JoCASS
Çukurova Anestezi ve Cerrahi Bilimler Dergisi
2018 Adana

COMPARISON OF PROCALCITONIN WITH C-REACTIVE PROTEIN IN THE DIAGNOSIS OF INFECTION AFTER CRANIOTOMY

KRANİOTOMİ SONRASI GELİŞEN ENFEKSİYON TANISINDA PROKALSİTONİNİN C-REAKTİF PROTEİNLE KARŞILAŞTIRILMASI

Rıdvan Açıkalın[1], Can Sezer[2], Metin Tuna[3]

1 *Department of Neurosurgery, Private Medical Park Hospital, Mersin, Turkey*
2 *Department of Neurosurgery, Seyhan State Hospital, Adana, Turkey*
3 *Department of Neurosurgery, Cukurova University, Adana, Turkey*

Sorumlu Yazar/Corresponding Author: Rıdvan Açıkalın E-mail: mdridvan@yahoo.com
Geliş Tarihi/Received: 12.04.2022 Kabul Tarihi-Accepted: 30.07.2022 Available Online Date/Çevrimiçi Yayın Tarihi: 31.08.2022
Cite this article as: Acikalin R, Sezer C, Tuna M. Comparing Procalcitonin to C-Reactive protein in Diagnosis of Craniotomi Associated Infection. J Cukurova Anesth Surg. 2022;5(2):128-136.
Doi: 10.36516/jocass.1101283

Abstract

Aim: Classical infection indicators fail to distinguish between the inflammatory reaction induced by neurosurgery and the postoperative infection. In our study, we investigated the sensitivity and specificity of Procalcitonin (PCT) and C-reactive protein (CRP) in differentiating the inflammatory reaction caused by neurosurgery and postoperative infection.

Methods: Our study was carried out in 44 patients with intracranial tumors in Çukurova University Faculty of Medicine Neurosurgery between May 2007 and December 2007. Changes in PCT, white blood cell count, CRP, and fever values during preoperative 1 and postoperative 4 days were examined.

Results: PCT values were found to be above 0.1 ng/ml in all the patients who developed infection in the study. In the light of the results we obtained, we can say that patients with PCT values above 0.1 ng/ml on the postoperative 2nd and 3rd days should be monitored more carefully in terms of postoperative infection. In our study, the majority of patients with CRP infection followed a similar kinetics to that of patients who did not develop infection. CRP values are above normal (CRP>5 ng/ml) in all patients with and without infection. This indicates that CRP will not be used as an important parameter for the follow-up of postoperative infections

Conclusions: Our study demonstrates that PCT is a safe parameter that can be useful in the diagnosis of fever of unknown postoperative etiology in neurosurgery.

Keywords: C-Reactive Protein, infection, procalcitonin, cranitomy

Öz

Amaç: Klasik enfeksiyon göstergeleri, beyin cerrahisinin yaratmış olduğu inflamatuar reaksiyonla, postoperatif gelişen enfeksiyonun ayırt edilmesinde başarısızdır. Biz çalışmamızda beyin cerrahisinin yaratmış olduğu inflamatuar reaksiyonla, postoperatif gelişen enfeksiyonun ayırt etmesinde Prokalsitonin (PKT) ve C-reaktif proteinin (CRP) sensitivite ve spesifisitesini araştırdık.

Yöntemler: Çalışmamız Mayıs 2007-Aralık 2007 tarihleri arasında, Çukurova Üniversitesi Tıp Fakültesi Beyin Cerrahisinde intrakranial tümörü olan 44 hastada yapılmıştır. Preoperatif 1 ve postoperatif 4 gün boyunca PKT, beyaz küre sayısı, CRP ve ateş değerlerindeki değişimler incelenmiştir.

Bulgular: Çalışmaya alınan enfeksiyon gelişen hastaların tümünde PKT değerleri 0,1 ng/ml'nin üzerinde bulunmuştur. Elde ettiğimiz sonuçlar ışığında postoperatif 2. ve 3. günde 0,1 ng/ml üzerinde PKT değeri olan hastaların postoperatif enfeksiyon açısından daha dikkatli monitörize edilmesi gerektiğini söyleyebiliriz. Çalışmamızda CRP enfeksiyon gelişen hastaların büyük kısmında, enfeksiyon gelişmeyen hastalardakine benzer bir kinetik izlemiştir. Enfeksiyon gelişen ve gelişmeyen tüm hastalarda CRP değerleri normalin üstündedir (CRP>5 ng/ml). Bu da CRP'nin postop enfeksiyonları takip açısından önemli bir parametre olarak kullanılmayacağını gösterir.

Sonuç: PKT, beyin cerrahisinde postoperatif etyolojisi bilinmeyen ateşin teşhisinde faydalı olabilen güvenli bir parametre olduğunu düşünmekteyiz.

Anahtar Kelimeler: C-Reaktif Protein, enfeksiyon, prokalsitonin, kraniotomi

Introduction

Despite prophylaxis, postoperative infection is seen between 0.5% and 1.5%. Postoperative infections are diseases with high mortality, morbidity and cost. Surgical site infection is an important socioeconomic problem because it can be resistant to treatment, recur, bring a heavy economic burden and cause mortality[1]. For this reason, early detection of infection and initiation of appropriate treatment are very important for both the patient and the prevention of the economic burden it will bring. For this reason, in addition to the necessity of early diagnosis and treatment, distinguishing whether the emerging picture is an infection, preventing unnecessary antibiotic treatment or making the decision to terminate the started antibiotic early are parameters that are gaining importance in the follow-up of patients[2].

It is known how the inflammatory response, which develops as a response of the host to infections, occurs. Similar inflammatory response may develop after any type of tissue damage such as pancreatitis, major trauma, burns and autoimmune diseases[2-4]. General systemic findings of systemic inflammation (SIRS=Systemic Inflammatory Response Syndrome) such as changes in body temperature, leukocytosis, tachycardia may have infectious or non-infectious etiology. Therefore, old and new indicators are expected to show the presence, source and severity of inflammation. Accordingly, one of the first targets was to determine whether the systemic inflammatory response syndrome (SIYS) [5]. is caused by infection or non-infectious trauma, burn, a process that leads to the formation of an immune complex, or an immunological process such as resection. For this purpose, cytokines such as TNF-α, IL-6, IL-8, C-reactive protein (CRP), β2 microglobulin, acute phase reactants such as erythrocyte sedimentation rate (ESR), ferritin, separately or in combinations of these were used[6].

Postoperative infection is often difficult to diagnose before clinical symptoms become evident. Magnetic resonance imaging can help diagnose soft tissue change, but it is expensive to use as a screening tool and may not be available. Although inflammatory markers such as C-reactive protein (CRP), white blood cell count (WBC), erythrocyte sedimentation rate (ESR) and body temperature (BT) are easily measured, their specificity is not high. Inflammatory response, which develops due to trauma without infection, causes an increase in these parameters[7-9]. For this reason, research and research are continuing an infection indicator that shows infective complications that may develop in the early postoperative period, is not affected by surgical trauma, is specific for bacterial infections, and also responds quickly to treatment after appropriate antibiotic treatment.

Procalcitonin (PCT) is a 116 amino acid glycopeptide produced by the C cells of the thyroid gland under normal conditions and is a precursor of calcitonin[10,11]. The PCT level is undetectable in healthy people. It is known that serum PCT levels increase significantly in cases of sepsis and severe invasive bacterial infection and decrease rapidly with appropriate antibiotic treatment. However, PCT level does not change in severe viral infections and other inflammatory diseases. In our study, we evaluated the CRP and PCT responses of patients with inflammatory reaction and postoperative infection caused by neurosurgery and investigated whether it helps the diagnosis of surgical complications.

Materials and Methods

This study was conducted on 44 patients with intracranial tumors who were treated in the Department of Neurosurgery of Çukurova University Faculty of Medicine between February 2007 and August 2007. All patients who applied to our clinic with the diagnosis of intracranial tumor on the

specified dates were evaluated. Patients with terminal cancer and pathological fractures, patients who received massive blood transfusion, patients with chronic organ failure, multiple trauma, patients who underwent surgery in less than three months, pregnancy, patients with infection at the time of admission or chronic rheumatic disease were excluded from the study.

Demographic data such as age and gender, clinical symptoms and treatments of each patient were recorded at the first admission. The patients were followed up for infection clinically and laboratory for 1 day preoperatively and for 5 days postoperatively. Wound swab samples were taken from patients with blood, urine, CSF, and wound site discharge from patients with fever above 38°C in axillary measurement.

In all of the patients included in the study, mass excision by craniotomy was performed under general anesthesia (total excision with intratumoral debulking or microsurgery).

Antibiotic prophylaxis with cefazolin sodium was administered to all patients 30 minutes before the operation and for 2 days postoperatively.

Blood samples were taken from all patients in the morning for 1 preoperative and 4 days after the operation, and fever was followed up at the same time 4 times a day. The blood samples to be tested for CRP and PCT were placed in dry tubes and centrifuged at 4000 rpm for 10 minutes. Serum was separated from blood samples after centrifugation. Serum samples taken for CRP were studied with the nephelometric method (Dade Behring, Germany BN II device) in the central laboratory of our hospital on the same day.

On the same day, blood samples were taken in the laboratory of our hospital with the Cryptor (BRAHMS Diagnostica-Berlin, Germany) method for PCT and Sysmex XT 2000-i (Roche Diagnostics Gmb H. Mannheim, Germany) device for WBC.

The data were transferred to electronic media and analyzed in SPSS 15.0 Computer Package Program. For group comparisons, an analysis of variance (ANOVA) was performed followed by a Tukey post-hoc test. Statistical significance was accepted at $p<0.05$.

Results

The mean age of 44 patients included in the study was 47 (±19), and the median was 48.5 (Lowest Value=4, Maximum Value=90). Of the patients, 23 (53.3%) were female and 21 (46.7%) were male; the mean age was 46.9 (age range: 4–90 years). Pituitary adenoma in 5 (1 male, 4 female), 5 glioblastoma (4 male, 1 female), 22 grade 1-3 glial mass (12 male, 10 female) and 6 meningiomas (1 male, 5 female) of the patients participating in the study female), 3 PCA (1 male, 2 female), 3 ependymomas (2 males, 1 females) were present.

There was no statistically significant difference between the infected and non-infected groups in terms of age and gender (P=0.983, P=0.587). The distribution and incidence of infections in the patients are shown in Table 1.

Table 1. Distribution of Infections Developing in Patients

Type of Infection	Number of patients	Distribution (%)	Ratio (%)
UTI	1	14,3	2,2
UTI + CCCSI	1	14,3	2,2
UTİ + M	1	14,3	2,2
M	3	42,9	6,7
UTI + LI	1	14,3	2,2
Total	7	100	15,9

UTI: Urinary tract infection, CCCSI: Catheter-connected circulatory system infection, LI: Lung infection, M: Meningitis

No pathological increase was observed in the measured axillary fever of the patients included in the study before the operation. When the preoperative and postoperative

fever values are compared among themselves, it is seen that the fever reaches the highest value on the postoperative 1st day after the operation and then increases in the group with infection, but gradually decreases in the group without infection. When the mean of groups with and without infection were compared, the difference was found to be statistically significant (P<0.001).

An increase in WBC values was observed after the operation (P=0.02). It was observed that the WBC value reached the maximum value on the 2nd postoperative day in all patients and in the infected group. (Fig 1) However, when the means of the two groups are compared, the difference is not statistically significant (P=0.093)

A statistically significant increase in CRP values was observed in all patients after surgery, especially on the postoperative 2nd day (p=0.001). Especially in the infected group, it peaked on the 3rd day and then gradually decreased. (Fig 2) The two curves of the infected and non-infected groups were not parallel to each other (p=0.001). When the means of the two groups are compared, the difference is statistically significant (p=0.006).

A statistically significant increase was found in PCT values from the second postoperative day in the patients included in the study (p=0.002). The daily linear changes of PCT values in groups with and without infection are shown in Figures 3. When the mean scores of the infected and non-infected groups were compared, PCT values were found to be higher in the infected group (p=0.002).

A statistically significant increase was found in the erythrocyte sedimentation rates in the patients included in the study (p=0.001). When the means of the two groups are compared, the difference is statistically significant (p=0.001). An increase was noted on the second and third postoperative days in the infected group.

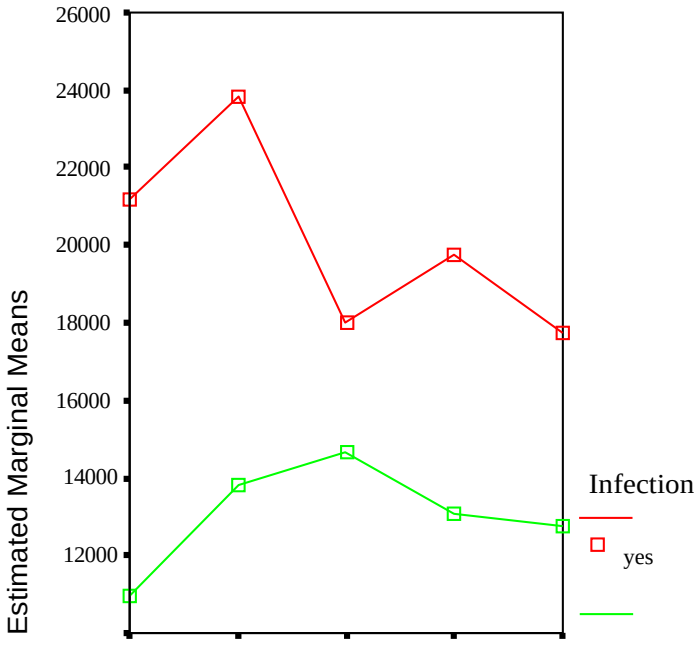

Figure 1. Daily Linear Changes of WBC Values

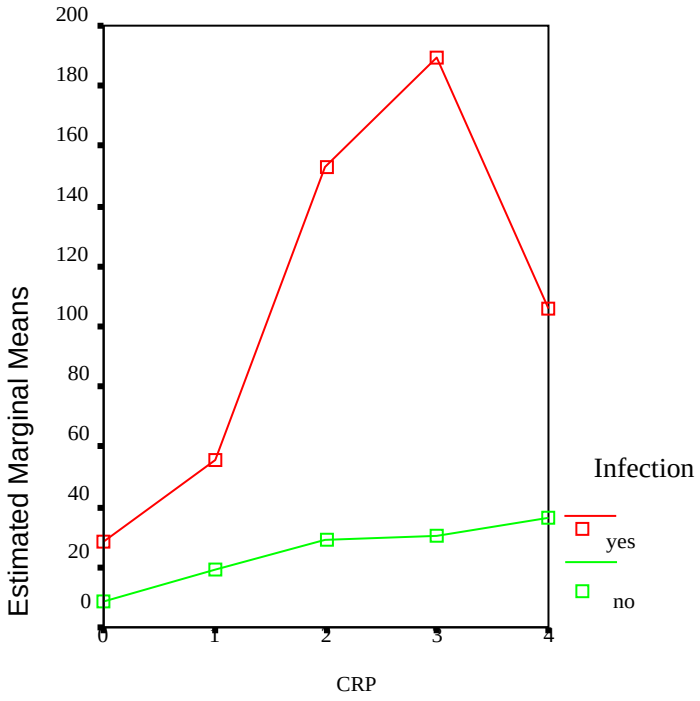

Figure 2. Daily Linear Changes of CRP Values in the Infected and Non-Infected Groups

Discussion

Postoperative fever above 38°C is common in the first few days after surgery. The cause of this fever is usually due to atelectasis due to surgery or to the inflammatory effect of the surgery. But it can be due to fever, embolism or infection. Therefore, it is important to determine the etiology of fever[12]. In the literature, CNS infections after neurosurgery constitute approximately 0.4% to 8% of all hospital infections. Age appears to be an important risk factor. The mortality rate due to meningitis cases developing after craniotomy may reach up to 30%[13].

In their study, Shimetani et al.[14] investigated CRP and PCT levels in serum and CSF in 30 patients with bacterial, viral or mycotic meningitis. They found that serum CRP levels were extremely elevated in 10% of all bacterial and viral meningitis cases, while PCT levels increased only in severe bacterial infections. They showed that there was no significant increase in PCT levels in CSF.

In the study of Mokart et al. on the role of PCT in the diagnosis of sepsis after major surgery, it was found that CRP levels were significantly higher in the group with PCT infection on postoperative 1st day, but CRP levels were similar in both groups[15].

In the study of Meisner' et al.[16], however, it was determined that the PCT value increased above 1 ng/ml in less than 9% of the cases after minor surgeries. The PCT value reached the highest level 24 hours after the operation in most of the patients.

In our study, the PCT levels of 44 patients who underwent surgical treatment were examined, the PCT levels in the non-infected group (n=34) ranged from 0.129 ng/mL to 0.159 ng/mL, the highest value did not exceed 1.15 ng/mL, and this value was reached after the first postoperative day. It has been observed that the mean tends to decrease after the first postoperative day.

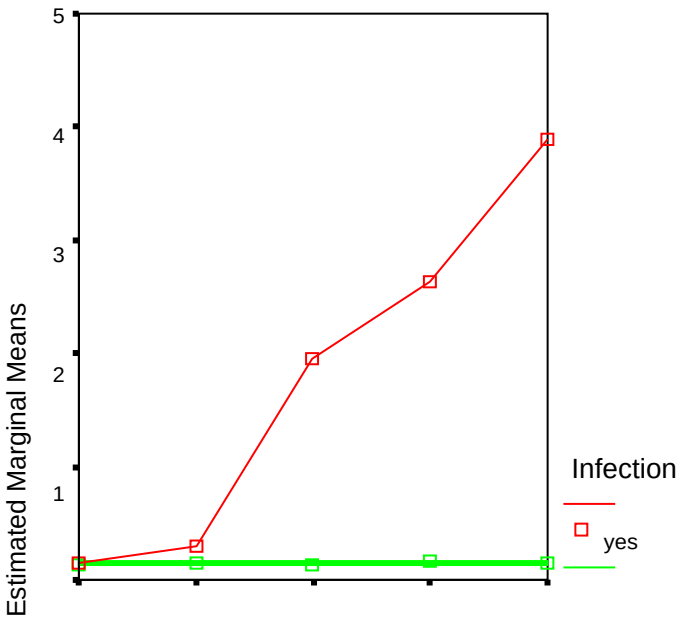

Figure 3. Daily Linear Changes of PCT Values in the Infected and Non-Infected Groups

PCT value above 1 ng/mL was detected in only one of the cases (2.7%). On the contrary, in the group with infection, PCT values increased significantly from the first postoperative day, and the mean value increased above 1.0 ng/ml on the second day. In the light of these results, it can be concluded that the inflammatory reaction caused by surgery does not cause a serious increase in PCT values and that PCT can be used in the early diagnosis of postoperative infections.

The mean preoperative value of CRP, which is one of the other parameters we looked at postoperatively, was found to be 12.0 (3-74.8) mg/L. When we look at the level of CRP after the operation, it was determined that the CRP values of the patients tended to increase after the operation (P=0.001). This increase was observed in both the infected and non-infected groups after craniotomy, and the mean of the infected group was found to be statistically significantly higher than the non-infected group (P=0.006). These results are similar to previous studies. Jensen[17] stated that in 50 patients who underwent lumbar disc surgery, CRP increased rapidly after the operation and reached peak values on the 2nd day. M. Neumaier et al. concluded that the CRP level is affected by the trauma site and, unlike other studies, where it reaches the maximum level on the second postoperative day, may be useful in detecting infection. However, they recommend basal and repetitive CRP measurement rather than a single CRP measurement[18]. Similar to this study, it supports other studies showing the value of CRP in surgical complications, especially deep surgical site infection[19,20].

The other parameter we used in our study was WBC. An increase in WBC values was observed in all cases after the operation (p=0.02). It was observed that WBC values reached the maximum value on the 2nd postoperative day in the non-infected and infected groups. However, when the means of the two groups are compared, the difference is not statistically significant.

Preoperative mean values of fever, which we evaluated in our study, were 36.9 Co. It was affected by the inflammatory response after surgery and started to decrease after peaking on the 1st day.

Postoperative complications occurred in 7 (3.1%) of the patients included in our study. Meningitis developed in 3 of the cases, urinary tract infection in 2, urinary tract infection and concomitant meningitis in 1, urinary tract and lung infection in 1, and lung infection in 1 case. In patients who developed postoperative meningitis, the PCT value increased approximately 100 times (3.12 ng/ml) on the 2nd day and was much higher than normal. CRP is postop. It entered a normal upward trend and started to decrease after reaching the peak value on the 2nd day. Like CRP in the WBC, it peaked on the 2nd day. The fever was found to be high on the 3rd day.

The findings in our study support the findings in the literature. PCT values were found to be above 0.1 ng/ml in all patients with systemic infection. In the light of the results we obtained, we can say that patients with PCT values above 0.1 ng/ml on the postoperative 2nd and 3rd days should be monitored more carefully in terms of postoperative infection.

In our study, the majority of patients who developed complications had CRP movements similar to those of patients who did not develop complications. CRP values are above normal (CRP>5 ng/ml) in all patients with and without complications. This indicates that CRP will not be used as an important parameter for the follow-up of postoperative infections.

In our study, another parameter in the etiology of fever was WBC. WBC does not follow a standard action like PCT and CRP after the operation. Despite this, WBC values were found to be well above the normal limit in patients who developed infections.

PCT is superior to WBC in detecting infections. Looking at the results of our study, we can say that the disadvantage of WBC is that it does not follow a standard kinetics after the operation. This makes WBC a less reliable parameter in determining the infective complications that may develop after the operation.

The results of our study support previous studies. Our study was conducted in a limited patient group (intracranial tumor) in neurosurgery and with a limited number of patients. However, it is a fundamental study in terms of evaluating the kinetics of PCT, a new infection parameter, after craniotomy and its superiority over other routinely used parameters.

Although PCT has been used in many surgical branches in recent years, the fact that our study is the first in the field of craniotomy makes it important for Neurosurgery. In the future, PCT's post-craniotomy system infections are followed-up, whether infection develops, the duration of antibiotic treatment, when it is to be decided, thus avoiding unnecessary and long-term antibiotics, as a result of which secondary infections caused by long-term antibiotic use are prevented and patient costs are reduced. and we think it will be a safe parameter.

Conclusion

Currently, there is no routinely used infection parameter that is specific for bacterial infections and is not affected by the inflammatory reaction caused by surgery. The fact that WBC follows a fluctuating pattern after the operation and is seriously affected by different surgical procedures applied to the same region makes WBC an unsafe parameter in the follow-up of infective complications after neurosurgery. The fact that PCT is not affected by the patient's age, gender, time until the operation, type of anesthesia and surgery shows that PCT can be used safely in neurosurgery in the early postoperative period for infection follow-up.

Author contributions

All authors contributed to the study conception and design. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

Authors declared no financial support.

Ethical approval

This study, in which patients participated on a voluntary basis, was conducted in accordance with all ethical procedures /standards and the Declaration of Helsinki.
This Article is Adapted from the Thesis. (Thesis number 224986, Kraniotomi sonrası gelişen enfeksiyon tanısında Prokalsitoninin C-Reaktif proteinle karşılaştırılması / Comparing Procalcitonin to C-Reactive protein in Diagnosis of Craniotomi Associated Infection, 2008, Çukurova Üniversitesi, Tıpta Uzmanlık Tezi. https://tez.yok.gov.tr/UlusalTezMerkezi/tezDetay.jsp?id=gTRMQRxYziZxdIeVUKmFJA&no=Ce7aBTqn5v0_ha-7-cmg7g)

References

1. Chung YG, Won YS, Kwon YJ, et al. Comparison of serum CRP and procalcitonin in patients after spine surgery. J Korean Neurosurg Soc. 2011;49(1):43-8. doi: 10.3340%2Fjkns.2011.49.1.43.
2. Arslan A, Olguner SK, Vedat AÇ, et al. Comparison of procalcitonin, C-reactive protein, white blood cell and body temperature in the diagnosis of ventriculostomy-associated infection. Cukurova Med J. 2019;44(1):69-76. doi: 10.17826/cumj.551752.
3. Klinger A, Buchfelder M, Schlaffer SM, et al. Infection surveillance in transsphenoidal pituitary surgery-comparison of lipopolysaccharide-binding-protein, interleukin 6, C-reactive protein, white blood cell count, erythrocyte sedimentation rate and body temperature. Acta Neurochir. 2013;155 (11): 2177-82. doi: 10.1007/s00701-013-1875-x.
4. Al-Jabi Y, El-Shawarby A Value of C-reactive protein after neurosurgery: a prospective study. Br J Neurosurg 2010;24(6):653-9. doi: 10.3109/02688697.2010.500408.
5. Boeken U, Feindt P, Gams E, et al. The influence of extracorporeal circulation and inflammatory responses such as SIRS and sepsis on secretion of procalcitonin. J Clin Basic Cardiol 1999;2(2):225-227.
6. Mokart D, Merlin M, Sannini A, et al. Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. Br J Anaesth. 2005;94(6):767-73. doi: 10.1093/bja/aei143.
7. Jaye DL, Waites KB. Clinical applications of C-reactive protein in pediatrics. Pediatr Infect Dis J 1997;16(8):735-47. doi: 10.1097/00006454-199708000-00003.
8. Anugu NR, Khan S. Comparing the Diagnostic Accuracy of Procalcitonin and C-Reactive Protein in Neonatal Sepsis: A Systematic Review. Cureus. 2021;13(11). doi: 10.7759/cureus.19485.
9. Covey DC, Albright JA. Clinical significance of the erytrocyte sedimentation rate in orthopaedic surgery. J Bone Joint Surg 1994;76(6):848-53. doi: 10.2106/00004623-199406000-00008.
10. Müler B, Kenneth LB. Procalcitonin: how a hormone became a marker and mediator of sepsis. Swiss Med Wkly 2001;131(41):595-602. doi: 2001/41/smw-09751
11. Meynaar I, Droog W, Batstra M, et al. In Critically Ill Patients, Serum Procalcitonin Is More Useful in Differentiating between Sepsis and SIRS than CRP, Il-6, or LBP. Crit Care Res Pract. 2011;15(1):594-645. doi: 10.1155/2011/594645.
12. Pile JC: Evaluating postoperative fever: a focused approach. Cleve Clin J Med 2006;73(1):62-6. doi: 10.3949/ccjm.73.suppl_1.s62.
13. Berker M, Hazer DB, Yücel T, et al. Complications of endoscopic surgery of the pituitary adeno- mas: analysis of 570 patients and review of the literature. Pituitary. 2012;15(3):288-300. doi: 10.1007/s11102-011-0368-2.
14. Shimetani N, Shimetani K, Mori M. Levels of three inflammation markers, C-reactive protein, serum amyloid A protein and procalcitonin, in the serum and cerebrospinal fluid of patients with meningitis. Scand J Clin Lab Invest. 2001;61(7):567-74. doi: 10.1080/003655101753218337.
15. Mokart D, Merlin M, Sannini A, et al. Procalcitonin, interleukin 6 and systemic inflammatory response syndrome (SIRS): early markers of postoperative sepsis after major surgery. Br J Anaesth. 2005;94(6):767-73. doi: 10.1093/bja/aei143.
16. Meisner M, Tschaikowsky K, Hutzler A, et al. Postoperative plasma concentrations of procalcitonin after different types of surgery. Intens Care Med 1998;24(1):680-4. doi: 10.1007/s001340050644.
17. Jensen CK, Brandslund I, Sogaard I. Lumbar disc surgery and variations in C-reactive protein, erythrocyte sedimentation rate and the complement split product C3d. Acta Neurochir 1988;90(1):42-4. doi: 10.1007/BF01541265.
18. Neumaier M, Scherer MA. C-reactive protein levels for early detection of postoperative

infection after fracture surgery in 787 patients Acta Orthopaedica 2008;79(3):428-32. doi: 10.1080/17453670710015355.
19. Sanzen L, Carlsson A S. The diagnostic value of C-reactive protein in infected total hip arthroplasies. J Bone Joint Surg (Br) 1989;71(1):638-41. doi: 10.1302/0301-620X.71B4.2768312.
20. Foglar C, Lindsey R W. C-reactive protein in orthopedics. Orthopedics 1998;21(1):687-91. doi: 10.3928/0147-7447-19980601-11.