

PATHOPHYSIOLOGY OF ACUTE POSTOPERATIVE PAIN AND SCIENTIFIC RATIONALE OF "PRE-EMPTIVE ANALGESIA"

 **FISIOPATOLOGIA DEL DOLORE ACUTO POST-OPERATORIO E RAZIONALE SCIENTIFICO DELLA "PRE-EMPTIVE ANALGESIA"**

 **FISIOPATOLOGÍA DEL DOLOR POSTOPERATORIO AGUDO Y FUNDAMENTO CIENTÍFICO DE "PRE-EMPTIVE ANALGESIA"**

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Abstract

Background: The dentoalveolar surgery, in particular the extraction of mandibular impacted third molars, is the most commonly performed one in Oro-Maxillo-Facial surgery. As demonstrated by clinical experience, this type of intervention can be affected by a series of post-operative sequelae, and Acute Postoperative Pain (APP) is the less tolerated by the patient. In recent decades, the practical need to minimize the pain that follows an extraction, together with improved understanding of the pathophysiological mechanisms of pain, led to the research of new analgesic techniques. An improvement was the idea to "prevent the pain development rather than treating it post-operatively", this innovation led us to develop the technique known as "Pre-Emptive Analgesia" (preventive analgesia). Despite the promising results obtained with "Pre-Emptive Analgesia" experimental models, clinical results are not unambiguous.

Objectives: The objective of this study is to describe the rational basis of "Pre-Emptive Analgesia" technique and its controversies presented in literature concerning this analgesic method.

Methods: The method consisted in a careful analysis of the pathophysiological mechanisms underlying the acute post-operative pain in order to explain the scientific rationale of "Pre-Emptive Analgesia".

Results: Even if the "Pre-Emptive Analgesia" has been amply demonstrated in experimental models, its practical application is still very much debated. The conflict subjects are the proper name and the definition of "Pre-Emptive Analgesia", as well as the drug choice that is used for the pre-emptive treatment and its treatment regimen (route of administration, timing, dose, dosage and duration of treatment). Another problem concerning the "Pre-Emptive Analgesia" is that most clinical studies concern major surgery in which painful stimuli differ widely in terms of intensity and duration from those obtained in ambulatory surgery with local anaesthetics. It is also demonstrated that "Pre-Emptive Analgesia" effectiveness is influenced by the type of surgery performed. Consideration should also be given to the fact that the acute post-operative pain, being a multidimensional experience, is linked to psychological factors that influence the results obtained with the "Pre-Emptive Analgesia".

Discussion and Conclusions: The concept of "Pre-Emptive Analgesia" evolved in the course of time until it was definitively given the correct rational basis on which it is based, but unfortunately it still remains a very controversial topic. Despite that, the clinicians' confidence about the potential of pre-emptive analgesia remains high. It is therefore clear that further studies are needed to arrive at an unanimous opinion in the scientific community regarding its clinical application in ambulatory oral surgery.

Abstract

Introduzione: La chirurgia dentoalveolare, in particolare l'estrazione dei terzi molari mandibolari inclusi, è l'intervento più comunemente eseguito nel campo della Chirurgia Oro-Maxillo-Facciale. Come dimostrato dall'esperienza clinica, questo tipo di intervento può essere gravato da una serie di sequele post-operatorie, di cui la meno tollerata dal paziente è il Dolore Acuto Post-Operatorio (Acute Postoperative Pain, APP). Negli ultimi decenni, la necessità pratica di minimizzare il sintomo doloroso post-avulsivo, assieme alla migliorata comprensione dei meccanismi fisiopatologici del dolore, hanno portato alla ricerca di nuove tecniche analgesiche. Una svolta si è avuta con l'introduzione dell'idea di "prevenire lo sviluppo del dolore anziché trattarlo post-operatoriamente", innovazione che ha portato a sviluppare la tecnica nota come "Pre-Emptive Analgesia" (analgesia preventiva). Nonostante i promettenti risultati ottenuti dalla Pre-Emptive Analgesia nei modelli sperimentali, i risultati clinici non sono altrettanto univoci.

Obiettivi: Il presente articolo si pone lo scopo di descrivere quello che è il razionale di base di questa tecnica e le controversie presenti in letteratura relativamente a questa metodica analgesica.

Metodi: I metodi sono consistiti in un'accurata analisi dei meccanismi fisiopatologici alla base del dolore acuto post-operatorio, allo scopo di spiegare il razionale scientifico della "Pre-Emptive Analgesia".

Risultati: Nonostante la "Pre-Emptive Analgesia" sia stata ampiamente dimostrata nel modello sperimentale, la sua applicazione pratica è ancora profondamente dibattuta. I motivi di contrasto spaziano dalla corretta denominazione e definizione della "Pre-Emptive Analgesia", fino alla scelta del farmaco da usare per il trattamento Pre-Emptive ed il suo regime di utilizzo (via di somministrazione, timing, dose, posologia e durata del trattamento). Un altro problema inerente la "Pre-Emptive Analgesia" riguarda il fatto che la maggior parte degli studi clinici si riferiscono ad interventi di chirurgia maggiore, in cui gli stimoli dolorosi differiscono molto per natura intensità e durata da quelli ottenuti in chirurgia ambulatoriale e anestesia locale. Inoltre è appurato che l'efficacia della "Pre-Emptive Analgesia" è influenzata dal tipo di chirurgia eseguita. Occorre infine considerare il fatto che il Dolore Acuto Post-Operatorio, essendo un'esperienza multidimensionale, è legata a fattori di carattere psicologico che influenzano i risultati ottenibili con la "Pre-Emptive Analgesia".

Discussione e Conclusioni: Il concetto di "Pre-Emptive Analgesia" si è evoluto nel corso del tempo fino ad arrivare a determinare in maniera definitiva il corretto razionale di base su cui si fonda, anche se rimane ancora oggi un argomento molto controverso. Nonostante questo, la fiducia dei clinici circa le potenzialità della "Pre-Emptive Analgesia" rimane alta. Appare quindi evidente la necessità di ulteriori studi per giungere ad un'opinione concorde nella comunità scientifica internazionale riguardo alla sua applicazione clinica in chirurgia orale ambulatoriale.



Resumen

Introducción: La Cirugía dentoalveolar, en particular la extracción de terceros molares mandibulares incluidos, es la cirugía más comúnmente realizada en Oro-maxilofacial. Como la experiencia clínica demuestra, este tipo de intervención puede ser cargado por una serie de secuelas postoperatorias; la menos tolerada por el paciente es el Dolor Agudo Post-Operatorio (Acute Postoperative Pain, APP). En las últimas décadas, la necesidad práctica para reducir al mínimo los síntomas de dolor post-avulsivo y para mejorar la comprensión de los mecanismos fisiopatológicos del dolor, han llevado a la búsqueda de nuevas técnicas analgésicas. Un avance se produjo con la introducción de la idea de "prevenir el desarrollo del dolor" en lugar de tratarlo Post-Operatorialmente; esta innovación ha llevado a desarrollar la técnica conocida como "Pre-Emptive Analgesia" (analgésia preventiva).

A pesar de los prometedores resultados de la "Pre-Emptive Analgesia" en modelos experimentales, los resultados clínicos no son igualmente únicos.

Objetivos: Este artículo pretende describir lo que es la base racional de esta técnica y las controversias en literatura sobre esta metodica analgesica.

Métodos: Los métodos consistieron en un análisis profundo de los mecanismos fisiopatológicos a la base del dolor agudo postoperatorio para explicar el fundamento científico de la "analgésia preventiva".

Resultados: La aplicación práctica de la "analgésia preventiva" es aún muy discutida. Los motivos de contraste concernen la denominación correcta de la "analgésia preventiva" y la elección del fármaco para el tratamiento preventivo y su régimen de utilización (vía de administración, dosis, tiempo, dosis y duración del tratamiento). Otro problema inherente a la "analgésia preventiva" es que la mayoría de los estudios clínicos se refieren a una cirugía mayor

en la que los estímulos dolorosos difieren por intensidad y duración de los obtenidos en cirugía ambulatoria y anestesia local. Es aclarado que la eficacia de la "analgesia preventiva" está influenciada por el tipo de cirugía realizada. También debe tenerse en cuenta el hecho de que el dolor postoperatorio, siendo una experiencia multidimensional, está vinculada a factores psicológicos que influyen en los resultados que se pueden alcanzar con la "analgesia preventiva".

Discusión y Conclusiones: El concepto de "Pre-Emptive Analgesia" se ha evolucionado con el tiempo hasta llegar a determinar definitivamente el correcto racional de base en el que se funda, pero, sigue siendo un tema muy controvertido. A pesar de esto, la confianza de los médicos sobre el potencial de la "analgesia preventiva" sigue siendo alta. Por lo tanto, es clara la necesidad de más estudios para llegar a una concorde opinión en la comunidad científica internacional sobre su aplicación clínica en la cirugía oral ambulatoria.

Background

Dentoalveolar surgery, in particular the surgical extraction of mandibular third molars, is the procedure most commonly performed in Oro-Maxillo-Facial Surgery (1) and it is also the most affected one by a series of post-operative squeals, of which the main are trismus (2), edema and Acute Postoperative Pain (3) (APP). Among these symptoms, pain is the less tolerated by patients and its inadequate treatment causes physical and psychological discomfort, and increases morbidity with negative impact on life quality (4). In recent decades, as a result of improved understanding of the pathophysiology of acute pain in both peripheral and central mechanisms, there has been a remarkable improvement in the clinical management of APP, e.g. anticipating the treatment timing or preventing the pain onset rather than treating it postoperatively. This revolutionary concept of "pain prevention", formulated for the first time by G. W. Crile at the beginning of the last century, is now the basis of the so-called "Pre-Emptive Analgesia" technique (5) ("preventive analgesia").

Objectives

This paper aims, through a detailed examination of the acute pain pathophysiology, to identify the rational basis of the "Pre-Emptive Analgesia" and to describe the methodological controversies raised in the scientific community about its clinical application.

Methods

Physiopathology of APP

Pain following surgical extraction of mandibular impacted third molars is a symptom that derives from the activation of a local inflammatory response in peripheral tissues affected by surgical trauma (6), which leads to the release of a variety of biochemical mediators and algogenic substances (the so-called "sensitizing soup") (7) by the free nerve endings (nociceptors) and extraneural sources of traumatized tissues (muscles, ligaments, mucous, blood vessels and nerves). For this reason, the Acute Post-Operative Pain is also called "inflammatory" or "nociceptive" pain.

From the clinical point of view, the increase of the release of inflammatory mediators appears to be related more to the extraction trauma, especially against the bone tissue support, rather than to its duration. Moreover, the intensity of the inflammatory mediators release is the basis of the physiological "curve of pain", i.e. the change in the post-operative period of the pain level experienced. The Post-Operative Acute Pain in fact reaches a moderate/severe level within the first 24 hours after the surgery and it reaches a peak at 3-5 or 6-8 hours after the extraction (8), and then if there are not any inflammatory complications it tends to decrease gradually and it usually disappears or its intensity becomes negligible after the second day (9).

The chemical mediators of inflammation, including potassium (K^+), histamine (H), acetylcholine (ACh), serotonin (5-HT), adenosine triphosphate (ATP), bradykinin (BK), leukotrienes (LT), substance P (SP) and prostaglandin (PG) (10, 11), reach their maximum local tissue concentration during the first 48-72 hours after the surgery, causing vascular and neuronal effects (12). The former are represented by the vasodilation and by increased vascular permeability, while the latter consists in peripheral and central modification of neuronal activity (sensitization) (13) and are responsible for

developing the APP (14). It is important to highlight that post-traumatic peripheral pain signals are transmitted in two phases, the first one occurs during the surgery, the second one during the healing of the surgical wound (7).

In the peripheral tissues, the overall action of inflammatory mediators determines the activation and sensitization of nociceptors (free nerve endings or peripheral nerves) (15), inducing spontaneous activity and amplification of responsiveness to stimuli (primary hyperalgesia), reduction of pain threshold (allodynia) and prolonged responses to stimuli above-threshold for pain (hyperpathia) (7), leading to an altered transduction and an increased conduction of pain impulses to the central nervous system (CNS). This magnification (6) of all nervous traffic and afferent algic stimuli also extends to the tissues surrounding the traumatized area (secondary hyperalgesia).

At central level it occurs, however, an increase in activity-dependent excitability of Nociception-Specific Neurons (NS) and of Wide Dynamic Range Neurons (WDR) of the spinal cord or the trigeminal nucleus (12) (being this nerve mainly interested in oral surgery), so that:

- 1) They become more susceptible and more responsive to afferent peripheral input, by favoring the phenomena of both primary and secondary peripheral hyperalgesia and allodynia;
- 2) They extend and amplify painful afferent inputs.

Pain signal transmission continues at a supraspinal level until it reaches the thalamus and other brain regions, where the pain stimulus is finally converted into subjective and emotional feelings perceived by the subject. Usually, the peripheral and central sensitizations occur together (12) and they both contribute to the state of painful post-traumatic hypersensitivity.

In sum, the pain that is associated with tissue damage causes a prolonged modulation of the somatosensory system, with an increased responsiveness of both central and peripheral pain pathways.

The "Pre-Emptive Analgesia" recognizes its rational basis in the prevention of molecules formation and their consequent release that can cause hyperalgesia in traumatized tissues (16) and also in the prevention or minimization of the central sensitization (11), which is inevitably linked to surgical trauma. In fact, the trauma prolongs and promotes the peripheral sensitization status. Preventing or minimizing only the peripheral sensitization is inadequate, because as soon as the sensitization of the CNS is established, the APP persists in an abnormal state of activation and can be stimulated also by subthreshold signals. The "Pre-Emptive Analgesia" tries therefore to reduce the overall APP level felt by the patient preventing the pain development in all its phases, or intervening on the activation of the nociceptive cascade due to surgical trauma (development of pain), blocking the arrival of the pain stimulus at the spinal cord (pain amplification) and avoiding that the afferent barrier generated by the tissue injury reaches the central nervous system until healing has occurred (maintenance of pain) (7).

Results

Disputes over "Pre-Emptive Analgesia"

Despite the scientific rationale, on which the "Pre-Emptive Analgesia" is based, is well defined, in recent years its application in clinical practice has been the subject of numerous methodological debates that led to confusion, misunderstandings and disagreements in the international scientific community (17). Even now, a shared opinion is not reached and the "Pre-Emptive Analgesia" definition and description continue to be subject matters for discussions. In fact, considering the scientific rationale on which it is based, the "pre-emptive analgesia" expression is nowadays obsolete, because:

- 1) it can be misunderstood, because the name of this technique should emphasize the pathophysiological phenomenon that it allows to prevent (i.e. the onset of central sensitization) instead of the final effect that it allows to obtain (prevention of pain);
- 2) it is a limited *expression*, since the "Pre-Emptive Analgesia" should not be simply considered as a "pre-operative" analgesia (18); but, considering its bi-phasic post-traumatic painful stimuli nature, it should be continued in a continuous and constant way (19, 20, 21) for the whole period in which the pain stimuli occur (pre-, intra-, post-operatively), so that a protective and preventive analgesia can be achieved (21, 22).

For these reasons, in order to try to eliminate the inherent limitations of the old name and to expand the concept of "prevention of pain" many different alternative names have been proposed in literature (such as "Preventive Analgesia", "Protective Analgesia", "Balanced Peri-Emptive Analgesia", "Pre-Emptive Antihyperalgesia") (17). Another issue, partly caused by the lack of agreement on its definition and description, is the evidence for successful treatments of this technique in animal experiments versus disappointing human clinical trial results. This difference is related to many factors, mainly the difficult identification of the "primary nociceptive event", at the time that the pre-emptive treatment should be already started. In fact, some authors restrict the painful stimuli as the onset of the surgical procedure while others as the entire duration of the surgical procedure, and as a result, some clinical studies have compared identical or very similar analgesic treatment started before versus after the first surgical incision, while others have compared the administration of different analgesic regimens, with each other or with placebo (11).

In the animal model, then, the nociceptive stimulus does not affect highly differentiated tissues with complex innervation, as opposed to clinical practice (23). Many reviews have also shown that clinical results, concerning "Pre-Emptive Analgesia", are influenced by different anatomical areas (degree and type of innervation), type of surgery (23) (orthopedic, oral, gynecological, etc.) and type and duration of anesthesia performed.

The debate over the "Pre-Emptive Analgesia" concerns the choice of the pharmacological pre-emptive drug and its dosage, timing, route of administration and treatment period (24). Although even now there is no agreement in literature, current strategies pay particular attention to the use of drug combinations with different mechanisms of action rather than a single analgesic agent. In addition, being local anesthetics equipped with pre-emptive effects (25), in order to evaluate the effectiveness of the "Pre-Emptive Analgesia" in ambulatory oral surgery, it should always be considered the possibility that the local anesthesia could mask the effect of the pre-emptive drug, explaining many discrepant clinical trial results. Moreover the surgeon's skills should also be considered (24). Another issue is whether other aspects that contribute to the overall peri-operative pain, such as psychological factors related to the patient, are sufficient in terms of intensity and duration to mask any benefits obtained by the pre-emptive treatment. In fact, despite its typical nociceptive nature, the constant pain level (ranging from moderate to severe), the pathophysiological mechanisms of development similar to those of other types of acute pain, the ability to reproduce (in specular inclusion cases) and to quantify it (VAS scales, NS, VRS, NRS) (26) and its "symptomatic" intrinsic nature makes the APP a subjective experience, and thus linked to psycho-affective factors that in the experimental model not necessarily exist and do not influence the results.

Discussion and Conclusions

Since its introduction in medical literature, the concept of "Pre-Emptive Analgesia" has undergone changes, until it reached a definitive correct rational basis. The main Pre-Emptive Analgesia features are (27):

- 1) The analgesic treatment starts before the nociceptive primary event is caused;
- 2) The preventive drug treatment is maintained throughout the perioperative period;
- 3) The onset of the central sensitization state, caused by the nociceptive primary event is prevented;
- 4) The central sensitization caused by peripheral inflammatory response is prevented.

To date, there are still many controversial points about the clinical application of the "Pre-Emptive Analgesia". In fact, clinical trial results tend to be disappointing. Moreover, the most of clinical trials refer to major surgery (23), in which painful stimuli differ greatly in intensity and duration from those of ambulatory surgery under local anesthesia. Another confounding factor is the different type of surgery and method chosen for conducting the study.

However, even now the "Pre-Emptive Analgesia" seems to be the most appropriate treatment for APP (28), although, considering the multidimensional nature of pain sensation, a good pain management should always be associated with appropriate clinical and psychological care. As always, then, the principle that prevention is better than cure seems to be valid.

Conflicts of interests

The authors declare that there are no conflicts of interest.

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