excessive edema [91].

Myorelaxants

Medications that are thought to reduce skeletal muscle tonus are often used on patients with chronic orofacial pain to reduce and prevent increased muscle activity caused by temporomandibular disorders [96]. They are mostly used

for chronic pain [97]. In addition to this, the administration of myorelaxants in combination with antispastic drugs such as benzodiazepines, baclofen, and tizanidine for chronic dysfunction has a greater effect in reducing pain [98].

Cyclobenzaprine is a central muscle relaxant and is used to treat headaches, fibromyalgia, and muscle spasms [99]. 8 mg of cyclobenzaprine per day, started the day before surgery and continued for 3 days, has been found to be ineffective on pain, edema, and trismus in impacted wisdom tooth surgeries [100].

Tizanidine is also a central muscle relaxant. It is used for upper motor neuron syndromes, muscle pain, and spasms related to the peripheral musculoskeletal system. Tizanidine 4 mg daily was started after surgery and continued for 2 days in an impacted wisdom tooth surgery and it was found that it did not increase the effects of dexibuprofen, with which it was used, on pain, edema, and trismus [101].

Studies that investigate the effect of muscle relaxants on complications that occur after impacted lower wisdom tooth surgeries are not sufficient for making healthy speculations and there is a need for further studies on this topic.

Vitamins

Vitamin B12 and folic acid deficiencies lead to structural and functional disorders in both the central and peripheral nervous systems [102]. The usability of Vitamin B complexes in the treatment of peripheral neuropathy and their cost effectiveness causes this medication to be commonly preferred [103]. Long term use of vitamin B12 (1x1, for a week to several months as long as needed) is useful for healing inferior alveolar nerve damage [104].

Vitamin D deficiency, especially found in cold climates, is a condition that can lead to bone mineralization and metabolic disorders. The administration of a single oral dose of 300,000 IU of cholecalciferol is useful for rapidly and safely increasing 25 (OH) D levels in adults and adolescents with vitamin D deficiency. A higher serum level of vitamin D leads to a less pronounced inflammatory response and a better and faster healing process [105].

Antimicrobial Mouthwashes

Fibrinolysis caused by infection at the extraction site plays a primary role in inflammation and poor healing processes [106]. The most effective method for reducing the risk of infection is the use of topical or systemic agents that help to remove oral bacteria [107]. In addition to mechanical debridement, mouthwashes have the advantage of acting locally on the surgical site. In general, they are cheap and have fewer side effects. Mouthwashes do not require prescriptions or any return to the and clinic, which renders them less costly for both the patient and the clinician [108].

Generally available mouthwashes contain chlorhexidine, benzydamine, volatile oils, cetylpyridinium chloride, sodium benzoate, triclosan, oxygenating substances, povidone-iodine, peroxidase, and fluoride [109]. While all of these have antimicrobial activity, chlorhexidine is considered the gold standard. Chlorhexidine decreases plaque, and provides broad spectrum activity against oral aerobes and anaerobes [110]. Chlorhexidine is a broad spectrum cationic antimicrobial agent [111] that acts on fungi and some viruses as well as on gram-positive and gram-negative bacteria. It forms a strong bond with the anionic regions of the cell membrane and wall, and its activity is particularly dependent on this cationic nature [112]. This bonding triggers events that affect the osmoregulatory and metabolic ability of the cell membrane and the enzymes it contains [113]. At higher concentrations, chlorhexidine may damage the structural integrity of the membrane and cause cellular materials to leak [114].

Using chlorhexidine only on the day of the operation does not provide benefits. When combined with a chlorhexidine mouthwash used for 7 days (3x1) postoperatively, it significantly reduces the incidence of alveolar osteitis [115,116].

Side effects of chlorhexidine are minimal. These include: dyeing of teeth, increased tartar formation, mucosal irritation, and changes in sense of taste [117]. That being said, more severe hypersensitivity reactions are also reported in the literature. These reactions range between lip and mucosal swelling to severe anaphylaxis. In light of this, it is important that the clinician and the patient be aware of such reactions [118].

A topical gel is an antimicrobial agent applied directly to the surgical site postoperatively. It may be more effective

than a mouthwash because the gel can prolong the amount of time for which the medication remains on the area where it is applied, may have a more direct effect on the alveolus, and may also provide more bioavailability. In addition, while the gel can be applied immediately after tooth extraction, mouthwashes are generally used after the first 24 hours due to the risk of clot dissolution [119]. Gels also have the effects of reducing the likelihood of postoperative infection, improving tissue regeneration, and accelerating wound healing [120]. Gels, like mouthwashes, reduce the incidence of alveolitis [119].

Flap Design

A primary closure involves achieving primary wound healing by repositioning the flap and using a suture after a wisdom tooth operation. In a secondary closure, the socket is open to the oral cavity and wound healing is secondary [121]. When flaps created by making a vertical incision and then shifting it to the lateral and closing with a primary closure and flaps opened in the form of an envelope and left for secondary wound healing are compared with regard to partially impacted wisdom teeth, the flap with primary closure gives a better result in the periodontal healing of the second molar tooth. On the other hand, there is less pain and swelling with a flap where no vertical incision is made [121-123]. Shifting the flap and making a primary closure on the area causes an increase in edema and trismus in partially impacted teeth [123-125].

Incisions are made to perform a clean surgical procedure and to provide adequate field of view on the surgical site [126]. A flap made in the form of an envelope reduces swelling [127] and trismus [128]. A triangular flap provides a better mouth opening after an operation compared to an envelope flap [129], but with greater risk for hematoma and wound dehiscence [130]. A modified triangle flap (Szymd incision: an incision starting from the retromolar region, and forming an arc from the distal edge of the second molar tooth to the mucogingival junction), results in less periodontal pocket depth and dehiscence than an envelope flap [127]. Another modification of the triangular flap - making the vertical incision at a distofacial angle from the distal part of the second molar tooth - causes less pain and swelling compared to an envelope flap [131]. The bayonet flap, which also includes the distobuccal mucosa of the second molar, results in less postoperative pain and less wound dehiscence compared to an envelope flap [132]. If the incision is made so as to start from the distal of the second molar toward the anterior, progress toward the distobuccal, and after passing the gingival crest, progress toward the posterior, taking the form of a comma, there will be a decrease in postoperative pain [133]. A pedicle incision (the initial incision progresses 1 cm at the distal of the third molar tooth from the buccal gingival sulcus and then curls toward the buccal sulcus, which allows for flap rotation) causes more swelling [134]. The use of flap retraction in the lingual region causes an increase in the incidence of temporary damage to the lingual nerve, but it has no protective or damaging effect on the incidence of permanent damage [135].

Not suturing the operated area results in less pain and swelling in lower wisdom teeth [136]. Placing the flap in its place after the flap has been lifted, without suturing, is also effective in reducing the trismus that occurs in the first two days [137]. The use of antibacterial sutures instead of silk sutures does provide benefits, even if little, in controlling the infection of the surgical site [138]. When the use of polyglactin 910 (Vicryl®) and irradiated polyglactin 910 (Rapid Vicryl®) sutures are compared, the irradiated suture is seen to result in less edema [139].

Drains

The use of tube drains to provide postoperative drainage in impacted wisdom tooth operations reduces postoperative swelling [140-144], trismus [140,141], and the incidence of alveolitis [145] and provides increased mouth opening and less pain during the first two days [146]. The use of a drain with a gauze soaked in chlortetracycline after extraction reduces the formation of alveolitis [147]. When drain placement positions after opening a triangle flap are compared, positioning the opening of the drain buccally (on the vertical incision line) instead of occlusally results in less bleeding and better wound healing [148]. The drain can be left in the surgical site for 72 hours following extraction, but if the drain tube is made of rubber, there can be pain caused by the rubber irritating the surrounding tissues. This pain decreases suddenly after the drain is removed [141].

Drainage can also be achieved by using a bismuth iodoparaffin paste (**BIPP**). Although leaving the mouth of the wound partially open results in less pain an swelling compared to making a primary closure, a primary closure provides better healing. The reason for this may be that the presence of the BIPP in the area of extraction prevents proper positioning of the flap [149].

Intraoral drainage requires additional care if the patient himself/herself is also to wash the socket, and this may result in delayed wound healing in some cases [149]. Whether in rubber form or with a gauze, placing a drain may prolong the operation time, which may result in more trauma for the patient. A rubber drain or a drain with a gauze remaining in the mouth for 48-72 hours may not be tolerated by patients due to its irritating effects [150]. At the same time, the drain can act as a source of infection and can be aspirated or swallowed if not placed solidly [143].

Low Level Laser Procedures

Low level laser therapy (LLLT) is used to alleviate pain, reduce inflammation and edema, and accelerate healing after oral and maxillofacial surgeries [151] and is effective on trismus and swelling [152-155].

LLLT has neuropharmacological effects important for the synthesis, release, and metabolism of a number of biochemical substances such as histamines and prostaglandins [156]. It achieves cellular biological stimulation through the inhibition of interleukin-6, monocyte chemotactic protein-1, interleukin-10, and tumor necrosis factor-α, accelerates tissue regeneration, improves wound healing, and reduces pain and swelling through anti-inflammatory mechanisms. It provides an analgesic effect by stimulating the synthesis of endogenous endorphins (β-endorphin), reducing the activity of C-fibers and bradykinin, and altering the pain threshold. However, because the standardization of LLLT procedures has not yet been established, the clinical results of LLLT may vary depending on each laser parameter (recurrent sessions, application technique, area of application, wavelength, duration of irradiation, amount of energy) [157-160].

When oral and non-oral procedures were compared, the conclusion was reached that a non-oral laser procedure has more effect on mouth opening and swelling [154, 161].

The contradictory results of studies are explained by different applications of treatment protocols such as laser wavelength, irradiation dose, position, and frequency [162]. More studies on LLLT are needed for the standardization of the parameters applied.

PRP (Platelet Rich Plasma)

PRP (Platelet Rich Plasma) has a platelet concentration containing 6-8 time the growth factor found in whole blood and is obtained by mixing blood using a two-stage centrifugation protocol [163]. PRP is the autologous concentrate of platelets suspended in plasma [164].

When PRP is being prepared, 5 ml of venous blood is collected from the antecubital fossa with aseptic techniques. A3.6 ml volume of this blood is placed in a tube containing 0.4 ml of citrate-phosphate-dextrose-adenine anticoagulant solution and mixed gently. The tube is placed in a centrifuge and equilibrated [165-167]. It is then subjected to centrifugation for 15 minutes at 2000 rpm [165,167] or for 10 minutes at 2400 rpm [166]. This process divides whole blood into a low red blood cell area and straw colored plasma. The uppermost region of this plasma contains fewer platelets (platelet poor plasma, PPP) and the middle region contains a higher platelet concentration and white blood cells (buffy coat). With a micropipette, the PRP and the stratum layer found 1 mm below the central region are collected in a sterile test tube. This is then centrifuged for 10 minutes at 3000 rpm [165,167] or 15 minutes at 3600 rpm [166]. After the second centrifugation, the upper half is removed and the lower half is used as PRP. PRP is activated with calcium chloride (CaCl) to form a PRP gel [165,167]. The PRP gel causes degranulation of α-granules found in platelets and release of growth factors. Thus, wound maturation and epithelization are accelerated and scarring is reduced. The use of PRP in surgical practice reduces bleeding and increases bone renewal. It also reduces postoperative edema and increases the interincisal mouth opening [167, 168]. It is a simple and low-cost technique that can be used to reduce postoperative pain and the incidence of alveolar osteitis [169].

PRF (Platelet Rich Fibrin)

PRF (Platelet Rich Fibrin) is an autologous growth factor reserve consisting of a polymerized fibrin matrix with a tetramolecular structure and containing platelets, leukocytes, cytokines and circulating stem cells. Slow polymerization during PRF preparation creates a fibrin network that enhances cell migration and proliferation in a manner similar to natural healing [170]. The fibrin matrix is the determining factor responsible for the true therapeutic potential of PRF [171]. This

fibrin membrane covers the wound suitably and can be sutured [172]. PRF is a soluble biological material that prevents foreign body entry into the surgical site and consequently foreign body inflammatory responses [170]. The preparation of PRF is simpler and faster because it does not require additional anticoagulants and chemical activators [173].

When PRF is being prepared, 9-20 ml of venous blood is drawn from each patient before extraction and placed in glass tubes without anticoagulants. The tubes are transferred to a centrifuge and centrifuged at 3000 rpm for 10 minutes. In the middle of the tube, a fibrin clot is formed that contains platelets located between the red blood cell layer at the bottom and the acellular plasma at the top. This clot is removed from the tube and the bound red blood cells are dissected. The PRF clot is then placed on the grid in the PRF box, covered with the compressor and lid, and converted into a membrane [174]. The PRF procedure reduces the severity of complications that occur immediately after surgery, reduces preoperative pocket depth, and accelerates bone formation. It achieves a reduction in postoperative edema and an increase in the interincisal distance [175]. PRF placed in the extraction socket is a valid method for accelerating wound healing, reducing postoperative pain, and accelerating soft and hard tissue regeneration [176]. PRF also reduces infection, pain, and other unwanted side effects [177]. Preventive treatment of localized osteitis can be achieved with PRF; a low-cost, autogenous, soluble, biological material [178]. In addition, PRF that is placed in a socket and sutured also reduces existing pain and analgesic use during the treatment of postoperative localized alveolitis [179].

The use of anticoagulants to achieve PRP is a disadvantage in terms of wound healing. PRF potentially increases wound healing, because it does not contain anticoagulants. In addition, it contains more white blood cells than PRP and causes white blood cells to increase in number, which increases the number of macrophages responsible for growth and the release of factors such as transforming growth factor beta, platelet derived growth factor, and vascular endothelial growth factor [180]. These cells and cytokines are of critical importance for wound healing. PRF protects and stabilizes grafts, is integrated into regenerative zones, facilitates cellular migration, and reinforces soft tissue healing [180, 181].

Cold Application

Cold application is a general term covering many techniques (such as ice packs, ice massages, gel packs, ice cubes in a plastic bag, ice in a towel, ice wrapped in paper towels) [182]. Postoperative extraoral cold treatment in the treatment area is an easy method to perform, which is done at -13 - -15 °C for 10 or 20 minutes[112,182]. This treatment causes vasoconstriction and as a result reduces postoperative swelling. It also has an analgesic effect because it reduces the speed of nerve conduction [112]. Cold application can reduce soft tissue inflammatory response due to pain, cell metabolism rate, muscle spasm, and trauma. Thus, it is believed to help to reduce the negative effects that an operation has on the quality of life of patients [183,184]. Another aspect of this treatment is psychological. Giving patients a task after the surgery may prevent them from focusing on their discomfort. The placebo effect achieved with a cold treatment may change a patient's pain perception [185].

Although this practice is frequently preferred after an impacted wisdom tooth surgery, it is contraindicated in some cases. Conditions under which local cryotherapy is generally contraindicated include: hypertension (due to secondary vasoconstriction), Raynaud's disease (blood vessels in the extremities may be extremely distressed during ice treatment), rheumatoid arthritis, a history of vascular disorders such as local extremity ischemia, freezing, or atherosclerosis, cold allergy (cold urticaria), paroxysmal cold hemoglobinuria, cryoglobulinemia, or any disease that produces a significant cold suppressor response [186].

Ozone Therapy

Ozone therapy is a method with therapeutic effects such as an antimicrobial effect, increased vascularity, and immunostimulation. Ozone is an allotropic form of oxygen and can be used in the form of gas, aqueous solution, and gel for topical therapeutic purposes. It can be used parenterally as IM, IV and autohemotherapy. The gel form of ozone is preferred due to benefits such as ease of application, the presence of ozone molecules at higher concentrations, and the longer term stability of the compound. Ozone gel, unlike ozone gas, is suitable for self-use by the patient and is thus easy to apply with no need for professional assistance, is well tolerated by patients, and can be applied in a shorter time. Using ozone gel twice daily for 5 days reduces postoperative pain, swelling and trismus [165,187].

Tissue Adhesives

Cyanoacrylate is the general name of fast sticking adhesives. These are 2 paste systems and are made ready to use by mixing before a procedure. Polymerization of the material starts within 10-15 seconds. The material is nonabsorbable and is removed from the wound edges and the surface of the mucosa within 7-10 days. Cyanoacrylate is generally used in external interventions and is not preferred much for internal interventions due to the possibility of reaction, toxicity, and carcinogenicity [1,2]. The effectiveness of cyanoacrylate in preventing pain in an impacted lower wisdom tooth surgery is similar to a suture, but its hemostatic effect is more than that of a suture. The application is as follows: a thick layer is formed along the incision line with the droplet method and after 20 seconds a second layer is formed in the same way [188,189].

Results

The most preferred method is the use of NSAIDs in the treatment of complications after third molar surgery. Other medicines mentioned (steroids, opioids, paracetamol, muscle relaxants and antibiotics), mouthwashes, surgical techniques and methods are applied in addition to NSAIDs. These additional approaches contribute to the antiinflammatory and analgesic properties of NSAIDs and make them more effective in the treatment of complications. However, these approaches alone are not more effective than NSAIDs. Due to the wide variety of NSAIDs and the constant introduction of new drugs into the market, it is difficult to determine the most effective NSAIDs.

Choosing the proper treatment method or medication from among the aforementioned treatment methods and medications according to the complication that is anticipated to occur is an important criterion in preventing or treating complications that occur after an impacted wisdom tooth surgery. Also, the method and medication that is effective on one patient not having the same effect on another patient among similar cases is one of the biggest problems that we encounter in controlling postoperative complications today. Because of the large number of individual factors in the formation of postoperative complications, it is not possible to place a general treatment protocol specific to a complication. Identifying a reliable, effective, easy, and inexpensive treatment and medication that is not affected by individual factors is the common point of all studies, and the fact that it hasn't been found until now is an indicator that research aiming for this will continue.

References

1. Singh H, Lee K, Ayoub AF(1996) Management of Asymptomatic Impacted Wisdom Teeth: A Multicenter Comparison. Br J Oral and Maxillofac Surg 34(5): 389-393.

2. Santosh P (2015) Impacted mandibular third molars: review of literature and a proposal of a combined clinical and radiological classification. Ann Med Health Sci Res 5(4): 229-234.

3. Mercier P, Precious D(1992) Risks and benefits of removal of impacted third molars. A critical review of the literature. Int J Oral Maxillofac Surg 21(1): 17-27.

4. Saheeb BDO, Obuekwe ON (2001) An audit of mandibular third molar surgery. Nig J SurgResearch 3(2): 66-74.

5. Rafetto LK (2015) Managing impacted third molars. Oral and maxillofacial surgery clinics of North America 27(3): 363-371.

6. Bouloux GF, Steed MB, Perciaccante VJ (2007) Complications of third molar surgery. Oral and Maxillofacial Surgery Clinics 19(1): 117-128.

7. Peterson LJ (2003) Postoperative patient management. In: Peterson LJ, Ellis E, Hupp JR, Tucker MR, editors. Contemporary oral and maxillofacial surgery. 4th ed. St. Louis: CV Mosby: pp. 214–220.

8. Filho JRL, Maurette PE, Allais M, Cotinho M, Fernandes C (2008) Clinical comparative study of the effectiveness of two dosages of dexamethasone to control postoperative swelling, trismus and pain after the surgical extraction of mandibular impacted third molars. Med Oral Patol Oral Cir Bucal 13: e129-e132.

9. Trindade PAK, Giglio FPM, Colombini-Ishikiriama BL, Calvo AM, Modena KCS, et al. (2011) Comparison of oral versus sublingual piroxicam during postoperative pain management after lower third molar extraction. Int J Oral Maxillofac Surg40(3):292-297.

10. Markovic AB, Todorovic L(2006) Postoperative analgesia after third molar surgery: contribution of the use of long-acting local anaesthetics, low-power laser and diclofenac. Oral Surg Oral Med Oral Pathol Oral Radiol Endod102(5):4–8.

11. Lyons, CJ, Bruce RA, Frederickson GC, Small GS (1980) Age of patients and morbidity associated with mandibular third molar surgery. The Journal of the American Dental Association101(2): 240-245.

12. Lago-Mendez L, Dinitz-Freitas M, Serna-Rivera C, Gude-Sampedro F, Rey JMG, et al. (2007) Relationships between surgical difficulty and postoperative pain in lower third molar extractions. J Oral Maxillofac Surg 65(5):979–983.

13. De Santana-Santos T, de Souza-Santos JA, Martins-Filho PR, da Silva LC, de Oliveira e Silva ED, et al.(2013) Prediction of postop-erative facial swelling, pain and trismus following third molar surgery based on pre-operative variables. Med Oral Patol Oral Cir Bucal 18(1):e65-e70.

14. Siddiqi A, Morkel JA, Zafar S(2010) Antibiotic prophylaxis in third molar surgery: A randomized double-blind, placebo-controlled clinical trial using the split-mouth technique. Int J Oral Maxillofac Surg39(2): 107-114.

15. Capuzzi P, Montebugnoli L, Vaccaro MA (1994) Extraction of impacted third molars: a longitudinal prospective study on factors that affect postoperative recovery. Oral Surg Oral Med Oral Pathol 77(4): 341-343.

16. Blondeau F, Daniel NG(2007) Extraction of impacted mandibular third molars: postoperative complications and their risk factors. Journal of the Canadian Dental Association 73(4): 325-325 e.6p.

17. Chuang SK, Perrott DH, Susarla SM, Dodson TB (2007) Age as a risk factor for third molar surgery complications. Journal of Oral and maxillofacial surgery 65(9): 1685-1692.

18. Perry PA, Goldberg MH (2000)Late mandibular fracture after third molar surgery: a survey of Connecticut oral and maxillofacial surgeons. Journal of oral and maxillofacial surgery58(8): 858-861.

19. Martin A, Perinetti G, Costantinides F, Maglione M (2015) Coronectomy as a surgical approach to impacted mandibular third molars: a systematic review. Head & face medicine 11(9): pp 1-11.

20. Seymour RA, Meechan JG, Blair GS(1985) An investigation into post-operative pain after third molar surgery under local analgesia. Br J Oral Maxillofac Surg23(6): 410-418.

21. Kaplan V, Eroglu CN (2016)Comparison of the Effects of Daily Single-Dose Use of Flurbiprofen, Diclofenac Sodium, and Tenoxicam on Postoperative Pain, Swelling, and Trismus: A Randomized Double-Blind Study. J Oral Maxillofac Surg 74: 1946.e1-1946.e6.

22. Cigerim L, Eroglu CN (2017). Comparison of Clinical Efficacies of Preoperatively Initiated Naproxen Sodium-Codeine Phosphate in Combination, Diclofenac Potassium, and Benzydamine Hydrochloride for Pain, Edema, and Trismus After Extraction of Impacted Lower Third Molar: A Randomized Double-Blind Study. doi: 10.1016/j.joms.2017.08.041.

23. Gopee P, Rikhotso E (2017) Impacted mandibular third molars: the efficacy of prophylactic antibiotics and chlorhexidine mounthwash in preventing postoperative infections. SADJ 72(5): 213-218.

24. Kazancioglu HO, Kurklu E, Ezirganli S (2014) Effects of ozone therapy on pain, swelling, and trismus following third molar surgery. Int J Oral Maxillofac Surg 43(5): 644-648.

25. Cappuzi P, Montebugnoli L, Vaccaro MA (1994)Extraction of impacted third molars: A longitudinal prospective study on factors that affect postoperative recovery. Oral Surg Oral Med Oral Pathol 77(4): 341-343.

26. Sekhar CH, Naranayan V, Baig MF (2001) Role of antimicrobials in third molar surgery: prospective, double-blind, randomized, placebo-controlled clinical trial. Br J Oral Maxillofac Surg 39(2): 134-137.

27. Sortino F, Messina G, Pulvirenti G (2003) Evaluation of postoperative mucosa and skin temperature after surgery of affected third molar teeth. Minerva Stomatol 52(7-8): 393-399.

28. Jackson DL, Moore PA, Hargreaves KM 1989 Preoperative nonsteroidal anti-inflammatory medication for the prevention of postoperative dental pain. JADA 119:641-647.

29. Markovic A, Todorovic LJ (2007)Effectiveness of dexamethasone and low-power laser in minimizing oedema after third molar surgery: a clinical trial. Int J Oral Maxillofac Surg 36(3): 226-229.

30. Moore PA, Brar P, Smiga ER, Costello BJ(2005) Preemptive rofecoxib and dexamethasone for prevention of pain and trismus following third molar surgery. Oral Surg Oral Med Oral Pathol Radiol Endod 99(2): e1-e7.

31. Dionne RA (1999) Additive analgesic effects of oxycodone and ibuprofen in the oral surgery model. J Oral maxillofac Surg 57(6): 673-678.

32. Lökken P, Olsen I, Bruaset I, Norman-Pederson K (1975) Bilateral surgical removal of impacted lower third molar teeth as a model for drug evaluation: A test with ibuprofen. Eur J Clin Pharm 8(3-4): 209-216.

33. Hill CM, Carroll MJ, Giles AD, PickvanceN (1987) Ibuprofen given pre- and post-operatively for the relief of pain. Int J Oral Maxillofac Surg 16(4): 420-424.

34. Primosch RE, Nichols DL, Courts FJ (1995)Comparison of preoperative ibuprofen, acetaminophen, and placebo administration on the parental report of postextraction pain in children. Pediatr Dent17(3): 187-191.

35. Dionne RA, Cooper SA (1978)Evaluation of preoperative ibuprofen for postoperative pain after removal of third molars. Oral Surg Oral Med Oral Path Oral Radiol Endod45(6): 851-856.

36. Bennie R, Boehringer L, McMahon S (1997) Postoperative analgesia with preoperative oral ibuprofen or acetaminophen in children undergoing myringotomy. Pediatric Anesthesia 7(5): 399-403.

37. Dionne RA, Campbell RA, Cooper SA, Hall DL, Buckingham B (1983) Suppression of postoperative pain by preoperative administration of ibuprofen in comparison to placebo, acetaminophen, and acetaminophen plus codeine. J Clin Pharmacol, 23(1): 37-43.

38. Hyrkas T, Ylipaavalniemi P, Oikarinen VJ, Paakkari I (1993) Preoperative intravenous diclofenac for postoperative pain prevention in outpatients. BrJ Oral Maxillofac Surg 31(6): 351-354.

39. Matthews RW, Sully CM, Levers BGH (1984) The efficacy of diclofenac sodium with and without paracetamol in the control of postsurgical dental pain. Br Dent J. 157(10):357-359.

40. Bamgbose BO, Akinwande JA, Adeyemo WL, Ladeinde AL, Arotiba GT, et al. (2005) Effects of co-administered dexamethasone and diclofenac potassium on pain, swelling and trismus following third molar surgery. Head & Face Medicine1(11): e1-e6.

41. Skjelbred P, Album B, Lokken P (1977)Acetylsalicylic acid vs. paracetamol:Effects on post-operative course. Eur J Clin Pharmacol 12(4): 257-264.

42. Hepso HU, Lokken P, Bjornson J, Godal HC (1976) Double-blind crossover study of the effect of acetylsalicylic acid on bleeding and post-operative course after bilateral oral surgery. Eur J Clin Pharm 10(3-4): 217-225.

43. Fossgreen J (1976) Ketoprofen. A survey of current publications. Scand J Rheumatol Suppl 1976(0): 7-32.

44. Kantor TG (1986) Ketoprofen: a review of its pharmacologic and clinical properties. Pharmacotherapy 6(3): 93-102.

45. Cooper SA, Gelb SB, Cavaliere MBM, Cohn P, Dyer C (1984) An analgesic relative potency assay comparing ketoprofen and aspirin in post-operative dental pain. Advances in Therapy 1(6): 410-418.

46. Cooper SA, Berrie R, Cohn P (1988) Comparison of ketoprofen, ibuprofen and placebo in a dental surgery pain model. Advances in Therapy 5: 43-53.

47. Morrison BW, Fricke J, Brown J, Yuan W, Kotey P, et al. (2000) The optimal analgesic dose of rofecoxib: overview of six randomized controlled trials. The Journal of the American Dental Association 131(12): 1729-1737.

48. Haas DA (1999) Adverse drug interactions in dental practice: interactions associated with analgesics: part III in a series. The Journal of the American Dental Association 130(3):397-407.

49. Killion KH, Kastrup EK (2003) Drug facts and comparisons. 57th ed. St. Louis: Facts and Comparisons.

50. Dionne RA (1999) Additive analgesic effects of oxycodone and ibuprofen in the oral surgery model. J Oral maxillofac Surg 57(6): 673-678.

51. Özkan BT, Durmuş E, Kalaycı A, Kurban S, Akça CN (2010) The Evaluation of Safety and Analgesic Efficacy of Paracetamol and Ibuprofen Followed by Impacted Third Molar Surgery.European Journal of General Medicine7(3): 310-316.

52. Piletta P, Porchet HC, Dayer P (1991) Central analgesic effect of acetaminophen but not of aspirin. Clin Pharmacol Ther 49: 350-354.

53. Amine MM, Laskin DM (1983) Prophylactic use of indomethacin for preventionof postsurgical complications after removal of impacted third molars. Oral Surg Oral Med Oral Pathol 55(5): 448-451.

54. Bjørnsson GA, Haanaes HR, Skoglund LA (2003) Randomized, double-blind crossover trial with paracetamol 1000 mg four times a daily vs ibuprofen 600 mg: effect on swelling andother postoperative events after third molar surgery. Br J Clin Pharmacol 55(4): 405-412.

55. Moore ND (2009) In search of an ideal analgesic for common acute pain. Acute Pain 11(3-4): 129-137.

56. Coulthard P, Bailey E, Patel N. Paracetamol (acetaminophen) for pain after oral surgery. Oral Surgery 2014; 7(2): 81-86.

57. Merry AF, Gibbs RD, Edwards J, Ting GS, Frampton C, et al. (2010) Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial. British journal of anaesthesia 104(1): 80-88.

58. Shipton EA, Roelofse JA, Blignaut RJ (2003) An evaluation of analgesic efficacy and clinical acceptability of intravenous tramadol as an adjunct to propofol sedation for third molar surgery. Anesth Prog 50(3): 121-128.

59. Collins M, Young I, Sweeney P, Fenn GC, Stratford ME, et al. (1997) The effect of tramadol on dento-alveolar surgical pain. Br J Oral Maxillofac Surg 35(1): 54-58.

60. Altunkaya H, Ozer Y, Kargi E, Ozkocak I, Hosnuter M, et al. (2004) The postoperative analgesic effect of tramadol when used as subcutaneous local anesthetic. Anesth Analg 99(5): 1461-1464.

61. Ong CKS, Lirk P, Tan JMH, Sow BWY (2005) The analgesic efficacy of intravenous versus oral tramadol for preventing postoperative pain after third molar surgery. J Oral Maxillofac Surg 63(8): 1162-1168.

62. Pang WW, Mok MS, Chang DP, Yang TF, Huang MH (1998) Intradermal injection of tramadol has local anesthetic effect: a comparison with lidocaine. Acta Anaesthesiologica Sinica36(3): 133-136.

63. El-Sharrawy EA, El-Hakim IE, Sameeh E (2006) Attenuation of C-reactive protein increases after exodontia by tramadol and ibuprofen. Anesth Prog 53(3): 78-82.

64. Ceccheti MM, Negrato GV, de Melo Peres MPS, Deboni MCZ, Naclerio-Homem MG (2014) Analgesic and adjuvant anesthetic effect of submucosal tramadol after mandibular third molar surgery. Oral Surgery Oral Medicine Oral Pathology and Oral Radiology117(3): 249-254.

65. Foy SP, Shugars DA, Phillips C, Marciani RD, Condrad SM, et al. (2004) The impact of intravenous antibiotics on health-related quality of life and clinical recovery after third molar surgeon. J Oral Maxillofac Surg 2004; 62(1): 15-21.

66. Curran JB, Kennett S, Young AR (1974) Evaluation of the use of prophylactic antibiotics in the third molar surgery. Int J Oral Surg 3(1): P. 1-6.

67. Ren YF and Malmstrom HS (2007)Effectiveness of antibiotic prophylaxis in third molar surgery: a meta-analysis of randomized controlled clinical trials. J Oral Maxillofac Surg 65(10): 1909-1921.

68. Martin MV, Kanatas AN, Hardy P (2005) Antibiotic prophylaxis and third molar surgery. Br Dent J198:327-330.

69. Vlcek D, Razavi A, Kuttenberger JJ (2014) Antibiotics in third molar surgery. Swiss Dent J 124(3): 294-302.

70. Lloyd CJ, Earl PD (1994) Metronidazole: two or three times daily-a comparative controlled clinical trial of the efficacy of two different dosing schedules of metronidazole for chemoprophylaxis following third molar surgery. Br J Oral Maxillofac Surg32(3): 165-167.

71. Ramos E, Santamaría J, Santamaría G, Barbier L, Arteagoitia I(2016) Do systemic antibiotics prevent dry socket and infection after third molar extraction? A systematic review and meta-analysis. Oral Surg Oral Med Oral Pathol Oral Radiol 122(4): 403-425.

72. Lodi G, Figini L, Sardella A, Carrassi A, Del Fabbro M, et al. (2012). Antibiotics to prevent complications following tooth extractions. Cochrane Database Syst Rev. 2012 Nov 14;11:CD003811. doi: 10.1002/14651858.CD003811.pub2.

73. Lacasa JM, Jimenez JA, Ferras V, Bossom M, Sola-Morales O, et al. (2007) Prophylaxis versus pre-emptive treatment for infective and inflammatory complications of surgical third molar removal: a randomized, double-blind, placebo-controlled, clinical trial with sustained release amoxicillin/clavulanic acid (1000 / 62.5 mg). Int J Oral Maxillofac Surg 36(4): 321-327.

74. Mitchell DA (1986) A controlled clinical trial of prophylactic tinidazole for chemoprophylaxis in third molar surgery. Br Dent J 160(8): 284-286.

75. Delilbasi C, Saracoglu U, Keskin A (2002) Effects of 0.2% chlorhexidine gluconate and amoxicillin plus clavulanic acid on the prevention of alveolar osteitis following mandibular third molar extractions. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 94(3):301-304.

76. Halpern LR and Dodson TB (2007) Does prophylactic administration of systemic antibiotics prevent postoperative inflammatory complications after third molar surgery? J Oral Maxillofac Surg 65(2): 177-185.

77. Kaziro GSN (1984) Metronidazole and arnica montana in the prevention of post-surgical complications, a comparative placebo controlled clinical trial. Br J Oral Maxillofac Surg22(1): 42-49.

78. Arteagoitia I, Diez A, Barbier L, Santamaria G, Santamaria J (2005) Efficacy of amoxicillin/clavulanic acid in preventing infectious and inflammatory complications following impacted mandibular third molar extraction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 100(1): e11-e18.

79. Moore PA (1999) Dental therapeutic indications for the newer long-acting macrolide antibiotics. J Am Dent Assoc130(9): 1341-1343.

80. Addy LD, Martin MV (2004) Azithromycin and dentistry-a useful agent. Br Dent J 197: 141-143.

81. Williams JD, Maskell JP, Shain H, Chrysos G, Sefton AM, et al. (1992) Comparative in vitro activity of azithromycin, macrolides (erythromycin, clarithromycin and spiramycin) and streptogramin RP 59500 against oral organism. Journal of Antimicrobial Chemotherapy 30(1): 27-37.

82. Malizia T, Tejada MR, Ghelardi E, Senesi S, Gabriele M, et al. (1997) Periodontal tissue disposition of azithromycin. J Periodontol 68(12): 1206-1209.

83. Blandizzi C, Malizia T, Lupetti A, Pesce D, Gabriele M, et al. (1999) Periodontal tissue disposition of azithromycin in patients affected by chronic inflammatory periodontal diseases. J Periodontol 70(9): 960-966.

84. Lo Bue AM, Sammartino R, Chisari G, Gismondo MR, Nicoletti G (1993) Efficacy of azithromycin compared with spiramycin in the treatment of odontogenic infections. J Antimicrob Chemother 31(Suppl. E): 119-127.

85. Smith SR, Foyle DM, Daniels J, Joyston-Bechal S, Smales FC, et al. (2002) A double-blind placebo-controlled trial of azithromycin as an adjunct to non-surgical treatment of periodontitis in adults: clinical results. J Clin Periodontol 29(1): 54-61.

86. Markiewicz MR, Brady MF, Ding EL, Dodson TB (2008) Corticosteroids reduce postoperative morbidity after third molar surgery: a systematic review and meta-analysis. J Oral Maxillofac Surg 66(9): 1881-1894.

87. Herrera-Briones FJ, Prados Sánchez E, Reyes Botella C, Vallecillo Capilla M (2013) Update on the use of corticosteroids in third molar surgery: systematic review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol. 116(5): e342-51.

88. Fujii Y, Nakayama M, Nakano M (2008) Propofol alone and combined with dexamethasone for the prevention of postoperative nausea and vomiting in adult Japanese patients having third molars extracted. Br J Oral Maxillofac Surg 46(3): 207-210.

89. Sekhavat L, Davar R, Behdad S (2015) Efficacy of prophylactic dexamethasone in prevention of postoperative nausea and vomiting. J Epidemiol Glob Health 5(2): 175-179.

90. Kim K, Brar P, Jakubowski J, Kaltman S, and Lopez E (2009) The use of corticosteroids and nonsteroidal antiinflammatory medication for the management of pain and inflammation after third molar surgery: A review of the literature. Oral Surg Oral Med Oral Radiol Endod 107(5): 630-640.¬

91. Schultze-Mosgau S, Schmelzeisen R, Frölich JC, Schmele H (1995) Use of ibuprofen and methylprednisolone for the prevention of pain and swelling after removal of impacted third molars. J Oral Maxillofac Surg 53(1): 2-7.

92. Al-ShamiriHM, Shawky M, Hassanein N (2017) Comparative Assessment of Preoperative versus Postoperative Dexamethasone on Postoperative Complications following Lower Third Molar Surgical Extraction. International journal of dentistry

93. Ristimäki A, Narko K, Hla T (1996) Down-regulation of cytokine-induced cyclo-oxygenase-2 transcript isoforms by dexamethasone: evidence for post-transcriptional regulation. Biochem J 318(1): 325-331.

94. Alexander RE, Throndson RR (2000) A review of perioperative corticosteroid use in dentoalveolarsurgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 90(4): 406-415.

95. Üstün Y, Erdoğan Ö, Esen E, Karsli ED (2003) Comparison of the effects of 2 doses of methylprednisolone on pain, swelling, and trismus after third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 96(5): 535-539.

96. Phero JC (1984) Pharmacotherapy for chronic facial pain. Dental clinics of North America 28(3):471-491.

97. McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A (1995). Anticonvulsant drugs for management of pain: a systematic review. Bmj 311: 1047-1052.

98. Van Tulder MW, Koes BW, Bouter LM (1997). Conservative treatment of acute and chronic nonspecific low back pain: a systematic review of randomized controlled trials of the most common interventions. Spine 22(18): 2128-2156.

99. Herman CR, Schiffman EL, Look JO, Rindal DB (2002). The effectiveness of adding pharmacologic treatment with clonazepam or cyclobenzaprine to patient education and self-care for the treatment of jaw pain upon awakening: a randomized clinical trial. Journal of orofacial pain 16(1): 64-70.

100. De Santana Santos T, Calazans ACM, Martins-Filho PRS, Silva LCF, De Oliveira E Silva ED, et al. (2011) Evaluation of the muscle relaxant cyclobenzaprine after third-molar extraction. J Am Dent Assoc142(10): 1154-1162.

101. Kirmeier R, Truscnegg A, Payer M, Acham S, Schulz K, et al.(2007) Evaluation of a muscle relaxant on sequelae of third molar surgery: a pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 104(3): e8-e14.

102. Güneş HN, Bekircan-Kurt CE, Tan E, Erdem-Özdamar S (2017) The histopathological evaluation of small fiber neuropathy in patients with vitamin B12 deficiency. Acta Neurologica Belgica 1-6.doi: 10.1007/s13760-017-0847-y.

103. Ang CD, Alviar MJM, Dans AL, Bautista-Velez GGP, Villaruz-Sulit MVC, et al. (2008) Vitamin B for treating peripheral neuropathy. The Cochrane Library. doi: 10.1002/14651858.CD004573.pub3

104. Lee CH, Lee BS, Choi BJ, Lee JW, Ohe JY, et al. (2016). Recovery of inferior alveolar nerve injury after bilateral sagittal split ramus osteotomy (BSSRO): a retrospective study. Maxillofacial plastic and reconstructive surgery38:25, pp.1-4.

105. Oteri G, Cicciù M, Peditto M, Catalano A, Loddo S, et al. (2016) Does Vitamin D3 Have an Impact on Clinical and Biochemical Parameters Related to Third Molar Surgery. Journal of Craniofacial Surgery 27(2): 469-476.

106. Cosyn J, Sabzevar MM (2007) Subgingival chlorhexidine varnish administration as an adjunct to same-day full-mouth root planing. II. Microbiological observations. J Periodontol 2007; 78(3): 438-445.

107. Sridhar V, Wali GG, Shyla HN (2011) Evaluation of the perioperative use of 0.2% chlorhexidine gluconate for the prevention of alveolar osteitis after the extraction of impacted mandibular third molars: a clinical study. J Maxillofac Oral Surg 10(2): 101-111.

108. Cho H, Lynham AJ, Hsu E (2017) Post-operative interventions to reduce inflammatory complications after third molar surgery: Review of the current evidence. Australian Dental Journal 62(4): 412-419.

109. Farah CS, McIntosh L, McCullough MJ (2009) Mouthwashes. Aust Prescriber 32(6): 162-164.

110. QuintasV,Prada-LopezI,DonosN,Suarez-QuintanillaD,TomasI (2015) Antiplaqueeffectofessentialoils and 0.2% chlorhexidine on an in situ model of oral biofilm growth: a randomised clinical trial. PLoS ONE 10:e0117177 10.1371/journal.pone.0117177

111. Lim KS, Kam PCA(2008)Chlorhexidine-pharmacology and clinical applications Anaesth Intensive Care 36(4): 502-512.

112. Gilbert P, Moore LE (2005) Cationic antiseptics: diversity of action under a common epithet.J Appl Microbiol 99(4): 703-715.

113. Hugo WB, Longworth AR (1966) The effect of chlorhexidine on the electrophoretic mobility, cytoplasmic constituents, dehydrogenase activity and cell walls of Escherichia coli and Staphylococcus aureus J Pharm Pharmacol 18(9): 569-578.

114. Chawner JA, Gilbert P (1989) Interaction of the bisbiguanides chlorhexidine and alexidine with phospholipid vesicles: evidence for separate modes of action.J Appl Bacteriol 66(3): 253-258.

115. Caso A, Hung LK, Beirne OR (2005) Prevention of alveolar osteitis with chlorhexidine: a meta-analytic review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 99(2): 155-159.

116. DalyB,SharifMO,NewtonT,JonesK,WorthingtonHV (2012)Localinterventionsforthemanagementof alveolar osteitis (dry socket). Cochrane Database Syst Revdoi: 10.1002/14651858.CD006968.pub2

117. Silvestri DL, McEnery-StonelakeM (2013) Chlorhexidine:usesandadversereactions.Dermatit24(3): 112-118.

118. Pemberton MN, Gibson J (2012) Chlorhexidine and hypersensitivity reactions in dentistry. Br Dent J 213: 547-550.

119. Minguez-SerraMP,Salort-LlorcaC,Silvestre-DonatFJ (2009)Chlorhexidineinthepreventionofdrysocket: effectiveness of different dosage forms and regimens. Med Oral Patol Oral Cir Bucal 14: 445-449.

120. Filipovic-ZoreI,DivicZ,DuskiR,GnjatovicN,GaliçN,et al.(2011) Impactofozoneonhealingafter alveolectomy of impacted lower third molars. Saudi Med J 32(6): 642-644.

121. Pasqualini D, Cocero N, Castella A, Mela L, Bracco P (2005) Primary and secondary closure of the surgical wound after removal of impacted mandibular third molars: a comparative study. International journal of oral and maxillofacial surgery 34(1): 52-57.

122. Korkmaz YT, Mollaoglu N, Ozmeriç N (2015) Does laterally rotated flap design influence the short-term periodontal status of second molars and postoperative discomfort after partially impacted third molar surgery? Journal of Oral and Maxillofacial Surgery 73(6): 1031-1041.

123. Khande K, Saluja H, Mahindra U (2011) Primary and secondary closure of the surgical wound after removal of impacted mandibular third molars. Journal of maxillofacial and oral surgery 10(2): 112-117.

124. Bielsa JMS, Hernández-Bazán S, Diago MP (2008) Flap repositioning versus conventional suturing in third molar surgery. Med Oral Patol Oral Cir Bucal 13(2):138-

142.

125. Ricard AS, Nau O, Veyret A, Majoufre-Lefèbvre C, Laurentjoye M(2015) Comparison between closure and absence of closure after removal of fully impacted mandibular third molar: a prospective randomized study. Revue de stomatologie, de chirurgie maxillo-faciale et de chirurgie orale 116(1) 12-17.

126. Kirk DG, Liston PN, Tong DC, Love RM (2007) Influence of two different flap designs on incidence of pain, swelling, trismus, and alveolar osteitis in the week following third molar surgery. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 104(1): e1-e6.

127. Alqahtani NA, Khaleelahmed S, Desai F(2017) Evaluation of two flap designs on the mandibular second molar after third molar extractions. Journal of oral and maxillofacial pathology21(2): 317-318.

128. Borgonovo AE, Giussani A, Grossi GB, Maiorana C (2014) Evaluation of postoperative discomfort after impacted mandibular third molar surgery using three different types of flap. Quintessence International 45(4): 319-330.

129. Rabi A, Haris PMM, Panickal DM, Ahamed S, Pulikkottil VJ, et al. (2017) Comparative Evaluation of Two Different Flap Designs and Postoperative Outcome in the Surgical Removal of Impacted Mandibular Third Molar. The journal of contemporary dental practice 18(9): 807-811.

130. Desai A, Patel R, Desai K, Vachhani NB, Shah KA, et al.(2014) Comparison of two incision designs for surgical removal of impacted mandibular third molar: A randomized comparative clinical study. Contemporary clinical dentistry 5(2): 170-174.

131. Koyuncu BÖ, Çetingül E (2013) Short-term clinical outcomes of two different flap techniques in impacted mandibular third molar surgery. Oral surgery, oral medicine, oral pathology and oral radiology 116(3): e179-e184.

132. Sandhu A, Sandhu S, Kaur T(2010) Comparison of two different flap designs in the surgical removal of bilateral impacted mandibular third molars. International journal of oral and maxillofacial surgery 39(11): 1091-1096.

133. Kumar S, Sarumathi T, Veerabahu M, Raman U (2013) To Compare Standard Incision and Comma Shaped Incision and Its Influence on Post–Operative Complications in Surgical Removal of Impacted Third Molars. Journal of clinical and diagnostic research 7(7): 1514-1518.

134. Goldsmith SM, De Silva RK, Tong DC, Love RM (2012) Influence of a pedicle flap design on acute postoperative sequelae after lower third molar removal. International journal of oral and maxillofacial surgery 41(3): 371-375.

135. Pichler JW, Beirne OR (2001) Lingual flap retraction and prevention of lingual nerve damage associated with third molar surgery: a systematic review of the literature. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 91(4): 395-401.

136. Hashemi HM, Beshkar M, Aghajani R (2012) The effect of sutureless wound closure on postoperative pain and swelling after impacted mandibular third molar surgery. British Journal of Oral and Maxillofacial Surgery 50(3): 256-258.

137. Osunde OD, Adebola RA, Saheeb BD(2012) A comparative study of the effect of suture-less and multiple suture techniques on inflammatory complications following third molar surgery. International journal of oral and maxillofacial surgery 41(10): 1275-1279.

138. Sala-Pérez S, López-Ramírez M, Quinteros-Borgarello M, Valmaseda-Castellón E, Gay-Escoda C(2016) Antibacterial suture vs silk for the surgical removal of impacted lower third molars. A randomized clinical study. Medicina oral, patologia oral y cirugia bucal 21(1): e95-e102.

139. Bertrand B, Foletti JM, Bruneau S, Stroumsa R, Mancini J, Guyot L, Chossegros C (2013) Comparison between Polyglactin 910 (Vicryl®) versus irradiated Polyglactin 910 (rapid Vicryl®) for mucosal suture after wisdom teeth avulsion Revue de Stomatologie, de Chirurgie Maxillo-faciale et de Chirurgie Orale 114(2): 63-66.

140. Koyuncu BÖ, Zeytinoğlu M, Tetik A, Gomel MM (2015) Effect of tube drainage compared with conventional suturing on postoperative discomfort after extraction of impacted mandibular third molars. British Journal of Oral and Maxillofacial Surgery 53(1): 63-67.

141. Chukwuneke FN, Oji C, Saheeb DB (2008) A comparative study of the effect of using a rubber drain on postoperative discomfort following lower third molar surgery. International journal of oral and maxillofacial surgery 37(4): 341-344.

142. Kumar B, Bhate K, Dolas RS, Kumar SS, Waknis P(2016) Comparative Evaluation of Immediate Post-Operative Sequelae after Surgical Removal of Impacted Mandibular Third Molar with or without Tube Drain-Split-Mouth Study. Journal of clinical and diagnostic research 10(12): ZC46-ZC49.

143. Cerqueira PRF, do Egito Vasconcelos BC, Bessa-Nogueira RV(2004) Comparative study of the effect of a tube drain in impacted lower third molar surgery. Journal of Oral and Maxillofacial Surgery 62(1): 57-61.

144. Handa A, Agwani KM, Surendra SS, Rana SS, Agrawal A, et al. (2016) Effects of Tube Drain With Primary Closure Techniques On Postoperative Trismus And Swelling After Removal Of Impacted Mandibular Third Molars. Journal of Dental and Medical Sciences 15(3): 92-100.

145. Aydintug YS, Bayar GR, Gulses A, Misir AF, Ogretir O, et al. (2012) Clinical study on the closure of extraction wounds of partially soft tissue-impacted mandibular third molars. Quintessence Int 43(10): 863-870.

146. Zandi M (2008) Comparison of corticosteroids and rubber drain for reduction of sequelae after third molar surgery. Oral and maxillofacial surgery 12(1): 29-33.

147. Akota I, Alvsaker B, Bjørnland T (1998) The effect of locally applied gauze drain impregnated with chlortetracycline ointment in mandibular third-molar surgery. Acta Odontologica Scandinavica 56(1): 25-29.

148. Hu T, Zhang J, Ma JZ, Shao LN, Gu YF, et al. (2017) A novel method in the removal of impacted mandibular third molar: buccal drainage. Scientific Reports doi:10.1038/s41598-017-12722-8

149. Holland CS, Hindle MO(1984) The influence of closure or dressing of third molar sockets on postoperative swelling and pain. Br J. Oral Maxillofac Surg 22(1):65-71.

150. Rakprasitkul S, Pairuchvej V(1997) Mandibular third molar surgery with primary closure and tube drain. Int J Oral Maxillofac Surg 26(3): 187-190.

151. Silveira PCL, Silva LA, Freitas TP, Latini A, Pinho RA (2011) Effects of low-power laser irradiation (LPLI) at different wavelengths and doses on oxidative stress and fibrogenesis parameters in an animal model of wound healing. Lasers Med Sci 26(1):125-131.

152. Ferrante M, Petrini M, Trentini P, Perfetti G, Spoto G (2013) Effect of low-level laser therapy after extraction of impacted lower third molars. Lasers Med Sci 28(3): 845-849.

153. Kahraman SA, Cetiner S, Strauss RA (2017)The Effects of Transcutaneous and Intraoral Low-Level Laser Therapy After Extraction of Lower Third Molars: A Randomized Single Blind, Placebo Controlled Dual-Center Study. Photomed Laser Surg 35(8):401-407.

154. Aras MH, Güngörmüş M (2010) Placebo-controlled randomized clinical trial of the effect two different low-level laser therapies (LLLT)-intraoral and extraoral-on trismus and facial swelling following surgical extraction of the lower third molar. Lasers Med Sci25(5):641-645.

155. Petrini M, Ferrante M, Trentini P, Perfetti G, Spoto G (2017) Effect of pre-operatory low-level laser therapy on pain, swelling, and trismus associated with third-molar surgery. Med Oral Patol Oral Cir Bucal 22(4):e467-472.

156. Pallotta RC, Bjordal JM, FrigoL, Leal Junior ECP, Teixeira S, et al. (2011) Infrared (810-nm) low-level laser therapy on rat experimental knee inflammation. Lasers Med Sci 27(1): 71-78.

157. Coluzzi DJ, Convissar RA (2004) Lasers in clinical dentistry. Dent Clin North Am 48: 11-12.

158. Boschi ES, Leite CE, Saciura VC, Caberlon E, Lunardelli A, et al. (2008) Anti-inflammatory effects of low-level laser therapy (660nm) in the early phase in carrageenan-induced pleurisy in rat. Lasers Surg Med 40(7): 500-508.

159. Brignardello-Petersen R, Carrasco-Labra A, Araya I, Yanine N, Beyene J, et al. (2012) Is adjuvant laser therapy effective for preventing pain, swelling, and trismus after surgical removal of impacted mandibular third molars? A systematic review and meta-analysis. J Oral Maxillofac Surg 70(8): 1789-1801.

160. Pires D, Xavier M, Araújo T, Silva JA Jr, Aimbire F, et al. (2011) Low-level laser therapy (LLLT; 780 nm) acts differently on mRNA expression of anti- and pro-inflammatory mediators in an experimental model of collagenase-induced tendinitis in rat. Lasers Med Sci 26(1):85-94.

161. Lanzafame RJ (2011) Photobiomodulation, tissue effects and bystanders. Photomedicine and Laser Surgery 29(8): 519-520.

162. Huang H, Williams RC, Kyrkanides S (2014) Accelerated orthodontic tooth movement: Molecular mechanisms. Am J Orthod Dentofacial Orthop 146(5): 620-632.

163. Miron RJ, Fujioka-Kobayashi M, Bishara M, Zhang Y, Hernandez M, et al. (2017) Platelet-rich fibrin and soft tissue wound healing: A systematic review. Tissue Eng. Part B Rev 23(1): 83-99.

164. Marx RE(2004) Platelet rich plasma: evidence to support its use. J Oral Maxillofac Surg62: 489-496.

165. Dutta SR, Passi D, Singh P, Sharma S, Singh M, et al.(2016)A randomized comparative prospective study of platelet-rich plasma, platelet-rich fibrin, and hydroxyapatite as a graft material for mandibular third molar extraction socket healing. Natl J Maxillofac Surg7(1): 45-51.

166. Nathani DB, Sequeira J, Rao BHS (2015) Comparison of platelet rich plasma and synthetic graft material for bone regeneration after third molar extraction. AnnMaxillofac Surg 5(2): 213-218.

167. Dutta SR, Singh P, Passi D, Patter P (2015) Mandibular Third Molar Extraction Wound Healing With and Without Platelet Rich Plasma: A Comparative Prospective Study J Maxillofac Oral Surg 14(3): 808-815.

168. Albanese A, Licata ME, Polizzi B, Campisi G(2013) Platelet-rich plasma (PRP) in dental and oral surgery: from the wound healing to bone regeneration. Immun Ageing 10: 23.

169. Rutkowski JL, Fennell JW, Kern JC, Madison DE, Johnson DA (2007) Inhibition of Alveolar Osteitis in Mandibular Tooth Extraction Sites Using Platelet-Rich Plasma. J Oral Implantol 33(3): 116-121.

170. Al-Hamed FS, Tawfik MA, Abdelfadil E, Al-Saleh MAQ (2017) Efficacy of Platelet-Rich Fibrin After Mandibular Third Molar Extraction: A Systematic Review and Meta-Analysis. J Oral Maxillofac Surg 75(6):1124-1135.

171. Kao RT, Murakami S, Beirne OR (2009) The use of biologic mediators and tissue engineering in dentistry. Periodontol 2000 50(1): 127-153.

172. Gülşen U, Şentürk M (2017) Effect of platelet rich fibrin on edema and pain following third molar surgery: a split mouth control study. BMC Oral Health 17: 79.

173. Yelamali T, Saikrishna D (2015) Role of platelet rich fibrin and platelet rich plasma in wound healing of extracted third molar sockets: A comparative study. J Maxillofac Oral Surg 14(2): 410-416.

174. Baslarli O, Tumer C, Ugur O, Vatankulu B(2015) Evaluation of osteoblastic activity in extraction sockets treated with platelet-rich fibrin. Med Oral Patol Oral Cir Bucal 20(1): e111-116.

175. Kumar N, Prasad K, Ramanujam L, Ranganath K, Dexith J, et al. (2015) Evaluation of Treatment Outcome After Impacted Mandibular Third Molar Surgery With the Use of Autologous Platelet-Rich Fibrin: A Randomized Controlled Clinical Study. J Oral Maxillofac Surg 73(6): 1042-1049.

176. Singh A, Kohli M, Gupta N(2012) Platelet Rich Fibrin: A Novel Approach for Osseous Regeneration. J Maxillofac Oral Surg 11(4): 430-434.

177. Gruber R, Varga F, Fischer MB, Watzek G(2002) Platelets stimulate proliferation of bone cells: involvement of platelet-derived growth factor, microparticles and membranes. Clin Oral Implants Res 13(5):529–535.

178. Hoaglin DR, Lines GK (2013) Prevention of localized osteitis in mandibular third-molar sites using platelet-rich fibrin. Int J Dentdoi: 10.1155 / 2013/875380

179. Chakravarthi S(2017) Platelet rich fibrin in the management of established dry socket. J Korean Assoc Oral Maxillofac Surg 43(3): 160-165.

180. Yerke LM, Jamjoom A, Zahid TM, Cohen RE(2017) The Effect of Platelet-Rich Fibrin, Calcium Sulfate Hemihydrate, Platelet-Rich Plasma and Resorbable Collagen on Soft Tissue Closure of Extraction Sites. J Funct Biomater 8(2): 17. doi: 10.3390/jfb8020017

181. Jang ES, Park JW, Kweon H, Lee KG, Kang SW, et al. (2010) Restoration of peri-implant defects in immediate implant installations by Choukroun platelet-rich fibrin and silk fibroin powder combination graft. Oral Surg Oral MedOral Pathol Oral Radiol Endod 109(6): 831-836.

182. Greenstein G (2007) Therapeutic Efficacy of Cold Therapy After Intraoral Surgical Procedures: A Literature Review.Journal of Periodontology 78(5):790-800.

183. Markiewicz MR, Brady MF, Ding EL, Dodson TB (2008) Corticosteroids reduce postoperative morbidity after third molar surgery: a systematic review and meta-analysis. J Oral Maxillofac Surg 66(9):1881–1894.

184. Ibikunle AA, Adeyemo WL (2016) Oral health-related quality of life following third molar surgery with or without application of ice pack therapy. Oral Maxillofac Surg 20(3): 239-247.

185. Staats PS, Staats A, Hekmat H (2001) The additive impact of anxiety and a placebo on pain. Pain Med 2(4): 267-279.

186. Michlovitz SL, Bellew JW, Nolan TP Jr (2011) Modalities for therapeutic intervention. 5th edition. Philadelphia: F.A. Davis.

187. Sivalingam VP, Panneerselvam E, Raja KV, Gopi G (2017). Does Topical Ozone Therapy Improve Patient Comfort After Surgical Removal of Impacted Mandibular Third Molar? A Randomized Controlled Trial. Journal of Oral and Maxillofacial Surgery 75(1): 51.e1-51.e9.

188. Ghoreishian M, Gheisari R, Fayazi M (2009) Tissue adhesive and suturing for closure of the surgical wound after removal of impacted mandibular third molars: a comparative study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 108(1):e14-e16.

189. Joshi AD, Saluja H, Mahindra U, Halli R (2011) A Comparative Study: Efficacy of Tissue Glue and Sutures after Impacted Mandibular Third Molar Removal. J Maxillofac Oral Surg10(4): 310-315.