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EFFICACY OF SHORT TERM CORTECOSTEROID THERAPY IN PATIENTS UNDERGOING MAXILLOFACIAL SURGERY. A SYSTEMATIC SCIENTIFIC REVIEW.

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Abstract

Glucocorticoids, also known as corticosteroids or steroids, are drugs derived from cholesterol. They are synthesized by the adrenal cortex, along with other hormones, such as cortisol and aldosterone. Glucocorticoid drugs are recommended for patients undergoing surgery in maxillofacial region due to their high efficacy against inflammatory and immune processes. However, these drugs are restricted due to their multiple and serious adverse effects. The objective of this study was to verify the efficacy of short term corticosteroids administered in maxillofacial surgeries, based on the characteristics of the patient so as to select the best therapeutic strategy. Articles in the databases such as PubMed, Medline, Cochrane Library, Scopus and Web of science were searched using keywords. A total of 27 articles were selected to address the proposed objectives. The results obtained show that it is effective and safe to use glucocorticoids on short term basis as pre or postsurgical therapy in maxillofacial surgery to control the processes of inflammation, pain, and edema.

Keywords – corticosteroids, anti-inflammatory, postoperative, maxillofacial surgery, dexamethasone, methylprednisolone

Introduction

Glucocorticoids, also known as corticosteroids or steroids, are drugs derived from cholesterol. They are synthesized by the adrenal cortex, along with other hormones, such as cortisol and aldosterone [1]. Corticosteroids comprise both naturally occurring steroid hormones synthesized in the adrenal cortex of vertebrates and laboratory-produced analogues of these hormones. The term "corticosteroid" includes natural glucocorticoids and mineralocorticoids, as well as their synthetic analogues [2]. Corticosteroids possess one of the most extensive ranges of clinical applications. Corticosteroids play a significant role in numerous physiological processes, such as regulating inflammation, stress response, and immune response, as well as carbohydrate metabolism, protein catabolism, blood electrolyte levels, and behavior [3].

When describing the mechanism of action of these drugs, it must be stated that the adrenal cortex oversees the synthesis of glucocorticoids, cortisol, hydrocortisone, and corticosterone, the hormones that are released throughout the day following a circadian rhythm that have numerous effects at metabolic, cardiovascular and nervous system levels [4,5]. These steroid hormones exert their mineralocorticoid or glucocorticoid function through binding to two types of nuclear receptors: the glucocorticoid receptor (GR or type II in the old nomenclature) and the mineralocorticoid receptor (type I). These act on different genes, produce changes (stimulation or inhibition) in protein synthesis and tissue response. The performance of these corticosteroids is regulated by the hypothalamus pituitary-adrenal cortex axis. Thus, the hypothalamic corticotropin-releasing hormone prompts the production of pituitary adrenocorticotropin, or ACTH, which then promotes cortisol output at the adrenal level. When cortisol levels are sufficient, and in order to avoid the excessive accumulation of cortisol, negative feedback to the axis occurs such that the

release of CRH, ACTH, and cortisol is interrupted [6,7]. Corticosteroids are analogs of endogenous glucocorticoids, and they prevent the entry of leukocytes into the inflammatory focus, disturb the action of fibroblasts and endothelial cells, and mitigate the performance or effects of numerous chemical mediators of inflammation [8]. As for the pharmacological effects of these drugs, it can be pointed out that they have anti-inflammatory actions, which are achieved through multiple mechanisms that include the inhibition of histamine release and consequent capillary vasodilation, the inhibition of prostaglandin synthesis, the inhibition of proinflammatory cytokines (COX2, PLA2, INOS IL, and TNF), and the increased synthesis of anti-inflammatory cytokines and annexin (which causes apoptosis). With regard to immunosuppressive actions, through a lymphocytic effect, T lymphocytes reduce the production of IL-2 and IFNγ, preventing the activation of Tc lymphocytes and natural killer (NK) cells. B lymphocytes, by contrast, are relatively resistant to the effects of glucocorticoids. They inhibit their proliferation only if they are administered before they are activated. At small doses, they do not affect the production of antibodies, but at high doses, an increase in catabolism and a slight decrease in synthesis are observed, perhaps due to indirect mechanisms [9].

Aim

The purpose of this article is to provide a comprehensive review of the effectiveness of short-term glucocorticoid administration using the recommended dosages and routes of administration.

Methodology

This research is a systematic review, and it was carried out in accordance with PRISMA declaration (Preferred Reporting Item for Systematic Reviews and Meta-Analysis). The aim was to gather the information available in different databases to respond to the proposed objectives.

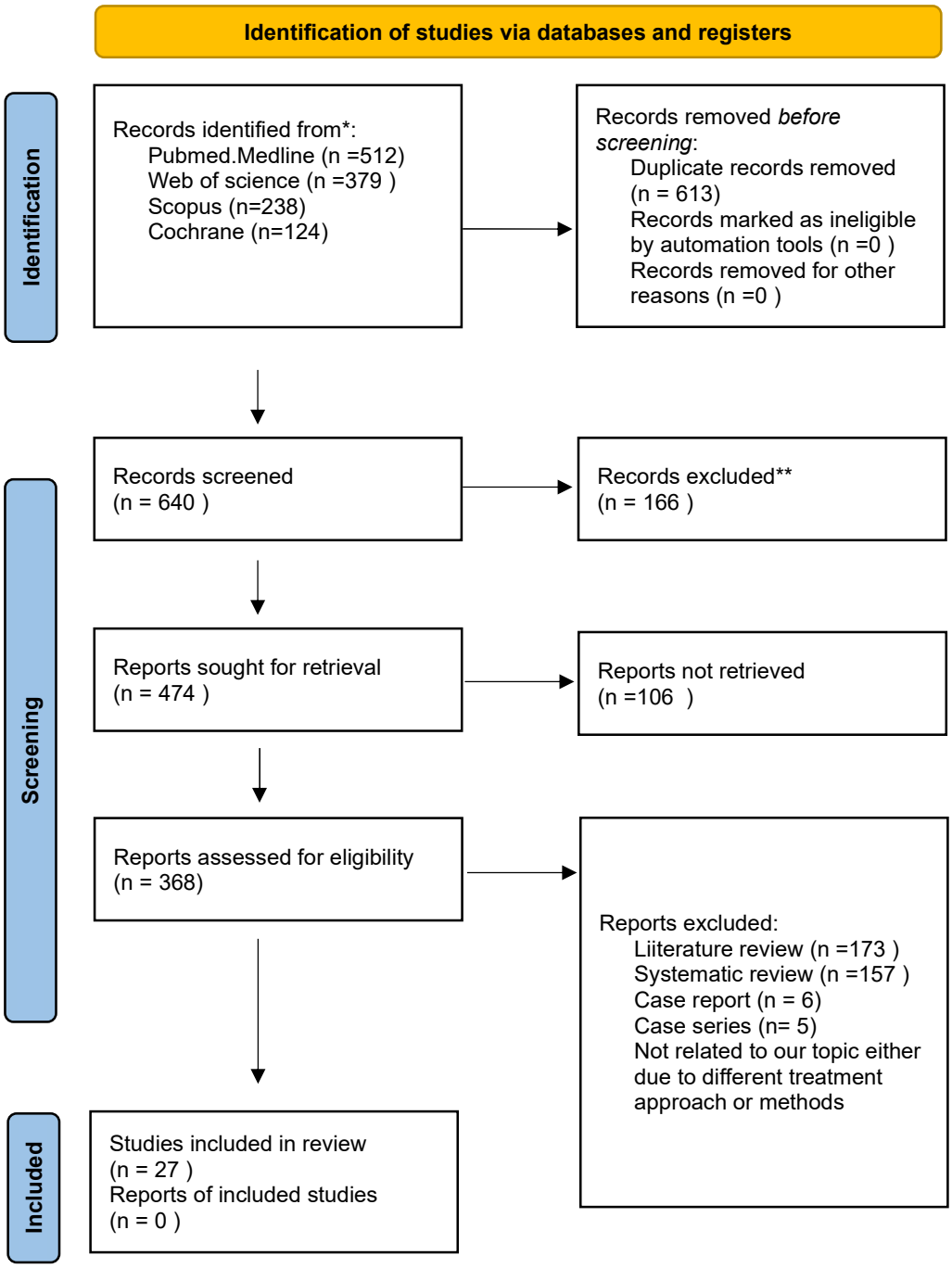
Search Strategy

Information was searched for in the PubMed, Medline, Scopus and Web of science databases, using free terms, as well as MeSH terms, in the indicated cases and combining them with the Boolean AND and OR operators. During the search, thesaurus keywords limited to the English language were used, such as corticosteroids, anti-inflammatory, postoperative, maxillofacial surgery, dexamethasone, methylprednisolone. Likewise, parentheses were used to specify search combinations, and quotation marks were used to carry out searches with terms containing multiple words. Searches were carried out for the journals with the greatest impact in the Google Scholar search engine, with the most recent randomized clinical trials to sustain the vast study carried out on the subject in question.

Results

Database search yielded a total of 1253 articles,and by using filters that covered each inclusion criterion and the relevant dates, searching only in English, and rejecting those that were found to be duplicates. Total number of articles was reduced to 27.(Figure 1)

Figure. 1- PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Discussion

The beneficial effects of systemic corticosteroid therapy in preventing acute postoperative sequelae of surgical procedures have been documented by many researchers. Methylprednisolone has demonstrated efficacy in the management and control of facial edema that occurs after orthognathic surgery. By decreasing the permeability of capillary endothelium, corticosteroids reduce edema and, consequently, the quantity of inflammatory cells, protein, and fluid that enters areas of tissue damage [10]. Prolonged administration of corticosteroids to a patient may result in the development of resistance to steroid-based therapies [11]. It has been demonstrated by Neupert that systemic steroids can reduce trismus and general discomfort. In orthognathic surgery, preoperative glucocorticoid therapy effectively reduces postoperative edema [12,13]. Systemic Lupus Erythematosus (SLE) patients who undergo long-term steroid therapy are more susceptible to complications [14]. According to Gersema et al, the concurrent administration of corticosteroids and oral surgery results in notable reductions in both edema and pain [15].However corticosteroid administration does have its disadvantages and therefore should be cautiously prescribed.

It is believed that the biological impact of glucocorticoids on the process of wound healing elevates the likelihood of various detrimental gastrointestinal occurrences, including gastritis, ulcer formation, and gastrointestinal hemorrhage [16].

A limited number of clinical trials have investigated the impact of glucocorticoids on orthognathic surgery-related edema. In 2017, Semper et al. compared a placebo to a preoperative dose of 0.5 mg/kg dexamethasone followed by a two-day postoperative dose of 0.25 mg/kg/day in minors undergoing mandibular or maxillary osteotomy. There was no statistically significant reduction in facial edema observed when photographs underwent subjective evaluation by an impartial observer [17].

Notably, a recent study demonstrated that intramuscular administration of group B vitamins as an adjuvant in corticosteroid therapy increased the analgesic effect of a glucocorticoid in the population examined [18]. Researchers have spent decades examining the safety implications of continuing to use glucocorticoids, but their findings have been contradictory. With respect to the pharmaceutical route of administration, the intramuscular route is among the most favorable options due to its demonstrated superiority over the oral route in diminishing postoperative pain and inflammation [19]. This contradicts the assertions of other authors, who advocate for the oral route. In the context of cervicofacial infections, where the adjunctive use of corticosteroids with antibiotics has begun to produce favorable outcomes, it is critical to understand that for optimal treatment outcomes and to ensure patient safety, glucocorticoids should never be administered in isolation in cervicofacial infections. They should always be combined with an antibiotic [20]. Emerging trends have identified a gene responsible for producing the advantageous effects of steroids while obviating any apparent adverse effects. Once the KLF15 gene (Krüppel-like factor 15) is activated, glucocorticoids often indicate an improvement in muscular resistance and a reduction in muscular dystrophy, according to scientific research [21].

The majority of the analyzed studies pertaining to maxillofacial surgeries relied on dexamethasone (4–8 mg) as the primary anesthetic and anti inflammatory drug. This indicates that administering

the medication intramuscularly may be more effective in reducing undesirable clinical manifestations associated with the intervention, including facial edema, and pain. In conjunction with antibiotic treatment, it may be advantageous to administer high doses of corticosteroids (hydrocortisone (200–1050 mg); dexamethasone (8–10 mg); methylprednisolone (1–3 mg/kg)) intravenously to patients with cervicofacial infections for a brief period of time. With respect to the individuals aged 10 to 16, no research has been identified that definitively establishes or clarifies the efficacy and safety of glucocorticoid administration during major oral cavity, facial skeleton, and cervical structure surgeries [22].

Postoperative pain in response to corticosteroids was assessed in three separate trials. A clinical trial assessed postoperative pain at various time intervals along a 10-centimeter line. The point of evaluation corresponded to the intensity of pain felt after 2, 4, 8, 12, 24, 48, and 72 hours and 7 days of open reduction internal fixation (ORIF). At the 72-hour mark, the trial found a statistically significant difference in favor of the steroid group, as indicated by a median visual analog scale (VAS) score of 0 in the steroid group and 2 in the control group [23]. A 24-hour postoperative pain assessment using the VAS area under the curve revealed that systemic corticosteroids had no significant therapeutic effect in one study [24]. After adjusting for other predictor variables, one trial that assessed VAS in the 24-hour postoperative period found a significant association between dexamethasone (DXM) and reduced postoperative pain compared to the no-steroid control (P =.04) [25]. The decision to forgo quantitative analysis was based on the observed heterogeneity in the outcome's assessment and measurement.

Two clinical investigations were conducted to assess the impact of corticosteroids on facial edema. A study examined facial edema at various time intervals (2 hours, 4 hours, 8 hours, 12 hours, 1 day, 2 days, 4 days, and 7 days) during the course of mandible fracture surgery [26]. At 72 hours, systemic corticosteroids demonstrated a significant treatment effect. A significant reduction in periorbital edema was observed in one study involving orbital surgery and a preoperative dose of 250 mg methylprednisolone, followed by three additional dosages every 6 hours, as compared to the use of a placebo [27].An increase in interpalpebral opening due to a reduction in orbital edema provides the benefit of facilitating precise clinical examinations during the postoperative phase.A quantitative analysis was not feasible due to the variation in the assessment and measurement of facial edema between the two trials.

It is important to acknowledge that postsurgical manifestations in adolescents and young adults aged 10–16 or 18–35 are influenced by two factors: the duration of the operation and the inclusion or exclusion of osteotomy [28]. It is of the utmost importance to comprehend that abrupt cessation of corticosteroid therapy is not feasible due to the adrenal glands' diminished or nonexistent cortisol production. Consequently, corticosteroid use must be progressively tapered off until the adrenal glands resume autonomous cortisol production. The utilization of these pharmaceuticals offers the benefit of being amenable to both single-use and combination with other medications, which contributes to improved outcomes in patient recovery and disease management. However,

it is important to note that iatrogenic Cushing's syndrome may result from cross-drug interactions between glucocorticoids and specific medications, including Ritonavir [29].

Amid ongoing debate, health professionals continue to be confronted with significant uncertainty regarding whether the administration of steroids in appropriate dosages would confer benefits in the form of anti-inflammatory and immunomodulatory properties or pose a life-threatening risk to patients. Research has demonstrated both their efficacy in reducing morbidity and the detrimental consequences associated with their extended and unfounded utilization. It can be stated that, in general, researchers advocate for the use of corticosteroids as preventive, postoperative, or even maintenance therapy to avert the recurrence or exacerbation of the injury or condition, with each patient receiving the recommended route of administration. In specific patients with particular systemic conditions, the administration of these hormones poses a risk and is contraindicated; therefore, it is advisable to explore alternative therapies that offer superior efficacy.

Conclusion

Despite the scarcity and controversy surrounding the information regarding corticosteroid administration, it is essential to acknowledge the widespread acceptance of their successful efficacy and high performance in combating inflammatory and immunological responses in surgical cases including in medical emergencies.Preoperative corticosteroid administration over a short duration is efficacious in postoperative sequelae prevention due to the drug's tissue therapeutic level being present at the initiation of the inflammatory response. A long-acting corticosteroid with a synergistic effect with nonsteroidal anti-inflammatory drugs (NSAIDs),could have increased risk of gastrointestinal hemorrhage and nausea. It has been demonstrated that intramuscular administration is more effective than oral administration at reducing postoperative inflammation and discomfort. Studies involving a variety of populations indicate that potential risks and adverse effects are minimal when the route, duration, and dosage of administration are taken into account.

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