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REVIEW

Effects of anemia and peri-operative medication on wound healing in cleft lip and palate patients

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ABSTRACT

Introduction: Wound healing complications among cleft lip and palate patients pose risks of additional surgeries, reduced scar quality, and increased patient morbidity. This literature review aims to explore the impact of anemia and drug usage associated with respiratory complications, frequently encountered in these patients, on wound healing.

Materials and Method: We conducted an extensive literature search without time constraints using PubMed and Google Scholar databases. The investigation into the effects of anemia and medications on wound healing was divided into three stages. The first stage examined the general effects of anemia and medications on wound healing. The second and final stages assessed wound healing in craniofacial and cleft lip/palate surgeries, respectively.

Results: Preoperative anemia exerts no substantial influence on wound healing unless hemoglobin levels drop below 5 g/dl. No studies reported detrimental effects of glucocorticoids on wound healing. The impact of salbutamol use on wound healing remains controversial, while data regarding ipratropium usage are insufficient.

Conclusion: Severe anemia is the only significant concern for wound healing, necessitating transfusion or improvement in anemia. It appears that short-term use of glucocorticoids after surgery does not have a negative effect on wound healing.It is worth noting that salbutamol and ipratropium usage may have detrimental effects, and while complete avoidance may not be feasible, their potential impact on wound healing should be considered.

Keywords: Anemia, cleft lip, cleft palate, glucocorticoid, ipratropium, salbutamol

INTRODUCTION

A wound is characterized as damage to the normal anatomical structure, initiating a complex cascade of reactions and interactions among cells and mediators. Numerous factors, both local (such as ischemia, infection, foreign bodies, and edema) and systemic (including diabetes mellitus, hypothyroidism, age, tissue perfusion, hypothermia, pain, trauma, and burns), have been identified as influential contributors to the intricate process of wound healing [1].

Wound healing complications in patients with cleft lip and palate present significant challenges, encompassing the potential for additional surgeries, compromised scar quality, and heightened patient morbidity [2]. While extensive research has examined the effects of various diseases and agents on wound healing, it is crucial to recognize that many of these agents and diseases are not routinely encountered by cleft lip and palate patients.

Anemia is a common condition among individuals with cleft lip and palate, with an observed preoperative prevalence of 81%[3]. Among systemic factors, anemia stands out as one that can disrupt tissue perfusion [1]. Iron deficiency anemia, predominantly observed in infants, including those with cleft lip and palate, often necessitates iron supplementation, typically commencing at four months for full-term breastfed infants (elemental iron 1 mg/kg daily, maximum 15 mg), and continues until the infant begins consuming iron-rich complementary foods [4]. Notably, cleft lip and palate patients often undergo surgery during the recommended iron supplementation period [4]. Despite these considerations, a consensus regarding the necessity of erythrocyte replacement in cleft lip and palate patients remains elusive, as does a clear consensus regarding the impact of pre-existing anemia on wound healing in these patients [3].

Furthermore, an investigation extending to the use of glucocorticoids, including "methylprednisolone" and "dexamethasone," as well as β2-Agonist agents such as "Salbutamol," frequently administered as bronchodilators in the intensive care unit for postoperative airway issues, is needed. These medications serve various roles in managing upper and lower airway obstructions (Table 1), and their potential effects on wound healing require careful consideration [5].

The impact of anemia and postoperative medication use is a subject of current interest in the field of wound healing among cleft lip and palate patients. This study is undertaken with the primary goal of investigating the influence of preoperative anemia and postoperative drug administration on the wound healing process in individuals with cleft lip and palate.

MATERIALS and METHOD

Binary combinations of the keywords "cleft lip,""cleft palate," "craniofacial," "wound healing," "steroid," "glucocorticoid," "salbutamol," "dexamethasone," "prednisolone," "ipratropium," and "anemia" were searched without time constraints on the PubMed and Google Scholar databases. Articles in English with an available full text were evaluated. The effects of anemia and medications on wound healing were investigated in three steps. The effects on general wound healing of anemia and medications were examined in the first step. Wound healing of craniofacial and cleft lip/palate surgeries was evaluated in the second and last steps, respectively.

RESULTS

When we analyzed the results, we obtained the following data concerning the effects of anemia and drug use, both of which serve as independent variables.

Anemia

Since the 1940s, the effect of preoperative anemia on wound healing has been discussed in the literature[6]. Some studies have stated that preoperative anemia has no effect on wound healing, while others have reported that anemia has a negative effect on wound healing [7-9].

Despite anemia, the peripheral circulatory system can protect the level of oxygen in the tissue, and wound healing is not affected if the level of oxygen in the tissue is within normal limits [10]. If the level of hematocrit is above 15%, wound healing is specified not to be interrupted [9]. In a study on wound complications in laryngectomized patients, prior radiation therapy, diabetes mellitus, preoperative hypoalbuminemia, anemia, and thrombocytosis were found to be independent etiological factors for wound complications [11].

Table 1. Medication Protocol in Intensive Care Unit for Airway Obstruction

Upper Airway Obstruction	Lower Airway Obstruction	Upper and Lower Airway Obstruction
Dexamethasone 4 x 0.15mg/kg	Methylprednisolone 2 x 1 mg/kg Salbutamol (Three doses every twenty minutes) (Loading dose)	Ipratropium 4 x 250 mcg/2 mL
Methylprednisolone 2 x 1 mg/kg	Salbutamol single dose every hour or 2 hours (Maintenance dose)	

In patients with aplastic anemia, it has been shown that anemia can be kept under control without disrupting wound healing during dental implant application [12]. Cleft palate can be associated with Diamond-Blackfan anemia [13,14]. As a consensus on this issue, preoperative anemia does not affect wound healing unless the level of hemoglobin is below 5 g/dl. In the literature, the importance of malnutrition has been emphasized, which can cause low hemoglobin levels.

Glucocorticoids

Glucocorticoids can easily pass through the membrane and bind to glucocorticoid receptors in the cytoplasm. The receptors are glucocorticoid receptor and mineralocorticoid receptor [15]. When glucocorticoid receptors are stimulated, chaperone proteins are activated, and these proteins affect the transcription of anti-inflammatory and inflammatory proteins in the nucleus. Glucocorticoids reduce the transcription of cytokines, chemokines, enzymes, peptides, inflammatory mediator receptors, and adhesion molecules that stimulate inflammation. Glucocorticoids are pharmacological agents used as drugs in asthma and chronic obstructive pulmonary disease due to their feature of reducing inflammation. In addition to glucocorticoids, β2 agonists are also used in the perioperative period to reduce airway obstruction in patients with cleft lip and palate in intensive care [16].

The effect of the anti-inflammatory feature of glucocorticoids on wound healing has been investigated since the 1960s. In the early period of wound healing, glucocorticoids have been shown to slow the migration of inflammatory cells and fibroblasts, inhibiting collagen formation, capillary regeneration, and epithelial migration [17]. Glucocorticoids are divided into six types according to duration of action and anti-inflammatory properties (Table 2).

The use of methylprednisolone has been shown to reduce TGF-β and IGF levels. Collagen deposition was decreased in wound healing due to the antagonistic effects of glucocorticoids [18].

The level of hydroxyproline was diminished in an animal model study of wound healing by 1 mg/kg dexamethasone. Additionally, this effect of dexamethasone was found to be dose-dependent [19].

In a review of 45 studies involving 5796 patients in the perioperative period, patients who received dexamethasone reported less pain, resulting in decreased use of opioids and analgesics. In the same study, patients who used dexamethasone had fewer follow-ups in the intensive care unit, but their blood glucose levels were higher compared to patients who did not use dexamethasone. Nevertheless, normal wound healing was observed [20]. In tonsillectomy patients, when prednisolone was used to decrease nausea and pain in the postoperative period, no serious complications were detected [21]. Furthermore, a single dose of dexamethasone was found to reduce pain without causing serious complications in adult tonsillectomy patients [22].

The utility of dexamethasone in maxillofacial fracture surgeries did not affect wound healing [23-25]. Corticosteroid applications were also shown not to increase the risk of infection and wound dehiscence in orthognathic surgery and oral interventions [26].

There were two studies in the literature investigating the relationship between cleft lip and palate patients and steroids. Dexamethasone was found to reduce airway problems, fever, and hospitalization in the postoperative period, while the drug did not increase the formation of fistulas in both studies [27,28].

Table 2. Types of glucocorticoids

Glucocorticoids	Duration of action	Anti-inflammatory potency	Equivalent dose
Cortisone	Short (<12 hours)	1	20 mg
Hidrocortisone	Intermediate (12-36 hours)	4	5 mg
Prednisone		4	5 mg
Methylprednisolone		5	4 mg
Dexamethasone	Long (>36 hours)	25	0.75 mg
Bethamethasone		25	0.75 mg

No studies reporting negative effects of glucocorticoids on wound healing were found in the literature[29].

β2-Agonists

When β2 agonists stimulate the membrane receptor, adenylate cyclase is activated. Increasing cAMP reduces the level of intracellular calcium. Muscle relaxation occurs due to decreased levels of calcium, which leads to bronchodilation.

The most commonly used β2 agonists are formoterol, salmeterol, and salbutamol (Table 3). Formoterol and salmeterol are long-acting β2 agonists, while salbutamol is short-acting. Salbutamol is used as a bronchodilator in intensive care units [30]. Salbutamol has been found to be a teratogenic agent and can cause cleft lip and palate deformity [31,32]. The effect of salbutamol on wound healing has been tested in different epithelial studies. There are different opinions in the literature regarding corneal epithelium and alveolar epithelium. In some studies, salbutamol was found to accelerate wound healing, while in others, it was found to impair wound healing. It was determined that salbutamol could slow down epithelial cell migration via the protein phosphatase-2A pathway in cellular research [33]. However, convincing clinical evidence is lacking.

Ipratropium

Ipratropium is used as an acetylcholine antagonist by blocking muscarinic cholinergic receptors. Bronchoconstriction is decreased due to the diminished contraction of smooth muscle by the antimuscarinic effect of ipratropium [34]. No studies were found in the PubMed and Google Scholar databases on the effect of ipratropium bromide, which is used for patients in the intensive care unit.

DISCUSSION

Understanding the impact of medications administered to address perioperative respiratory tract complications, a common occurrence in cleft lip and palate patients, as well as the influence of anemia on wound healing, holds significant relevance for plastic surgeons. This knowledge equips them with the ability to make necessary dosage adjustments or medication changes, enabling the anticipation of potential complications and the provision of informed guidance to patients and their families.

In preoperative assessment of every cleft lip and palate patient, a comprehensive blood count should be routinely conducted. It is noteworthy that mild anemia typically does not exert an adverse influence on surgical outcomes. However, when hemoglobin concentrations fall within the range of 8 to 10 g/dl, it becomes imperative to assess the patients' developmental stages. If there are no underlying developmental concerns, proceeding with the surgical procedure may be deemed appropriate. It is important to acknowledge that there is a dearth of specific data pertaining to the wound healing process in cleft lip and palate patients undergoing surgery, as indicated in -4. Nonetheless, it is essential to underscore that erythrocyte replacement is generally unnecessary unless severe anemia is evident.

Our review of the existing literature did not uncover any clinically proven evidence suggesting that the use of glucocorticoids is detrimental to wound healing. When administered in short-term and low doses to address airway problems in patients, glucocorticoids have not been shown to impair wound healing, as outlined in Table 4. While the available literature remains limited in addressing the potential impact of salbutamol on wound healing, it is prudent to consider that salbutamol may have the potential to disrupt the wound healing process, as summarized in Table-3. Similarly, no studies specifically investigating the effects of salbutamol on wound healing can be found in the existing literature, thus precluding any commentary on its safety. In cases of postoperative airway problems, the recommendation is to

Table 3. Types of β2 agonists

β2 agonists	Selectivity	Receptor binding affinity	Onset of action	Duration bronchodilator effect	Agonist activity	Lipid solubility
Salbutamol	Moderately high	High	Fast	Short	Full	Low
Formoterol	High	High	Fast	Long	Full	Moderate
Salmeterol	Very high	High	Slow	Long	Partial	High

Table 4. The effect of anemia, β2 agonists and ipratropium on wound healing

	Wound Healing	Wound Healing in Craniomaxillofacial Surgery	Wound Healing in Cleft Lip and Palate Surgery
Anemia	If severe, disrupts wound healing	Opposite results - the data is inadequate	No study
Dexamethasone	Disrupts wound healing	With low dosage, no effect	With low dosage, no effect
Methylprednisolone	Disrupts wound healing	With low dosage, no effect	With low dosage, no effect
Salbutamol	Disrupts wound healing	Disrupts wound healing	No study
Ipratropium	No study	No study	No study

preferentially opt for a single dose or to reduce the doses of glucocorticoids.

This discussion underscores the importance of individualized assessment and decision-making in managing cleft lip and palate patients, taking into account their unique medical profiles and specific needs. Further research is warranted to establish a more comprehensive understanding of the effects of medications and anemia on wound healing in this patient population.

CONCLUSION

Severe anemia is the only significant concern for wound healing, necessitating transfusion or improvement in anemia. It appears that short-term use of glucocorticoids after surgery does not have a negative effect on wound healing.It is worth noting that salbutamol and ipratropium usage may have detrimental effects, and while complete avoidance may not be feasible, their potential impact on wound healing should be considered.

Author contribution

Study conception and design: GGÜ, FÖ; data collection: GGU and FDMO; analysis and interpretation of results: GGU and FDMO; draft manuscript preparation: GGU, FDMO and FO. All authors reviewed the results and approved the final version of the manuscript.

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Ethical Approval was not required due to the nature of the study.

Conflict of interest

The authors declare that there is no conflict of interest.

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