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Pain Control in Third Molar Surgery

Control del Dolor en Cirugía de Tercer Molar

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ABSTRACT: The sensation of pain at the surgical site may be increased and persist for long periods after the noxious stimulus has been removed. Post-operative pain from the extraction of impacted molar may cause serious discomfort to the patient resulting in considered moderate to severe in intensity. Analgesia for this surgical procedure is related to the use of nonsteroidal anti-inflammatory drugs, steroids, analgesics of central and peripheral actions used in combination or individually. The aim of this review is to show an update about the use and the physiological bases for indications of the analgesic therapy in third molar surgery.

KEY WORDS: third molar, pain, oral surgery.

INTRODUCTION

Pain can be produced peripherally, as a result of tissue damage and inflammation (inflammatory pain), central nervous system damage (neuropathic pain) or due to alterations in the normal function of the nervous system (functional pain) (Borsook, 2012). Hypersensitivity to pain may be a common post-operative symptom in surgical procedures. The sensation of pain at the surgical site may be increased and persist for long periods after the noxious stimulus has been removed, characterizing the process of hyperesthesia. Such increase in sensitivity may also result in pain at another area surrounding the surgical site which characterizes the concept of allodynia (Kelly *et al*., 2001).

There are two mechanisms involved in painful hypersensitivity: Peripheral sensitization, (threshold reduction and increase in the responsiveness of the peripheral afferent nociceptive terminals) and central sensitization (peripheral lesions trigger chemical change-over in the descendent pain control system) (Kelly *et al*.).

Post-operative pain from the extraction of impacted molar may cause serious discomfort to the patient (Chaparro-Avendaño *et al*., 2005). This is categorized as being of short to moderate duration, reaching its maximum intensity at the first post-operative twelve hours (De Menezes & Cury, 2010). Pain resulting from this kind of surgery is used as one of the main parameters for assessment of pharmacological efficacy of different analgesia methods. This article aims to review the literature regarding the main pharmacological methods for pain control in surgery of impacted molar.

PHYSIOPATHOLOGY

Inflammation produced by trauma at the surgical site and surrounding tissues is directly proportional to tissue damage (Osunde *et al*., 2012) and directly involved in tissue healing; therefore, a meticulous surgical technique is primordial to attenuate such condition. Classical signs of inflammation include pain, swelling, erythema, redness and loss of function, and

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several inflammatory mediators are involved, such as: prostaglandin, histamine, bradykinin and serotonin (Gersema & Baker, 1992).

During inflammation, prostaglandin and histamine levels are increased (Kelly *et al*.). Bradykinin plays a vast role in pro-inflammatory pharmacology, including a strong potential in pain production (Gersema & Baker). Prostaglandins are derived from arachidonic acid, which originates from the cellular membrane phospholipids. These are released though the action of phospholipase, activated by mechanical, chemical or physical stimuli (Gersema & Baker).

The metabolism of arachidonic acid follows through two main pathways: the cyclooxygenase (COX) or the lipoxygenase. COX is responsible for the production of prostaglandins (PGE2, PGD2, PGF2), Prostacyclin and Thromboxane A2; on the other hand the lipoxygenase leads to the formation of a family of compounds collectively named leukotrienes. The byproducts of these two ways play a key role in the inflammatory process (Kim *et al*., 2009).

Two isoforms of COX have been identified, COX-1 and COX-2, which have specific mechanisms of action, COX-1 is mainly constitutive of several organs and tissues, such as the gastric mucosa and kidneys, while COX-2 besides being constitutive of organs such as the brain, pancreas and kidneys, is highly inducible such as in the inflammatory processes and cancer (Turini & DuBois, 2002). COX-2 also influences ovulation, medullary bone synthesis, osteoblasts and osteoclasts activities and regulation of endothelial and platelet response (Giovanni & Giovanni, 2002). Non-steroidal anti-inflammatory drugs can suppress the COX pathway.

In 2002 high levels of a splice variant of COX-1 mRNA that retained intron 1 were isolated in the canine cerebral cortex and heart tissue. The splice variant has been called by various names such as cyclooxygenase-3 (COX-3), COX-1b, or COX-1v. The expression of COX-3 mRNA has been detected in human cerebral cortex, but there has been limited success in isolating the resultant enzyme. It is possible that the COX-3 pathway may be the primary central mechanism by which drugs such as paracetamol and phenacetin exert their analgesic and antipyretic effects (Simmons *et al*., 1999; Botting, 2000; Willoughby *et al*., 2000; Chandrasekharan *et al*., 2002; Serhan *et al*., 2002).

NON-STEROIDAL INFLAMMATORY DRUGS (NSAIDS)

NSAIDs act by inhibiting the COX-1 and COX-2 and are divided according to their effectiveness in inhibiting each isoform: selective COX-2 inhibitors; preferential COX-2 inhibitor; relatively poor selectivity and NSAIDs with weak inhibition of both COX-1 and COX-2 (many salicylates) (Katori & Majima, 2000); adverse effects associated with the use of NSAIDs are described in Table I (Kam & So, 2009).

A third isoform of COX (COX-3), which is selectively inhibited by analgesic/antipyretic drugs (such as acetaminophen, phenacetin, antipyrine and dipyrone) are strongly inhibited by some NSAIDs. This action of COX-3 may represent a primary central mechanism through which drugs act in the inhibition of pain and fever (Chandrasekharan *et al*.). Some studies indicate that COX-3 is less potent and produces less prostaglandin E2 (PGE2) as compared to COX-1 and COX-2 (Kam & So).

Two classic studies, evaluated the main adverse effect comparing non-selective and selective COX-2 drugs. Silverstein *et al*. (2000) in a work entitled CLASS (Celecoxib Long-term Arthritis Safety Study), evaluated and compared for six months 4.573 patients, using celecoxib (400mg twice a day), ibuprofen (800mg, three times a day) or diclofenac (75mg, twice a day), and Schnitzer *et al*. (2004) evaluated 18.325 patients during 52 weeks, comparing the use of lumiracoxib – the most selective of coxibs (400mg once a day), naproxen (500mg twice a day), or ibuprofen (800mg, three times a day); both studies concluded that adverse gastrointestinal effects are much less significant with the use of selective COX-2 drugs, compared to conventional NSAIDs (Schnitzer *et al*.).

De Menezes & Cury compared the efficacy of nimesulide and meloxicam for pain control, swelling and trismus after impacted molar surgery. They concluded that nimesulide is more effective in controlling swelling and trismus, however, similar in pain control. It was also found that nimesulide has a higher anti-inflammatory effect by suppressing the production or release of histamine, leukotrienes, pro-inflammatory cytokines and enzymes released by leukocytes (De Menezes & Cury). As a unique feature, nimesulide increases the cellular activity of endogenous glucocorticoids (Rainsford *et al*., 2006). Another study compared nimesulide (300mg) and ibuprofen (400 mg), and concluded that nimesulide has an onset of

Table I. Adverse Effects Associated with NSAIDs

Gastrointestinal Effects	Susceptibility to gastric bleeding and dyspepsia (Kam & So, 2009)
Hematologic	Modulation of platelet function and inhibition of thromboxane production (Kam & So)
Nephrotoxicity	Associated with the chronic use of NSAIDs (Kam & So)
Anaphylactoid reactions	Patients with hypersensitivity to NSAIDs (Kam & So)
Oral lichenoid hypersensitivity reactions	The two classes of medications historically associated are NSAIDs and antihypertensive agents (Yuan & Woo, 2015)
Simultaneous oral and cutaneous pemphigus vulgaris	Presents in the oral cavity are rare (Matz *et al.,* 1997)
Steven Johnson syndrome and toxic epidermal necrolysis	In Europeans (Lonjou *et al.,* 2008)

analgesic effect faster and more intense (Bocanegra *et al*., 2005).

Gutta & James (2013) in a double-blind, randomized trial tested the preemptive effect of ketorolac, intravenously, and found a decrease in pain and increase in length period for administration of rescue medication compared to placebo (Gutta & James). Different doses of meloxicam (7.5 and 15mg) were evaluated in the removal of inferior third molar surgery, with or without osteotomy. There was significant difference between the drug responses only with respect to the need for rescue medication in surgeries with osteotomy, suggesting the utilization in the concentration of 15mg for such procedure (Calvo *et al*., 2007).

In a different study, Morisson *et al*., evaluated the analgesic efficacy of rofecoxib (50mg), ibuprofen (400mg) and placebo for pain control in 152 patients undergoing oral surgery. Concluded that the analgesic potency of rofecoxib is similar to ibuprofen, but the action time for rofecoxib is superior (Morisson *et al*., 1999); Daniels *et al*. (2001) compared the analgesic effect of parecoxib, ketorolac or placebo and indicated that parecoxib 20mg and 40mg presents analgesic efficacy comparable to ketorolac 60mg. Parecoxib 40mg has a greater duration of action (Daniels *et al*.). In other study was compared Celecoxib (400 mg) and ibuprofen (400mg), the authors concluded that celecoxib has greater pain relief and lesser need of rescue medication (Cheung *et al*., 2007).

STEROIDAL ANTI-INFLATOMRY DRUGS (CORTICOSTEROID) IN ORAL SURGERY

Corticosteroids are synthesized at the cortex of the adrenal glands, they are steroids with a greater relative effect on the metabolism of carbohydrates, rather than the regulation of water and electrolytes, act by inhibiting the secretion of phospholipase A2 and stimulate the secretion of lipocortin (phospholipase A2 inhibitory protein) (Kim *et al*.). Corticosteroids receptors are virtually found in every cell in the body and exert a variety of physiological responses. They act as transcription factors for specific genes, stimulating or inhibiting its expression, which in this cellular level, their regulatory effects over the immune system (including effect on cytokines) are performed. In consequence of the change of gene expression and protein synthesis, its effect is not immediate, but it becomes apparent after a few hours, which has an impact on its clinical use (Yagiela *et al*., 1998).

The suppression of each stage of the inflammatory response appears to be the primary action of corticosteroids, such as the cellular recruitment (vasodilatation and diapedesis), inhibition of the formation of granulation tissue and the inhibition in secretion of enzymes (phospholipase, collagenase and elastase) and pro-inflammatory mediators (prostaglandins and prostacyclins) (Herrera-Briones *et al*., 2013; Holte & Kehlet, 2002).

The use of corticosteroids is palliative, and not curative, therefore the goal is to decrease the severity of symptoms that the patient may experience (Yagiela *et al*.). It is known that corticosteroids in different dosages are useful in the control of swelling and trismus (Herrera-Briones *et al*.).

A single large dose or therapy of corticosteroids for a few days has few side effects, the potential adverse effects are proportional to the intensity and duration of therapy; when prescribed for more than a week some signs of toxicity and suppression of the hypothalamic-pituitary-adrenal axis can be seen with effects such as hyperglycemia and glycosuria, swelling, hyperkalemia, altered distribution of body fat, increased susceptibility to infection and poor healing of wounds

(Nesbitt, 1995; Holte & Kehlet; Kim *et al*.). The use of corticosteroids is contraindicated in cases of ocular herpes, glaucoma, tuberculosis and psychosis, and relatively contraindicated in peptic ulcers, hypotension, diabetes mellitus, osteoporosis and chronic infection. The risk-benefit ratio must be considered before instituting therapy (Gersema & Baker). Corticosteroids reduce trismus and inflammation derived from third molar surgery and the beneficial effects seem to be greater when administered preoperatively compared with the postoperative use (Herrera-Briones *et al*.,). Braxendale evaluated the effectiveness of 8mg of dexamethasone and placebo in a single preoperative dose and found significantly lower pain score on the first postoperative day in patients using dexamethasone (Baxendale *et al*., 1993).

Another study assessing the use or not of dexamethasone 6mg, 12 hours preoperative and 12 hours postoperatively, found fifty percent of reduction of swelling and postoperative pain in the group with the medication (Schmelzeisen & Frölich, 1993). On the other hand, Neupert *et al*. (1992) assessing dexamethasone 4mg ??preoperatively, observed little difference in swelling, proving the need of adequate dose for its beneficial post-operative outcomes (Neupert *et al*.).

Beirne & Hollander (1986) evaluated the use of methylprednisolone and placebo in 32 patients and found significantly less edema and pain in the group with the medication, and Dione *et al*. (2003) demonstrated that dexamethasone alone is very effective in reducing inflammation and postoperative swelling, and when used in combination with ketorolac, has a greater reduction and control of postoperative pain, they also showed that PGE2 and thromboxane B2 (TxB2) levels are decreased with ketorolac but only TxB2 is reduced with dexamethasone. It was postulated that PGE2 is the major prostanoid responsible for peripheral pain and that ketorolac can reduce PGE2 levels in a certain critical level, capable of producing analgesia (Dionne *et al*., 2003). Buyukkurt *et al*. (2006) recommended in their study, the combination of prednisone and diclofenac for the management of edema, trismus and pain control, rather than to the use of diclofenac alone. In a study evaluating the levels of PGE2 in urine and saliva regarding the administration of placebo, ibuprofen, dexamethasone or a combination of the latter two (Buyukkurt *et al*.). Mehra *et al*. (2013) found that patients taking NSAIDs associated or not with dexamethasone show lower levels of PGE2 in the urine. It was also highlighted that the combination of drugs provides an improvement in postoperative parameters evaluated (Mehra *et al*.).

Christensen *et al*. (2013) in a double-blind study evaluated four types of combinations involving bupivacaine and lidocaine, methylprednisolone and placebo. The results indicated significant reduction of pain and postoperative swelling with the association between bupivacaine and methylprednisolone (Christensen *et al*.). The use of corticoids is suggested for a short period of time to prevent the adverse effects, as it is used in oral surgery. As an aid in the control of pain, they should still be associated with analgesic drugs (Alexander & Throndson, 2000; Markiewicz *et al*., 2008; Kim *et al*.; Alcântara *et al*., 2014). The plasma half-life is not a good indicator of the duration of the biological activity of each steroid. It is best reflected in the period of hormonal suppression of corticotropin by the pituitary gland after administration of a single dose of the corticoid. The long-acting dexamethasone is 30 times more potent than hydrocortisone, which is similar to natural cortisol.

OPIOIDS DRUGS IN ORAL SURGERY

Opioids are derived from opium and therefore are included in the class of the group of drugs that act on neuronal opioidergic receptors. Such receptors are implied in regulation of the pain sensation, producing analgesia sensation. They are used primarily in therapy of high intensity pain, from chronic to acute. The modulation is made by endogenous opioids (physiological) such as endorphins and encephalins, which are neurotransmitters.

There are three types of opioid receptors: mu, kappa and delta. The pharmacological effects of opioids may be useful or adverse, according to the dose and situation; each drug can produce effects of different intensity, depending on their specificity for one or other receptors as well as other characteristics (Yagiela *et al*.). Opioids, through their G protein-coupled receptors, inhibit adenylate cyclase and thereby reduce the content of intracellular cyclic-AMP. They also have effect on cationic channels, as they promote the opening of potassium channels and inhibit the opening of voltage-dependent calcium channels. This reduces both neuronal excitability and neurotransmitter release (Yagiela *et al*.). However, they do not show any anti-inflammatory activity (Herrera-Briones *et al*.).

The side effect of opioids is in the central nervous system, opioids can produce analgesia,

euphoria and dysphoria (at doses greater than those used for analgesia), respiratory depression, sedation, miosis, cough suppression, and nausea. Peripherally, in high doses, may also act in the gastrointestinal tract, causing constipation and biliary constriction. In the cardiovascular system they can cause hypotension and in smooth muscle it is observed an antidiuretic effect and bronchoconstriction (Yagiela *et al*.).

Breivik *et al*. (1999) compared the analgesic effect of diclofenac, paracetamol and codeine, alone or in combination. Found that the combination of diclofenac (100mg) with paracetamol (1g) with or without codeine, was in the overall results, superior to the others, pointed out that, when combined with codeine, adverse effects were observed (Breivik *et al*.). Garibaldi & Elder (2002) tested codeine at different concentrations (5, 7, 15 and 30 mg) alone or associated with ketorolac (10 mg). The duration of analgesic treatment decreased with increasing opioid dose and recommended the combination of 10mg of ketorolac with 15mg of codeine as the best cost-effective, with good analgesic efficacy and fewer adverse effects (Garibaldi & Elder). In a study of 119 patients, the preemptive effect of paracetamol (1g) + Codeine (60 mg), ibuprofen (600mg), diclofenac (100mg) or placebo were evaluated. The authors found no major difference between the analgesic response or side effects except for placebo (Joshi *et al*., 2004).

CLINICAL CONSIDERATIONS

The pain resulting from the removal of impacted third molar surgery, is considered moderate to severe in intensity, and is used as a parameter for evaluating the effectiveness of different drug therapies. Analgesia for this surgical procedure is related to the use of NSAIDs, steroids, analgesics of central and peripheral actions used in combination or individually.

The selective COX-2 NSAIDs were developed in order to provide lower gastrointestinal discomfort to patients with chronic use of conventional NSAIDs. However, other aspects besides the gastrointestinal safety profile should be considered. The adverse effects associated with selective COX-2 NSAIDs appear after their long-term use. For inflammatory modulation related to this type of surgery, their use is restricted to a short period of time, justifying its use with safety, without the referred collateral effects (Silverstein *et al*.; Schnitzer *et al*.). Its use compared to conventional NSAIDs, have longer duration of action, greater analgesic efficacy and lower gastrointestinal adverse effects (Morrison *et al*., 1999; Daniels *et al*.; Cheung *et al*.).

Compared to other conventional NSAIDs, nimesulide was more effective in controlling postoperative pain and inflammation, as well as present a faster onset of action (Bocanegra *et al*.; Rainsford *et al*.). Drug's cost must be considered in the prescription of drugs to the patient.

According to the literature reviewed, the use of non-steroidal anti-inflammatory drug was effective in limiting the swelling and trismus postoperatively, related to removal of impacted 3M (Beirne & Hollander; Schmelzeisen & Frölich; Buyukkurt *et al*.; Herrera-Briones *et al*.). To obtain satisfactory effect, their use should be made in a preemptive manner and in appropriate dosage (Baxendale *et al*.; Herrera-Briones *et al*.). By interfering in the hypothalamic-pituitary-adrenal axis, this class of drugs should be used for a maximum of five days (Kim *et al*.).

The works studied, showed that certain associations of anti-inflammatories and analgesics may be more effective than the use these medications alone (Dionne *et al*.; Buyukkurt *et al*.; Kim *et al*.; De Menezes & Cury; Mehra *et al*.). Opioids can be a good choice for patients who do not tolerate the use of NSAIDs. The prescription of pharmacological methods of analgesia should follow some principles that include: selection of a drug with sufficient potency to control the anticipated pain, the medication should be administered before the onset of pain, using the lowest doses necessary at regular and frequent intervals (Mutlu *et al*., 2013).

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RESUMEN: La sensación de dolor en el sitio quirúrgico puede ser mayor y persistente por largos periodos de tiempo después de que el estímulo nocivo ha sido retirado. El dolor postoperatorio desde la extracción de un molar impactado puede causar molestias moderadas o severas en intensidad. La analgesia para estos procedimientos son relacionadas con el uso de fármacos antiinflamatorios no esteroidales, esteroides, analgésicos de acción central y periféricos utilizados en combinación o individualmente. El objetivo de esta revisión es mostrar una puesta al día en el uso y las bases fisiológicas para la indicación de terapia analgésica en cirugía de tercer molar.

PALABRAS CLAVE: tercer molar, dolor, cirugía oral.

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