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Questioning the Relevance of Normal White Blood Cell Count under 10,000 Cells per Microlitre in Millard Criteria as an Absolutely Required Parameter for Cleft Lip Repair Surgeries: A Case-Based Literature Review

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ABSTRACT

Leukocytosis, defined as an elevated white blood cell count, has long been regarded as a crucial indicator of inflammation or infection in surgical procedures. In the context of cleft lip surgeries, normal white blood cell count has often been considered an absolute requirement for proceeding with the procedure, as it is believed to signal the presence of a potentially infectious or inflammatory state. Therefore, leukocytosis is thought to be a strong precautionary factor. However, recent evidence challenges this long-held belief, suggesting that elevated white blood cell counts may not necessarily be indicative of adverse outcomes in cleft lip surgeries. To explore this notion, we conducted a comprehensive literature review focusing on two case studies involving unilateral cleft lip patients with presurgical white blood cell counts exceeding 10,000 per microlitre. Both cases underwent successful cleft lip repair and demonstrated excellent post-surgical outcomes without any signs of inflammation or infection. Both cleft lip repair surgeries results showed no complications, and the patient exhibited optimal wound healing and an aesthetically pleasing outcome at the follow-up appointments. These cases challenge the assumption that normal white blood cell count is an absolute requirement for cleft lip surgeries and call for a reconsideration of its significance in predicting post-surgical outcomes. While leukocytosis is an essential parameter to identify potential infectious or inflammatory states, our findings suggest that it should not be solely relied upon in isolation when assessing the suitability for cleft lip surgery and predicting the adverse outcomes in cleft lip surgeries. Further studies are warranted to establish a more nuanced understanding of leukocytosis in the context of cleft lip surgeries, including its association with other clinical parameters and potential alternatives for evaluating surgical candidacy and predicting the adverse outcomes in cleft lip surgeries.

KEYWORDS: leukocytosis, cleft lip surgery, white blood cell count, inflammation, infection, post-surgical outcomes.

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INTRODUCTION

Leukocytosis, often defined as an elevated white blood cell (WBC) count greater than 11,000 cells per microlitre (11.0×10^9 per litre) in non-pregnant adults, is a relatively common finding with a wide differential. It is important for clinicians to be able to distinguish malignant from non-malignant etiologies, and to differentiate between the most common non-malignant causes of leukocytosis. Leukocytosis sometimes referred to as a leukemoid reaction. This level of elevation can occur in some severe infections, such as *Clostridium difficile* infection, sepsis, organ rejection, or in patients with solid tumours. Leukocytosis greater than 100,000 per microlitre is almost always caused by leukemias or myeloproliferative disorders.[1]

Orofacial clefts include a range of congenital deformities most commonly presenting as cleft lip with or without cleft palate (CLP) or isolated cleft palate (CP). Cleft lip, with or without cleft palate, represents one of the most common birth defects in the world. With a prevalence of one in 500 to 2500 live births, clefts confer significant physical, psychological,

and socioeconomic effects on both the patient and the family.[3] Cleft lip with or without cleft palate (CLP) is the second most common congenital birth defect in the U.S. trailing only Down syndrome. There are roughly 7,000 infants born with orofacial clefts in the U.S. annually.[3] Beyond the physical effects on the patient, cleft lip with or without cleft palate (CLP) also has significant psychological and socioeconomic effects on both patient and family, including disruption of psychosocial functioning and decreased quality of life (QOL). It is associated with increased mortality from many causes, including suicide as well as substantial healthcare costs. Cleft lips can be unilateral or bilateral, and may extensively involve the alveolus or palate. Affected individuals may present with other congenital anomalies and may be part of a genetic syndrome.[4]

Although the timing of cleft lip repair surgeries is contingent on a myriad of factors, clinicians universally agree to perform the repairs accordingly to the “rule of 10s” popularized by Millard.[5] Originally advised by Wilhelmsen and Musgrave in their paper aboit cleft lip surgery complication in 1966,[6] this rule referred to performing surgery once patients had reached the following cutoffs: weight greater than 10 pounds (4.5 kilograms), haemoglobin level greater than 10 grams per decilitre, and a white blood count count less than 10,000 cells per microlitre. Millard later modified this proposed cutoff in his 1976 to the recommendation that is most frequently quoted to this day, recommending that repairs be performed only when a patient weighs heavier than 10 pounds (converted to 4.5 kilograms) which usually happens in sync with 10 weeks of age, haemoglobin level greater than 10 grams in every 100 millilitres of blood (Hb level > 10 grams/dL), and not more than 10 thousand of leukocytes or white blood cells count in every microlitre of blood (WBC < 10,000/uL).[5-8] Translation to those points: the body weight and age criteria demands a child to have mature cells and tissue before enduring surgical and anaesthetic procedures. At the same point, a child should have had proper body size that enables surgeons to manipulate the tissue without magnification aid. Adequate haemoglobin level will provide good tissue perfusion and oxygen delivery to cells needed for anaesthetic procedure, while leukocyte count will define a child is free from systemic infection that risks jeopardizing the surgery.

Efforts are ongoing to uncover the epidemiology and etiology of this condition. The WHO-supported international collabo-rative research on craniofacial anomalies project establishes a global network to compile a comprehensive database and coordi-nate research strategies. Optimal management of a child with cleft lip demands an organized multidisciplinary effort involving the fields of otolaryngology, plastic surgery, maxillofacial surgery, orthodontistry, speech therapy, pediatrics, nursing, genetics coun-seling, audiology, psychology, and social work.[9]

There is a continuous increase in major oral and maxillofacial (OMF) surgical procedures in developing countries due to poverty, lack of awareness and late presentation of patients to healthcare facilities for treatment. Oral and maxillofacial surgery (OMFS) is a surgical specialty expanding its frontiers of surgical anatomic definition involving a range of surgical procedures and adjunctive treatment of diseases, injuries and defects.[10] It encompasses the functional and aesthetic aspects of the hard and soft tissues of the OMF region. While there are different criteria for classifying OMF surgical procedures into minor or major, a common criterion used in literature is that which classified OMF surgeries into minor or major based on the use of local anaesthesia or general anaesthesia respectively.[11]

The immune system largely depends on white blood cells (WBCs). There are five basic white blood cell (WBC) types: neutrophils, eosinophils, basophils, lymphocytes and monocytes, with each type having a specific role or immune function.[12] As the immune system's "army", WBCs defend the body against microorganisms and foreign substances. Following surgery, whether minor or major, the responses are that of acute increases (occurring within minutes to hours) in the WBC count. The changes are, however, more profound with major surgeries. The changes in the different leucocyte counts following either physical or psychological stress have been utilised to measure the physiological stress response. Surgical stress elicits a characteristic response involving the increased circulating concentrations of stress hormones such as cortisol and catecholamines. This is known to activate mature granulocytes in the bone marrow and tissues to rapidly release cells from the margins of blood vessel walls, spleen or bone marrows where they are stored by a process called demargination, as leucocytes spend most of their life in these storage areas. This process of demargination eventually increases the circulating pool of leucocytes in the blood.[11]

The effects of major surgical trauma on peripheral WBC count have been extensively studied in developed countries in various specialties such as orthopaedic surgery, cardiovascular and thoracic surgery, and abdominal and urological surgery. These studies documented the increased neutrophil and decreased lymphocyte counts, whereas monocyte, eosinophil and basophil counts were not significantly altered by surgery. While changes in white blood cell counts are well documented in other surgical fields, this is not the case in OMFS in our environment.[11]

CASE 1

A 6-month-old baby boy with an incomplete right sided cleft lip seeked help of surgical repair with his white blood cell count of 13,150 per microlitre. Preoperative investigations ruled out any signs of infection or systemic illness. The cleft lip repair surgery was performed without any problems during the surgery or complications after the surgery, and the patient exhibited optimal wound healing and an aesthetically

favourable outcome at the follow-up appointments (see **Figure 1**).

Figure 1. A 6-month-old baby boy with an incomplete right sided cleft lip and his white blood cell count of 13,150 per microlitre.

CASE 2

A 6-month-old baby boy with a complete left sided cleft lip and palate seeked help of surgical repair with his white blood cell count of 19,680 per microlitre. Preoperative investigations ruled out any signs of infection or systemic illness. The cleft lip repair surgery was performed without any problems during the surgery or complications after the surgery, and the patient exhibited optimal wound healing and an aesthetically favourable outcome at the follow-up appointments (see **Figure 2**).

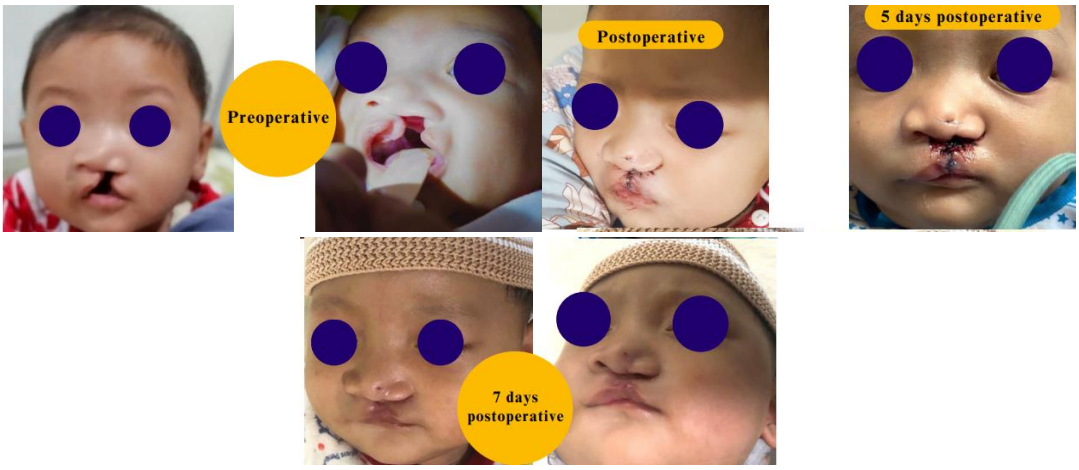

Figure 2. A 6-month-old baby boy with a complete left sided cleft lip and palate and his white blood cell count of 19,680 per microlitre.

METHODS

To build the core idea in this study, we conducted a comprehensive literature review exploring cleft lip surgeires with preoperative white blood cell counts exceeding 10,000 cells per microlitre and the associated post-surgical results, employing scientific references from 2013 to 2023 obtained from the Google Scholar database, with the keywords of "white blood cell count", "leukocytosis" and "cleft lip surgeries". Relevant articles were collected, reviewed, and utilized as comparison reference to the results of the two aforementioned cases. We added supplemental references when necessary for deeper discussion regarding the relevance of normal white blood cell count as an absolutely required parameter for cleft lip surgeries.

RESULTS

Both cases underwent successful cleft lip repairs, and their two sessions of post-surgical evaluations on their 5th and 7th day after the repair surgery showed both surgical wounds healed with favourable post-surgical results. Anticipated post-surgical complications associated of infection risk like wound dehiscence or prolonged time of post-surgical inflammation (like redness, swelling, exudation) did not occur.

DISCUSSIONS

For many years the "Rule of 10s" or Millard criteria has been the standard of value in term of deciding the most appropriate

timing for elective cleft lip surgery.[7,8] Until recently, clinicians including surgeons and anaesthetists have followed this convention without exploring the possibility of whether earlier cleft surgery could be safe and more effective. However, one study conducted by Chow and colleagues in 2016 started questioning the half-century paradigm, explained in their study of 1,313 cleft lip surgeries that the risks associated with performing surgery in patients who violate the Rule of 10s has undergone dramatic reductions and highlighted the need to continually validate and evaluate the dogma.[8] A year later, Hammoudeh and colleagues in 2017 conducted a prospective study consisting of more than 30 consecutive early cleft lip and nasal repairs, challenged the "Rule of 10s" or Millard criteria in term of the age of surgery, and presented a clear evidence to counter the absolute obligation to follow the 10 week of age criterion. Their study showed that planning and executing the repair surgery earlier than 10 weeks of age, even within the neonatal period, can be both safe and effective, and early repair would also facilitate the family to move past the experience of dealing with cleft lip deformity sooner and cruise toward a road of earlier healing, feeding, and better bonding.[13]

The two aforementioned studies disputed the results of previous research conducted by Moghadamyeghaneh and colleagues in 2015 with subjects of colorectal surgery patients. His study reported that 5.6% of colorectal cancer patients who underwent elective colorectal resection had pre-surgical asymptomatic leukocytosis and they found strong association between that clinical condition with increased post-surgical mortality, morbidity, and complications such as unplanned re-intubation, post-surgical ventilator dependency, and surgical site infection. They also linked a strong association between pre-surgical asymptomatic leukocytosis with pre-surgical dehydration and serum albumin level.[14] However, we believe it is not an apple-to-apple fairness to compare studies on cleft lip repair surgery with studies on malignancy surgery, because cleft lip deformities only deal with local anatomical defects without involving systemic problems while malignancy problems always involve more complicated systemic problems.

Determining the normal range of white blood count for children as a guideline is still challenging and not as easy as determining the normal range of white blood count for adult people because normal range of white blood cell count in children varies according to the age and overall health.[15-17] The normal range of white blood counts for children according to age group are shown in **Table 1**.[18]

Table 1. Normal white blood counts according to age groups and genders (cell count in each microliter of blood, /µL).[17] Highlightted row is the age group in which most cleft lip surgeries performed.

Gender / Age	Male	Female
First 2 weeks	8,000 – 15,400	8,200 – 14,600
2 – 4 weeks	7,800 – 15,900	8,400 – 14,400
5 – 7 weeks	8,100 – 15,000	7,100 – 14,700
8 weeks – 5 months (age when most cleft lip surgeries performed)	**6,500 – 13,300**	**6,000 – 13,300**
6 months – 2 years	6,000 – 13,500	4,900 – 13,200
3 – 5 years	5,100 – 13,400	4,400 – 12,900
6 – 17 years	4,400 – 12,900	3,800 – 10,400
Adult	3,800 – 9,600	3,400 – 9,600

In a conversation with our surgeon author (oral communication, January 2024), we noticed he and a few Indonesian plastic surgeons had also performed many cleft lip repair surgeries for babies with white blood count more than 10,000 in each microlitre of blood, or with age of younger than 10 weeks, or with body weights of less than 10 pounds, with favourable post-surgical results. A few minor post-surgical complications in such patients indeed happened, for

example suture knot dehiscence, but all were caused by hand rubbing trauma. He stated that his pre-surgical precaution never relied too much on the white blood count but rather clinical signs and symptoms of upper airway infection such as fever,[19] coughing,[20] and rhinorrhea.[21] His approach to anticipate smaller babies and their smaller tissue dimension is by using a surgical loupe during surgeries.[22]

Leukocytosis is not a disease itself, but the sign of an underlying disorder of variable etiology. It is a common laboratory finding, often due to relatively benign conditions, as the normal reaction of bone marrow to infection or inflammation leads to an increase

in the number of white blood cells, predominantly polymorphonuclear leukocytes and less mature cell forms (the “left shift”). Other causes, much less common but more serious, include primary bone marrow disorders. Physical stress and psychological/emotional stress can also elevate white blood cells counts. There is an association between stress and impairment of the immune system in human, and stress may affects white blood cells qualitatively and quantitatively.[23] Alterations in the number of circulating white blood cells differentials have also been associated with malignancy.[24] Certain drugs can trigger leukocytosis in adults, like corticosteroids,[25-26] lithium,[27] and beta agonists.[23] Increased eosinophil or basophil counts, resulting from a variety of infections, allergic reactions and other causes, can lead to leukocytosis in some patients.[23] In the simple words, clinicians should not easily but falsely point leukocytosis as an indisputable clinical mark of infections.

The predicting effect of white blood cell count has assumed a prominent role in the overall management of the surgical patient in recent surgery practice. This has led to diverse research in various surgical specialties such as neurosurgery, cardiovascular, orthopaedics, abdominal, urological and gynaecological surgery to evaluate the effect of regional procedures on the white blood cell count. Relying on such data, clinicians have been using white blood cell count to identify patients with an occult infection who are at a high risk of experiencing complications following surgery.[11]

However, normal pediatric laboratory values for white blood cell count are all above 10,000 cells/µl, and may be as high as 30,000 cells/µl in newborns, have different ranges according to age groups, therefore making a cut-off point for normal value is more difficult than doing so for adult people and it is unwise to standardize as the same cut-off point of 10,000 cells/µl as one of adult people.[14-17]

Looking back to our two cleft cases, both cases would definitely fall into the condition of leukocytosis if clinicians use the 'Rule of 10s' or the Millard criteria as the guideline, but if the clinicians use the white blood count guideline according to age groups and genders as described in **Table 1**, as a result our first case was actually still within the normal range of white blood count and therefore uncomplicated postoperative results are expected.

Based on the aforementioned views and insights, we believe clinicians should not rely heavily on the white blood cell count as a sole indicator for pre-surgical infection,[8] and instead should reorganize and put greater attention in the clinical symptoms and signs when assessing the pre-surgical risk of infection.

CONCLUSION

This study revisited the general consensus in which normal white blood cell count considered an absolute requirement for cleft lip surgeries and call for a reassessment of its significance in predicting post-surgical outcomes. Further studies are warranted to establish a more nuanced understanding of leukocytosis in the context of cleft lip surgeries, including its association with other clinical parameters and potential alternatives for evaluating surgical candidacy and predicting the adverse outcomes in cleft lip surgeries. When taking into consideration the current advances in surgical technique and diminished risks of anaesthesia, surgeons should only apply “the Rule of 10s” from Millard as a guideline instead of a strict rule in cleft repair surgery. Surgeons should address each patient individually and adhere more rigidly to “the Rule of 10s” when the infant does not have characteristics warranting expedited repair.

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