Analgesic drugs in dentistry: a narrative review

Bianca D'Orto*
Carmen Baldi*
Vanessa Bonafede*
Andrea Pacifici°
Imma Ianniceli*
Matteo Nagni*

*Dental School, Vita-Salute San Raffaele University, Milan, Italy and Department of Dentistry, IRCCS San Raffaele Hospital, Milan, Italy
°Libero Professionista PhD Sapienza University of Rome, Rome, Italy.

Abstract

Pre- and post-operative pain are among the most difficult problems to manage in dental practice. There are various factors that could influence these conditions: from the patient's susceptibility to the clinical practice performed. However, an adequate management of both allows to considerably improve the patient's compliance and, at the same time, the satisfaction of the latter. All articles and reviews considered in this brief review, were searched on the online platform of scientific reading sites such as PubMed and Medline, selecting the most current ones, up to January 2022. Considering the keywords "Analgesic drugs", "dentistry" AND "dental pain", randomized controlled trials (RCTs), prospective studies, observational studies, reviews, and retrospective studies were considered.
The aim of this narrative review is to describe the several therapeutic techniques allowed to reduction of pre- and post-operative pain during clinical dental practice, so as to be able to outline in a linear and concise way some brief clinical guidelines that can be easily consulted.

Keywords: analgesic drugs, dentistry, dental pain, drug-kinetics, drug-dynamics.

INTRODUCTION

Pre- and post-operative pain management appears to be one of the main issues that dentists have to deal with in their daily practice. To undergo dental treatment without pain is the patient's main wish.
IASP (international association for the study of pain) defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage".
Depending on the pathogenesis, pain can be classified into four main categories:

1. nociceptive, transient pain in response to a peripheral stimulation.
2. inflammatory, instantaneous pain related to a painful hypersensitivity resulting from inflammatory tissue damage. Depending on the site involved, it is subdivided into:
   - superficial somatic (skin or mucous membranes)
   - deep somatic (muscles, bones, joints)
   - visceral (internal viscera)
3. neuropathic, pain occurring in the peripheral or central nervous system, in the absence of a nociceptive insult.
4. psychogenic, pain caused by an abnormal interpretation of perceptual messages, in the absence of verifiable damage to the nervous system.

Biochemical basis of dental pain

Dental pain is predominantly inflammatory and is caused by the release of chemical mediators from tissue cells, mediators that are referred to as 'prostanoids'.
This category of chemical mediators, which includes a whole series of molecules such as histamine, bradykinin, thromboxane A_2, prostaglandins (PGE_2, PGD_2, $PGF_{2\alpha}$), and substance P, is capable of overcoming cell membrane defences so that it can interact with specific high-affinity protein receptors located at nerve endings (with a greater prevalence in C a-myelin fibres).
As a result of trauma and surgery, prostanoids are released into soft tissue, hard and connective tissue. Histamine, bradykinin and substance P sensitise nerve endings, leading to oedema formation during the early stages of inflammation; prostaglandins, on the other hand, protract pain sensation. Thus, it can be argued that the main contributors to primary hyperalgesia (i.e. an increased response to a painful stimulus) are prostanoids, fatty acids derived from arachidonic acid, a constituent part of membrane phospholipids. Phospholipase A_2, after being released from membranes following trauma, converts arachidonic acid into PGH_2, which leads to the release of prostanoids through the activity of a particular enzyme, COX-2 (type 2 cyclooxygenase). COX-2 is inhibited non-selectively by non-steroidal analgesic drugs (NSAIDs).

WHO Analgesic Scale

However, pain is generally identified as a subjective nociceptive sensation, which is why it is not easy for the

clinician to quantify and localise the pain stimulus. To this end, the WHO has developed an analgesic pain scale, which is a classification of pain from one to ten according to the nociceptive sensation experienced by the patient, where one is the minimum pain and ten is the maximum pain. It is a very useful and validated scale and represents a guideline for pain therapy in dentistry. Thus, the choice of drug will be related to the mechanism of action and the potency of the pain.
Analgesics are more effective in preventing the onset of pain than in relieving existing pain, as long as they are administered regularly.

MATERIALS AND METHODS

All articles and reviews considering the topic of pain management in dentistry were searched on the online platform of scientific reading sites such as PubMed and Medline, selecting the most current ones, up to January 2022, including any language. Considering the keywords “Analgesic drugs”, “dentistry” AND “dental pain”, randomized controlled trials (RCTs), prospective studies, observational studies, reviews, and retrospective studies were considered. Textbooks relevant to the topic were then examined, and the citations of each retrieved article and those of reviews and expert opinions were examined to include as much knowledge as possible.

LITERATURE REVIEW ON ANALGESIC DRUGS IN DENTISTRY

Pharmacological types

The analgesics used in dentistry are numerous and belong to different categories; therefore, their use must be thoughtful and specific to the individual clinical case.

Analgesic drugs with central mechanism of action

Paracetamol

Paracetamol or acetaminophen is an active ingredient with antipyretic and analgesic activity and has a weak anti-inflammatory effect. It is considered a quite safe drug, so that its use, with the appropriate dosage, is also recommended for paediatric patients.
From the chemical point of view, paracetamol is a derivative of para-aminophenol, obtained by acetylation of the latter. Paracetamol is now available by several routes of administration:

- oral
- rectal
- parenteral

It has a synergistic action with NSAIDs and opioids. Recommended doses should be between 1000 and 1500 mg.
The administration of paracetamol 1000 mg + codeine 60 mg at the end of oral surgery reduces pain intensity and prolongs postoperative analgesia.
Side effects may possibly include liver toxicity; kidney damage; allergic reactions, on the other hand, are quite rare.
Doses of paracetamol of 500 mg + codeine 30 mg are indicated in less severe odontostomatological pain.

Corticosteroids

Corticosteroids, also called cortico-adrenal hormones or corticoids, are a group of steroid hormones synthesised in the cortical of the adrenal gland. They can be divided into three categories: glucocorticoids, mineralocorticoids and sex hormones.
Corticosteroids cause important anti-inflammatory effects mainly through a reduction in capillary permeability. The anti-inflammatory effect of glucocorticoids (cortisol, prednisone, etc.) is mostly mediated by an inhibition of the transcription of genes that regulate the production of most inflammatory cytokines and type 2 cyclo-oxygenase.
The most widely used in dentistry are triamcinolone, betamethasone and dexamethasone, which have half-lives of 24-48 hours, 36-54 hours and 36-54 hours respectively.
The effectiveness of synthetic corticosteroids in oral surgery is still controversial, as there are no protocols universally accepted by the international scientific community.
However, the active ingredients most commonly used in oral surgery and their respective dosages are:

- Methylprednisolone
  Dosage: (0.5-1 mg/kg/day) for a normal-weight adult about 40 mg one hour before surgery (half-life 2.4-3.5 hours) and after 12 hours. Same dosage every 12 hours on subsequent days for no more than 24-48 hours to avoid cortico-adrenal inhibition.
- Dexamethasone
  Anti-inflammatory and anti-reactive activity 8-10 times greater than prednisolone.
  Dosage: 8-16 mg dexamethasone one hour before surgery and 8-16 mg every six hours for no more than 24-48 hours to avoid cortico-adrenal inhibition.

However, even these substances are not free of various side effects, such as delayed wound healing, suppression of adrenergic activity, hyperglycaemia, water-saline retention, hirsutism, acne, skin streaks, obesity, etc.
All these side effects only become apparent when administered in large doses and over long periods of time. Single doses, on the other hand, are considered safe for healthy patients.
Corticosteroids have therapeutic indications in dentistry in cases of:

- non-herpetic mucosal lesions
- nerve damage caused by surgery or trauma
- phlebitis
- prophylaxis of preoperative surgical oedema
- endodontic therapy (to relieve pain of peri-apical origin)
- prophylaxis of PONV (post-operative Nausea and Vomiting)

A meta-analysis by Markiewicz MR. et al. 2008, conducted to evaluate the effect of corticosteroids in the control of lockjaw, oedema, and pain following lower third molar surgery, revealed that peri-operative administration of corticosteroids results in a reduction of post-operative oedema and lockjaw.

Antibiotics

In dentistry, antibiotics are drugs prescribed daily by the clinician for both prophylaxis and therapy against bacterial infections. Despite this, the use of antibiotics as attenuators of nociceptive stimuli is still a matter of debate in the scientific community today.

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These drugs can be administered locally or systemically. The systemic use of antibiotics, particularly after third-molar extraction, has been proposed by several authors; however, this use does not seem to have any additional effectiveness compared to local antibiotic administration in preventing inflammatory oedema and post-operative pain.

The use of antibiotics is indicated in the immuno-compromised patient or in cases where an active infection is present at the time of surgery. In such cases, the administration of an antibiotic can more effectively prevent the symptoms of infection and the resulting post-operative pain.

In dentistry, the prescription of antibiotics is empirical because the dentist does not know which microorganisms are responsible for the infection, as samples from the root canal or peri-apical region are not commonly taken and analysed. However, it has recently been seen that the additional use of PACS (portable air cleaners) during dental practice can reduce the amount of bacterial micro-particles, thus being able to help the anti-bacterial action provided by antibiotics. The effectiveness of the PAC is confirmed from a microbiological point of view as there is a reduction ranging from 69 to 80% in professional dental hygiene activity and from 62 to 66% during simple surgery activity.

However, the most widely used antibiotic is amoxicillin, due to its sufficiently broad spectrum, efficacy, low incidence of resistance, pharmacokinetic profile, tolerance, and dosage.

The main antibiotics prescribed in the adult dental patient have been summarised in **Table 1**.

Adverse effects of antibiotics, particularly of the beta-lactam class (the most used drugs in dentistry) include anaphylaxis, bacterial resistance, dysentery, or other allergic reactions, especially skin rashes, which may occur during or days after treatment.

Macrolides, tetracyclines, erythromycin, clindamycin and ketoconazole are potentially toxic and particularly contra-indicated in patients with liver disease. In addition, tetracyclines may interfere with glycaemic control in diabetic patients.

Analgesic drugs with peripheral mechanism of action

Non-steroidal analgesic drugs (NSAIDs)

They are called 'non-steroidal' because they do not have a steroidal structure like that of cortico-steroid drugs. The category of non-steroidal anti-inflammatory drugs is extremely broad and includes many active ingredients that can be classified rendering to their chemical structure and action. NSAIDs commercially available are about 25-30.

It is a category of drugs with a variety of effects, including antipyretic, anti-inflammatory and analgesic effects, and inhibition of platelet release and free radicals.

NSAIDs inhibit cyclooxygenase (COX), the enzyme responsible for converting arachidonic acid into prostaglandins and thromboxanes.

About anti-inflammatory therapy, the identification of two different forms of cyclooxygenase has been of fundamental importance: COX 1 and COX 2.

The first is involved in general homeostasis and is found in most tissues and organs. COX 2, on the other hand, is not detected in tissues and only appears in response to certain stimuli. Based on this difference, anti-inflammatory therapy has increasingly shifted to selective COX-2 inhibitors, referred to as coxib drugs.

NSAIDs reduce the inflammatory response to surgical trauma, more or less intensely depending on the drug used. The administration of NSAIDs with predominantly anti-inflammatory activity should begin a few hours before dental surgery to prevent the inflammatory process.

The anti-platelet effects are mainly exerted at the site of the operation and on the gastric mucosa, leading, in the latter case, to a haemorrhagic gastropathy pathology. The effects on the gastric mucosa consist of microbloodings which correlate with the duration of drug therapy. NSAID-induced gastric mucosal lesions are related to a combination of inhibition of gastric cyclooxygenase and cytoprotective prostaglandin deficiency, resulting in altered mucosal blood flow.

Those most at risk of gastropathy following the use of NSAIDs are:

- female patients over 60 years of age
- patients on oral anticoagulant and/or antiplatelet therapy
- patients with a history of gastric ulceration
- poly-therapy patients
- patients with previous NSAID intolerance

Caution is required when using COXIBs in patients:

- diabetics
- hypertensives
- hyper-lipidemic
- smokers

NSAIDs are contraindicated in the presence of ischaemic heart disease and/or cerebrovascular disease; cardiac insufficiency; post-operative aorto-coronary bypass surgery.

For patients with swallowing difficulties, suspensions and granules are preferable to solid tablets.

Instead, an injection formulation is recommended in patients refractory to oral administration and if an immediate analgesic effect is desired.

Table 1. Main antibiotics prescribed to the adult dental patient and dosage.

ACTIVE PRINCIPLE	DAILY DOSE	MAINTENANCE DOSE
Amoxicillin with or without clavulanic acid	1000 mg	500 mg every 8 h or 875 mg every 12 h
Clindamycin	600 mg	300 mg every 6 h
Clarithromycin	500 mg	250 mg every 12 h
Azithromycin	500 mg	250 mg every 24 h
Metronidazole	1000 mg	500 mg every 6 h

In addition, acetyl salicylic acid, a widely used NSAID, may interfere with glycaemic control in diabetic patients.

Opioids

Opioids represent the treatment of choice for acute post-operative pain, both moderate and severe. Those most commonly used in dental practice include codeine and tramadol, which fall into the category of weak opioids. Morphine, and its related compounds, act as agonists through a stereo-selective interaction with saturable membrane receptors, which are unevenly distributed throughout the central nervous system.
The prescription of opioids may be indicated in acute or chronic pain because of their obvious analgesic effects; however, they do not exempt significant risks such as respiratory depression, altered mental status, nausea, vomiting, pruritus, constipation, urinary retention and slowed bowel movement. Moreover, the main unfavourable effects seem to be dose-dependent.
The administration of opioids by the dentist in the presence of chronic pain, particularly if the pathology is unknown, must be supported by an additional approach with pain specialists.

Local anaesthetics

This is a heterogeneous group of active ingredients which, acting at different sites and with different mechanisms of action, induce anaesthesia.
The term “local anaesthesia” refers to the loss of sensation in a specific area. These drugs can be used either topically (creams, gels) or infiltrative (plexic or truncular anaesthesia).
However, it is important to emphasise that local anaesthetics do not induce analgesia because, unlike anti-inflammatory drugs, they do not inhibit the synthesis and release of pain mediators, nor do they interact with pain receptors.
It is known, however, that long-acting local anaesthetics prolong the duration of post-operative analgesia, especially in more complex implant-prosthetic rehabilitations. Bupivacaine and ropivacaine are useful for this purpose. Bupivacaine is widely used in oral surgery mainly for soft tissue infiltration, prolonging post-operative analgesia, especially when combined with adrenaline; this anaesthetic drug is very effective in soft tissue infiltration after oral surgery (such as extraction of third molars included) and in implantology. Bupivacaine and ropivacaine, which are long-acting local anaesthetics, should only be used in the adult population, as they may cause undesirable reactions in children and the disabled.
Among the local anaesthetics that have a great validation in clinical practice is lidocaine: the latter is used at a concentration of 2%, often in combination with adrenaline (a vasoconstrictor drug). The combination of these two compounds (lidocaine at 2% and adrenaline diluted 1:100,000) is an effective preparation to obtain a powerful analgesic effect before dental procedures such as fillings, apicoectomy, devitalizations, dental extractions, or whatever.
Nevertheless, it too is not free from side effects, such as possible mucosal reactions, skin rashes, and even anaphylactic shock, although this latter reaction occurs in people allergic to lidocaine, a condition extremely rare.
Local anaesthetics may be toxic in the event of overdose, or in the event of incorrect intravascular injection. Toxic effects on the cardiovascular system are manifested by a decrease in blood pressure, up to and including ventricular fibrillation, an extremely serious but very sporadic event.
A further adverse reaction to local anaesthetics is methemoglobinemia, the oxidation of haemoglobin from the ferrous to the ferric state, which can cause cyanosis in fetus. This is particularly attributable to prilocaine and benzocaine; for this reason, the FDA advises against the use of these drugs in pregnancy.
Anaesthetics with and without vasoconstrictors are summarized in **Table 2**, with the corresponding maximum dosage.

Post-operative pain management

A preliminary estimate of postoperative pain is useful for the establishment of a predefined analgesic scheme, using non-opioid analgesics administered singly or in combination, possibly with opioid drugs.

- In the presence of mild pain, an administration of:
  - Ibuprofen 200/400 mg every 4/6 hours as needed.
- In the case of mild to moderate pain, the administration of:
  - Ibuprofen should be about 400/600 mg every 6 hours at regular intervals for the first 24 hours; thereafter as required.
- Then, in the presence of moderate-to-severe pain, the administration of: Ibuprofen 400/600 mg combined with paracetamol 500 mg every 6 hours at regular intervals for the first 24 hours; thereafter as needed.
- Finally, in the presence of severe pain, an administration of:
  - Ibuprofen 400/600 mg combined with paracetamol 500 mg and hydrocodone 10 mg every 6 hours at regular intervals for the first 24/48 hours; then ibuprofen 400/600 mg combined with paracetamol 500 mg as required.

Table 2. Posology of main anaesthetics prescribed in dentistry.

	MAXIMUM DOSE WITH VASOCONSTRICTOR	MAXIMUM DOSE WITHOUT VASOCONSTRICTOR
LIDOCAINE 2%	7 mg/kg	4,4 mg/kg
ARTICAINE 4%	7 mg/kg (adult) 5 mg/kg (child)	/
MEPIVACAINE	2% 6,6 mg/kg	3% 4,4 mg/kg

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Injection formulations for increasing severity of pain

- Paracetamol
  Vials: 1,000 mg
  Dosage: 1,000-2,000 mg every 6-8 hours
  (Maximum daily dose 8,000 mg).
- Tramadol
  Vials: 100 mg
  Dosage: 100 mg every 6-8 hours.
- Pentazocine lactate
  Vials: 30 mg
  Dosage: 30 mg every 3-4 hours.

CONCLUSION

In the treatment of pain in dentistry, the clinician must consider several key points to establish the most suitable and appropriate therapy for the clinical case in question:

- drug-kinetics, drug-dynamics and drug-genetics of the therapeutic medium used
- effective, and possibly immediate, analgesic treatment
- elimination of the source of the painful stimulus possible, through dental procedures
- assess the possible adverse effects of each individual drug class
- analysing and assessing the medical and dental history of the individual patient before any drug therapy is initiated
- favouring the use of NSAIDs over opioids.

It is therefore of fundamental importance to be able to establish and understand the patient's requests to analyse the degree and type of pain that the patient is suffering; this will allow the determination of adequate analgesia to reduce the nociceptive sensation before the dental procedure is performed.

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