BioSCIENCE Original Article
DOI: https://doi.org/10.55684/2024.82.e00013

Comparison of CRP and IL-6 as inflammatory markers after immediate tonsillectomy

Comparação da PCR e IL-6 como marcadores inflamatórios após amigdalectomia imediata

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ABSTRACT

Introduction: In palatal tonsillectomy, as in any surgical procedure, trauma induces an immune, endocrine and metabolic response, with the release of several cytokines reflecting its size and other factors. Serum levels of IL-6 and CRP may be useful in evaluating operative techniques and therapeutic strategies.

Objectives: To evaluate the laboratory variation of IL-6 and CRP between pre- and immediate postoperative periods of palatine tonsillectomies, with or without adenoidectomy, comparing groups according to surgical indication.

Methods: 20 patients, with or without adenoidectomy, had serum samples taken to measure IL-6 and CRP during anesthetic induction and just before discharge. Group I, with inflammatory indications, had 15 patients, while group II, with obstructive indications, had 5. Pre- and postoperative dosages were compared, as well as levels and variations between groups.

Results: CRP levels were not altered by the operation, while IL-6 levels were significantly altered (p<0.001). It was hypothesized that patients with inflammatory surgical indications had higher baseline CRP and IL-6 levels. IL-6 also appeared to increase more in patients undergoing palatal tonsillectomies with adenoidectomy.

Conclusion: The surgical indication of an inflammatory nature seems to have a significant impact on preoperative CRP levels, which were higher compared to the levels of those without an inflammatory indication. On the other hand, the type of surgical procedure seemed to influence the variation in IL-6 levels (p=0.03).

KEYWORDS: Interleukin-6. C-reactive protein. Palatal tonsillectomy. Immune response.

RESUMO

Introdução: Na tonsilectomia palatina, como em qualquer procedimento cirúrgico, o trauma induz resposta imune, endócrina e metabólica, com liberação de diversas citocinas refletindo o seu tamanho e outros fatores. Os níveis séricos de IL-6 e PCR podem ser úteis na avaliação de técnicas operatórias e estratégias terapêuticas.

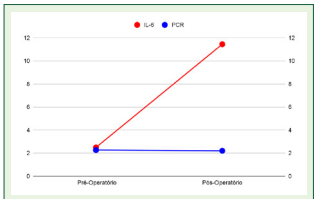
Objetivos: Avaliar a variação laboratorial da IL-6 e PCR entre pré e pós-operatório imediato de tonsilectomias palatinas, com ou sem adenoidectomia, comparando grupos conforme indicação cirúrgica.

Métodos: 20 pacientes, com ou sem adenoidectomia, realizaram coletas séricas para dosagem de IL-6 e PCR na indução anestésica e logo antes da alta. O grupo I, com indicação inflamatória, teve 15 pacientes, enquanto o grupo II, com indicação obstrutiva, teve 5. As dosagens pré e pós-operatórias foram comparadas, bem como os níveis e variações entre os grupos.

Resultados: Os níveis de PCR não sofreram alterações pela operação, enquanto os de IL-6 sim e considerável (p<0,001). Foi levantada a hipótese de que pacientes com indicações cirúrgicas inflamatórias tiveram níveis basais de PCR e IL-6 maiores. A IL-6 também pareceu aumentar mais nos pacientes submetidos à tonsilectomias palatinas com adenoidectomia.

Conclusão: A indicação cirúrgica de natureza inflamatória parece apresentar impacto significativo nos níveis de PCR pré-operatória, que se mostrou mais elevada em comparação aos níveis daqueles sem indicação inflamatória. Por outro lado, o tipo de procedimento cirúrgico pareceu influenciar a variação dos níveis de IL-6 (p=0,03).

PALAVRAS-CHAVE: Interleucina-6. Proteína C reativa. Tonsilectomia palatina. Resposta imune.



Line graph comparing IL-6 and PCR results between pre- and PO

Central message

Any surgical procedure induces an immune, endocrine, and metabolic response, with the release of several cytokines reflecting its size and other factors. Serum IL-6 and CRP levels can be useful in the evaluation of operative techniques and therapeutic strategies. Thus, comparing them in the pre- and postoperative period of palatine tonsillectomies, with or without adenoidectomy, is opportune to evaluate the intensity of aggression with the 2 techniques

Perspective

Surgery in the presence of inflammation has a significant impact on preoperative CRP levels, which are higher compared to those without inflammation. On the other hand, the type of surgical procedure influences the variation of IL-6 levels. This study compares situations with and without inflammation in otorhinolaryngological procedures. Its knowledge helps in the management of patients undergoing surgical trauma.

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Conflict of interest: None | Financial source: None | Received: 05/01/2024 | Accepted: 28/02/2024 | Corespondence: pedronicolaudesouza1@hotmail.com | Associate Editor: Rafaela Fernandes Gonçalves

How to cite:
Przysiezny PE, Spuldaro LG, de Souza PN, Barreto DR, Gil I, Hammerschmidt R. Comparação da PCR e IL-6 como marcadores inflamatórios após amigdalectomia imediata. BioSCIENCE. 2024;82:e013

INTRODUCTION

Palatal tonsillectomy (PT) consists of surgical removal of the palatine tonsils, while adenoidectomy consists of removal of the pharyngeal tonsil. Palatine and pharyngeal tonsils are clusters of lymphoid tissues located in the posterior oropharynx and posterosuperior regions of the nasopharynx, respectively. Both procedures are widely performed in otorhinolaryngology[1], especially in pediatric patients2. These operations are indicated in the treatment of inflammatory, obstructive or mixed situations (overlapping inflammatory and obstructive components).[1,3] These procedures are not without complications. The most commonly reported are: respiratory distress syndrome, hyperemesis, bleeding, and pain.[1,4]

PT, with or without adenoidectomy, produces open tissue repair (by second intention).[4] During it, surgical trauma induces immune, endocrine, and hematopoietic responses that result in local and systemic changes.[5] Inflammation in surgical trauma is associated with the release of several chemical mediators, such as pro-inflammatory cytokines and acute phase proteins.[5]

Cytokine levels do not directly reflect immune status, but indicate activation of the underlying immune system, providing insights into the impact of the operation on the metabolic and immune systems. These inflammatory mediators are related to the extent of surgical trauma and the presence of complications.[5] In summary, inflammation, cytokine levels, and CRP range from mild to severe responses during the procedure, and are influenced by surgical time, extent of dissection, type of sutures, presence of foreign bodies, and complications.

There is also activation of the sympathetic nervous system, with the release of catecholamines and increased cortisol production, which also stimulates the production of pro-inflammatory cytokines, such as IL-1 (InterLeucine), IL-2, IL-6, IL-8 and TNF (Tumor Necrosis Factor), in addition to anti-inflammatory factors such as IL-13 and IL-10.[5]

The acute phase mediators of the inflammatory response, most commonly used to assess surgical trauma, are IL-1, TNF, IL-6, and CRP (C-reactive protein).[5]

IL-6 is the earliest marker of tissue damage, considered the best marker of acute inflammatory phase response6 and the major mediator of hepatic secretion of most acute phase proteins.[7] IL-6 is secreted by many types of cells. B and T lymphocytes and monocytes are the main sources, with special attention to Th1 lymphocytes (T helper lymphocytes), which are the main producers.[7] Sentinel cells, especially macrophages, are the first to synthesize IL-6.[1,2] After stimulation, plasma concentrations of IL-6 are detectable in 60 min, peaking between 4-48 h, and may persist for up to 10 days.[5,7,8] The amount of IL-6 released seems to be related to the extent of tissue trauma.[8]

CRP, on the other hand, is one of the acute phase proteins, released into the bloodstream in the presence of acute inflammatory processes.[7] This happens through cytokines such as IL-1, TNF, and IL-6, produced by sentinel cells after stimulation. Mainly in hepatocytes, these cytokines stimulate the synthesis and release of acute phase proteins in the blood. Serum CRP levels rise between 4-10 h after the stimulus, reaching a peak of up to 1,000 times their initial concentration at about 48 h7, being an excellent marker of acute phase response. It is used clinically for postoperative (PO) monitoring of the inflammatory response, follow-up and diagnosis of chronic diseases such as rheumatologic diseases, and cardiovascular risk assessment. In the postoperative period, they have greater sensitivity to detect complications than ESR, leukocytosis, heart rate, and fever.[1,8] CRP, unlike IL-6 and other PFAs, does not undergo diurnal and/or nighttime variations in its concentrations.[7] CRP levels can be increased up to 30 days after trauma.[5] Although IL-6 and CRP are widely studied inflammatory mediators, their specific role in the post-PD inflammatory response, with or without adenoidectomy, has not yet been fully elucidated. No similar studies were found in the PubMed and Cochrane databases using the descriptors 'Tonsillectomy', 'Interleukin-6' and 'C-reactive protein'. Understanding the post-PT inflammatory response and its relationship with IL-6 and CRP clinical implications is interesting. These markers can guide therapeutic strategies, compare surgical techniques, and evaluate drug therapies to improve postoperative outcomes.

Thus, this study aims to compare the inflammatory mediators IL-6 and CRP before and immediately after PT, with or without adenoidectomy, and to compare outcomes between patients with inflammatory or obstructive surgical indications.

METHOD

This is a prospective study approved by the Human Research Ethics Committee of the Angelina Caron Hospital and Maternity (Registration: 5.272.843, CAAE: 56106322.0.0000.5226). Patients who spontaneously sought the otorhinolaryngology outpatient clinic of the hospital, with indication for PT (with or without adenoidectomy), were invited to participate. Twenty patients were included out of a total of 31, meeting the criteria for explanation, reading, and written acceptance of the ICF, in addition to being classified as ASA I (American Society of Anesthesiologists).

Patients with: 1) hematological disorders; 2) neurological disorders; 3) craniofacial congenital malformations; 4) tonsils with an asymmetric appearance, raising the suspicion of malignancy; 5) hypersensitivity to medications used; 6) signs and/or symptoms of any acute disease in the preoperative period or in the immediate postoperative period; 7) use of immunosuppressive drugs; 8) surgical treatment of any nature with less than 30 days of evolution; 9) ASA II, III or IV patients; 10) change in the standard anesthetic plane; 11) failure in the first attempt at peripheral venipuncture for drug administration within the operating room; 12) failure in the first attempt at peripheral venipuncture to collect blood samples; 13) withdrawal at any of the times of blood sample collection; 14) allergic condition of any nature in the PO. Peripheral venous blood samples for IL-6 and CRP were collected

during anesthetic induction and approximately 6 h after the end of the operation.

The patients were divided into groups according to the surgical indications: 1) group I (inflammatory surgical indication) was patients with surgical indication for recurrent or chronic pharyngotonsillitis characterized by 7 infections in 1 year, 5 for 2 consecutive years or 3 per year for 3 consecutive years and sore throat for more than 3 months, associated with tonsillar inflammation9; 2) group II (obstructive surgical indication) was patients with hypertrophic tonsillitis generating snoring and/or obstructive sleep apnea syndrome, with concomitant inflammatory and obstructive surgical indications.

The patients remained fasted for 12 hours preoperatively, underwent the procedures on the day of their hospitalization, and all operations were performed by the same surgeon.

Statistical analysis

The Mann-Whitney U test was used for non-parametric data and the chi-square test. To compare the ordinal dependent variables, within each group, the Wilcoxon test was used. Results with $p < 0.05$ were considered statistically significant.

RESULT

Participants ranged in age from 6 to 28 (15.05) years. Of the total of 20 participants, 13 were under 18 years of age and 11 were women.

In the classification of surgical indications into 2 groups (with isolated or non-isolated inflammatory indication and with obstructive indication), 15 patients had an inflammatory indication (group I); of these, 10 had an isolated inflammatory surgical indication and 5 also had an obstructive indication; 5 had only an obstructive indication (group II).

PT and adenoidectomy

Ten patients had their palatine tonsils removed exclusively, and 10 underwent PT with adenoidectomy. Of the 10 with obstructive surgical indication (5 mixed and 5 isolated), adenoidectomy was performed in nine (90%). Only 1 with mixed surgical indication did not undergo adenoidectomy. It was also performed in 1 patient with isolated inflammatory surgical indication.

Adenoidectomy was performed in association with PT in all patients under 12 years of age. The youngest age was 6 years old and the oldest was 13. All patients aged 16 or older underwent only PT, without adenoidectomy.

Comparison between IL-6/PCR

Preoperative and postoperative IL-6

The values revealed for IL-6 were low, with 11 patients presenting values undetectable by the method (below 1.[5] pg/mL), 8 of which were in group I and 3 in group II. Among the 9 with detectable results, a mean of 2.38 ± 0.[71] pg/mL was found.

Serum IL-6 PO values were significantly higher ($p = 0.04$), rising in all patients. There was no undetectable value and there were only 3 within the reference value, leaving 17 with results above. The lowest value found was 5.[1] pg/mL, the highest was 25.[1] pg/mL, and the mean was 11.45 ± 3.56 pg/mL ($p < 0.001$).

Pre- and postoperative PCR

The preoperative CRP measurement also revealed low values. Those below the reference (0.3 mg/dL) were detected in 4 patients, including an undetectable value (below 0.2 mg/dL); 12 had them within the reference range (between 0.3 mg/dL and 4.0 mg/dL); values above the reference (4.0 mg/dL) were measured in 4, among which the highest was 10.78 mg/dL. The mean CRP values measured were 2.27 ± 1.98mg/dL.

In the postoperative period, the lowest CRP value found was 0.29 mg/dL and the highest was 11.03 mg/dL, with a mean of 2.21 ± 1.85; There was a decrease of 2.65% relative to the preoperative period. No undetectable results were found. A value below the reference was seen in 1 patient. Values within the reference were found in 15, and those above the reference in 4 patients.

There was no statistically significant variation between pre- and postoperative CRP ($p = 0.91$).

Comparison between IL-6 and PCR

Figure 1 shows the unified results of IL-6 and CRP measurements in the pre- and postoperative periods, in all patients. It should be noted that the averages are calculated based only on the detectable results. Thus, 19 patients were used to calculate the mean preoperative CRP (1 undetectable result) and only 9 to calculate the mean preoperative IL-6 (11 undetectable). It is noted, then, that the real values of the averages are even lower.

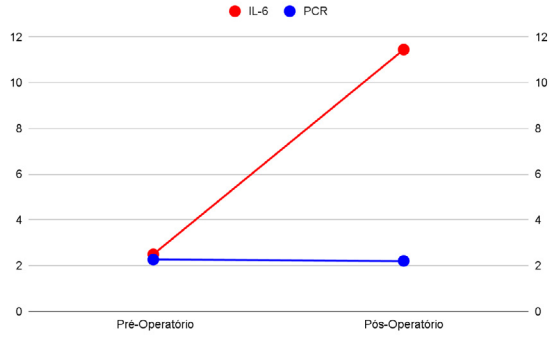

FIGURE 1 — Line graph comparing IL-6 and PCR results between pre- and PO

Comparison between the groups

IL-6 between groups I and II

The preoperative means were 2.47 ± 0.85 pg/mL for group I and 2.10 ± 0.1 pg/mL for group II and the postoperative means were 11.00 ± 3.04 pg/mL for group I and 12.82 ± 5.3 pg/mL for group II. There was a variation in the mean in percentage with an increase of about 445.34% in group I and about 610.47% in group II (variation with an increase in the overall mean of 481.09%, Figure 2). It was not possible to determine a statistically significant influence of the surgical indication on IL-6 values ($p = 0.11$).

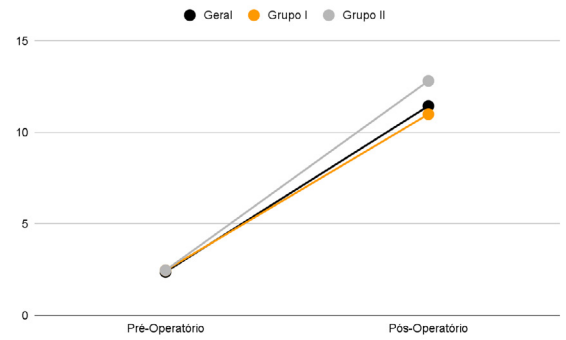

FIGURE 2 — Line graph comparing the results of IL-6 pre- and PO

IL-6 in PT without and with adenoidectomy

In patients undergoing PT without adenoidectomy, there was an increase between pre- and PO from 2.70 ± 0.92 pg/mL to 10.07 ± 2.86 pg/mL, approximately 372.96%. In the group of patients undergoing PT with adenoidectomy, the procedures led to a mean IL-6 score of 2 ± 0.1 pg/mL to 12.82 ± 3.62 pg/mL, an increase of 641%. The increase was also significantly greater (p = 0.03) in IL-6 in those who underwent PT with adenoidectomy. Figure 3 shows the comparison between pre- and PO IL-6 according to the operation performed.

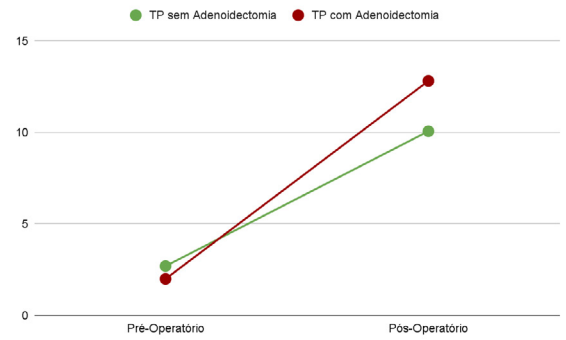

FIGURE 3 — Line graph comparing the results of IL-6 pre- and PO according to the procedure performed

PCR between groups I and II

Patients with an indication for inflammatory surgery (group I) had a mean preoperative CRP of 2.57 ± 2.34 mg/dL, while those with an indication for obstructive surgery (group II) had a mean preoperative score of 1.13±0.43 mg/dL. The mean POs were 2.53 ± 2.30 mg/dL in group I and 1.23 ± 0.43 mg/dL in group II. There was a variation in the mean in percentage, with a decrease of about 1.55% in group I and an increase of about 8.84% in group II (variation with a decrease in the overall mean of 2.64%). It was not possible to confirm the influence of surgical indication on the CRP value (p = 0.07).

Figure 4 compares CRP levels both pre- and PO in the different groups of patients.

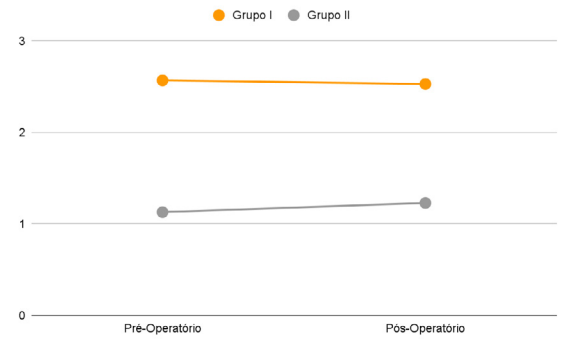

FIGURE 4 — Column graph comparing the results of pre- and postoperative CRP according to the surgical indication

PCR between PT without adenoidectomy and PT with adenoidectomy

There was a mean decrease of 2.65% in CRP between pre- and PO. When comparing patients who underwent different surgeries, the results were similar: an increase of about 1.01%, from 3.02 ± 2.48 mg/dL to 3.05 ± 2.51 in those who underwent PT without adenoidectomy alone, and a decrease of about 3.52%, from 1.42 ± 1.15 to 1.37 ± 0.89 in those who underwent PT with adenoidectomy.

Figure 5 shows the comparison between pre- and postoperative PCR according to the procedure performed.

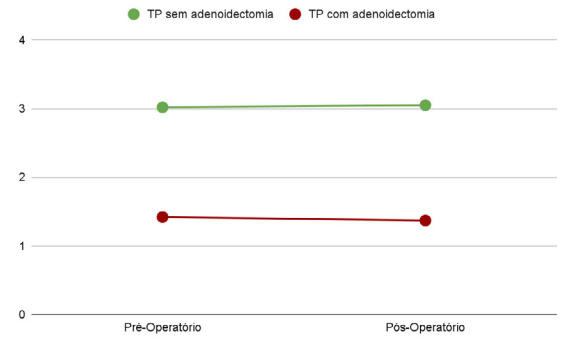

FIGURE 5 — Line graph comparing the results of pre- and PO PCA according to the procedure performed

DISCUSSION

Baby CM (2019)[12] demonstrated that the majority (51.47%) of patients who underwent PT were aged between 0-5 years and Vieira et al (2003)[13] found obstructive surgical indication in 76% of their 359 procedures. Patel et al (2014)[14] had a mean age of 6.5 years among those who underwent pulmonary tuberculosis and found obstructive indications in 67% of the 2369 patients. Shotts et al (2021)[15] also demonstrated obstructive indication in 54.76% of the 11348 patients operated, whose overall mean age was 12.21 years.

The limiting factor in this study was the puncture for blood collection immediately before hospital discharge. Eleven children did not allow data collection and, therefore, the sample differed in relation to age and surgical indication from other studies. Thus, the mean age was 15.05 years, with 75% with inflammatory surgical indication (10 exclusive and 5 with mixed

indication) and 25% with exclusive obstructive indication.

In addition, 10 exclusively removed the palatine tonsils and 10 associated it with adenoidectomy, which was performed in 9 with obstructive surgical indication and in 1 isolated inflammatory surgical indication. This is a common surgical procedure in the pediatric public, a fact confirmed in this study since it occurred in all patients under 13 years of age. Those over 16 years of age only underwent labor.

Giuliani et al (2021)[16], in a prospective study with 14 patients undergoing abdominoplasty, measured IL-6, CRP, and other serum mediators at 5 time points. They observed that IL-6 increased intraoperatively, being more significant in the 24 h after surgery, with a progressive decrease until the 14th postoperative day; CRP showed a large increase in the first hours after the procedure, remaining elevated until the 14th postoperative day.[16]

Barretto et al (2017)[17] evaluated the behavior of serum CRP in the first 3 weeks after primary total knee arthroplasty in 103 patients. They concluded that the serum CRP value showed a sudden increase on the 3rd day after proceeding. Two-thirds of the patients remain with elevated CRP in the 3rd postoperative week.[17]

Kordeluk et al (2016)[18] in a randomized, double-blind study with patients under 16 years of age and diagnosed with obstructive sleep disorder, compared the techniques of PT (with adenoidectomy), conventional PT with monopolar electrocautery, and PITA (Partial Intracapsular Tonsillectomy and Adenoidectomy). CRP, IL-6, among others, were evaluated in the pre- and postoperative periods. They concluded that PITA compared to conventional PT with monopolar electrocautery was associated with lower morbidity; however, the inflammatory response did not differ significantly in the first 24 h postpartum.

Silveira et al (2012)[5] studied 2 groups, 1 with 10 patients who underwent open cholecystectomy and 1 with 10 who underwent laparoscopic cholecystectomies. Comparing the serum levels of IL-6 and IL-10 measured at 4 time points, they demonstrated that there was an increase regardless of the type of procedure, proving that, for any type of trauma, there is a systemic inflammatory response. In addition, these authors concluded that serum IL-6 levels were significantly higher in the laparotomic cholecystectomy group, denoting an increased inflammatory response in open procedures compared to video-assisted procedures.

Most studies have shown that the severity of intraoperative tissue trauma implied greater IL-6 production, even with similar surgical durations.[5,6,8,16] Thus, commonly endoscopic surgeries, for example, have lower serum levels of IL-6 than their open counterparts.[8]

In this study, there was a statistically significant increase ($p < 0.001$) in IL-6 between the preoperative period and the first postoperative hours, in agreement with the known dynamics of IL-6 (plasma increase in IL-6 concentrations after 60 min, peaking between 4-48 h).[5,6,7,8,19] However, the operation did not cause a statistically significant variation in CRP ($p = 0.91$); the preoperative mean of 2.27 mg/dL was 2.21 mg/dL. This data can be explained by the fact that serum CRP levels begin to increase between 4-10 h after the stimulus, reaching peak values of up to 1,000 times their initial concentration in about 48-72 h.[7,17,20] It can be seen that CRP is not very useful in the postoperative evaluation of surgeries such as PT, in which patients are discharged from the hospital within a few hours.

Thus, IL-6, in comparison with PCR, in the first 6 h after the postoperative period of PT, with or without adenoidectomy, corroborates Oliveira et al 2011[21], verifying that IL-6 represents the most relevant and clear marker of the degree of tissue injury during the surgical procedure.

In this study, 11 patients were excluded, most of whom had isolated obstructive surgical indication. Thus, there was no quantitative sample matching, since group I had 15 and group II, 5 patients. However, some data can be analyzed. When comparing serum IL-6 variations between pre- and PO in groups I and II, a greater increase was demonstrated in group II. However, there is a risk of quantitative bias, as 11 patients did not have their IL-6 levels detected in the preoperative period. Comparing the CRP measurements, a higher mean value was observed for group I, but this influence could not be confirmed ($p = 0.07$). When comparing the serum variations in CRP between pre- and PO in group I and II, a greater increase was demonstrated in group II, with only 1 undetectable patient. Due to the higher CRP mean values in group I and the higher increase in serum CRP and IL-6 mean values occurred in group II, it would be possible to hypothesize that patients with inflammatory surgical indication would have higher baseline CRP and serum IL-6 levels. However, more studies are needed to confirm this hypothesis.

There is also a difference in variations according to the surgical procedure. In PT without adenoidectomy, the mean serum IL-6 level ranged from 2.7 pg/mL to 10.07 pg/mL, whereas in PT with adenoidectomy it went from 2 pg/mL to 12.82 pg/mL, a significantly greater increase in IL-6 in patients undergoing PT with adenoidectomy ($p = 0.03$). However, in relation to CRP, there was an inversion, with an increase from 3.02 mg/dL to 3.05 mg/dL in patients undergoing PT without adenoidectomy only, and a decrease from 1.42 mg/dL to 1.37 mg/dL in patients undergoing PT with adenoidectomy. The initial premise was that PT with adenoidectomy would confer greater variations in IL-6 and CRP, however, this was only verified with IL-6.

CONCLUSION

It was observed that IL-6 had a greater increase in PO dosages up to 6 h after the end of the operation. Thus, it is legitimate to observe that IL-6 is more sensitive than PCR to evaluate the postoperative inflammatory process of PT, with or without adenoidectomy, in the first 6 hours after surgery. Surgical indication of

an inflammatory nature seems to have a significant impact on preoperative CRP levels, which was higher than those without inflammatory indication. On the other hand, the type of surgical procedure seemed to influence the variation of IL-6 levels (p = 0.03).

Authors' contributions

Conceptualization: Paulo Eduardo Przysiezny, Rogerio Hammerschmidt
Research: Leonardo G Spuldaro, Pedro N de Souza
Project Administration: Dioggo R Barreto, Isabela Gil
Writing (original draft): All authors
Writing (proofreading and editing): Rogerio Hammerschmidt

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