Procalcitonin or C-Reactive Protein: The better Identifier of Treatment Response in Urinary Tract Infection among Adults

Umer Naseer, Abdul Rehman Arshad*, Bassam Khalid**, Taimoor Saleem**, Fatima Naseer***, Mahnoor Qamar****

Department of General Medicine, Combined Military Hospital Peshawar/National University of Medical Sciences (NUMS) Pakistan,
*Department of General Medicine, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan,
**Department of General Medicine, Combined Military Hospital Lahore/National University of Medical Sciences (NUMS) Pakistan, ***Department of
General Medicine, Central Park Medical College, Lahore Pakistan, ****Department of General Medicine, Rashid Latif Khan University, Lahore Pakistan

ABSTRACT

Objective: To ascertain the better marker between Procalcitonin and C reactive protein (CRP) in predicting response of treatment in patients suffering from urinary tract infections.

Study Design: Comparative cross sectional study.

Place and Duration of Study: Pak Emirates Military hospital, Rawalpindi Pakistan, from July 2020 to July 2021.

Methodology: It included individuals with clinical and laboratory evidence of isolated urinary tract infections. After consent, patients' samples for baseline investigations (including urine cultures, Procalcitonin and CRP) were taken before the start of tablet Nitrofurantoin (100 mg twice daily 500mg daily for 7 days) and on third day of treatment. Outcomes of treatment were also recorded. Treatment of non-responders was later modified as per culture reports.

Results: A total of 200 individuals were included in the study. It comprised of 185(92.5%) females and 15 (7.5%) males. Their mean age was 40.4±9.64 years. Out of these subjects, 179 (89.5%) individuals recovered with the first line empirical antibiotic while 21 (10.5%) did not respond to it. 152 (76.0%) cultures showed organism growth with most common ones being Escherichia Coli (42.5%), Klebsiella spp(12.5%), Enterococcus(12.5%) and Pseudomonas spp (4%).Mean serum Procalcitonin levels on day zero and day 3 were 0.53±0.2 and 0.44±0.17 respectively. Similarly, mean serum CRP levels on day zero and day 3 were 74.4±24.9 and 61.97±21.6 respectively. Percentage fall of Procalcitonin and CRP on third day of antibiotic therapy was 16.01±8.4 and 15.96±8.58 respectively (p value 0.382).

Conclusion: There was no significant difference between Procalcitonin and CRP in predicting the response to antibiotic therapy in urinary tract infections.

Keywords: C Reactive Protein, C Reactive Protein, Procalcitonin, urinary tract infection, UTI.

INTRODUCTION

The urinary tract infection (UTI) is one of the common sites of infections in the body. It is actually the infection involving any part of the urinary system which includes kidney, ureter, bladder and any part of urethra.[1] It can be caused by bacteria, fungus, protozoa or virus etc. These infections occur when the infective organism usually from the skin or the rectal region enter the urinary tract through the urethra.[2,3] The infection to urethra and bladder is more common than the infection to kidney (pyelonephritis) but is less severe than the latter.[4] There are a number of factors which pose increased risk to the development of urinary tract infection in the adults. These factors include age (elders or children), pregnancy, sexually active individuals, poor hygiene, previous history of urinary tract infection, female gender (due to shorter length of urethra), menopause etc.[5-7] The sign and symptoms of these infections can vary depending on the site of infection. The infection of urethra and bladder can present with dysuria, increased frequency of urination, feeling to urinate with empty bladder, hematuria, pain in lower abdomen or groin. While the infections of kidney present with fever, chills, nausea, vomiting, lower back pain or loin pain. These sign and symptoms can also be absent in certain people like young children or elderly people.

The urinary tract infections are the third most common infection worldwide after respiratory tract and gastrointestinal tract infection. In the developed countries, its incidence ranges from 100 to 180 million cases per year.[8] This burden of disease has led to formulate effective diagnostic and therapeutic approach with subjective evidence to identify and treat the illness. The diagnostic modalities available for the patients with suspected urinary tract infection

Correspondence: Dr Umer Naseer, Department of General Medicine, Combined Military Hospital, Peshawar Pakistan
Received: 22 Jan 2023; revision received: 23 Mar 2023; accepted: 29 Mar 2023

includes lab investigations and imaging modalities. Lab investigations include Complete Blood Picture, raised inflammatory markers (like Erythrocyte sedimentation rate, C reactive protein), and urinalysis which can reveal increased pus cells, RBCs and urine culture can reveal the growth of culprit pathogen. After the diagnosis is made, the treatment is started which primarily involves Antibiotics, hydration, rest and analgesics for symptomatic relief. It takes a few days to ascertain whether the choice of antibiotic initially started based on the local guidelines is effective for the particular patient or not. For that matter, one cannot solely rely on clinical signs and symptoms. Rather one seeks any subjective evidence which detects early whether the particular treatment needs to be changed especially in a critically ill patient.[9,10]

Procalcitonin is a precursor protein released in response to bacterial infections primarily and is one of the sensitive markers to rise early in an infection especially respiratory tract infection.[10] CRP is an acute phase protein that raise in any form of infection or inflammation in any part of the body. This study was done in order to ascertain which amongst the above two markers can help us detect the response to treatment in urinary tract infection, earlier than the other.

METHODOLOGY

This was a comparative cross sectional study study conducted at Pak Emirates Military Hospital Rawalpindi, Pakistan, from July 2020 to July 2021 after taking approval from ethical committee of the institute (Reference No. A/28/EC/218/2020 dated 1st June 2020). The method of sampling was non randomized convenient sampling. The sample size was estimated through open epi online calculator for sample size estimation using the reference prevalence of 11.1% referred from local study mentioned previously.[9] It came out to be 150 using confidence interval of 95% and Power of 0.8.

Inclusion Criteria: All individuals with sign and symptoms suggesting urinary tract infection (which includes dysuria, increased frequency of urination, feeling to urinate with empty bladder, hematuria, pain in lower abdomen or groin etc) confirmed by objective laboratory investigations were included in the study. This includes positive urine dipstick for nitrites or leukocytes and more than 20 WBCs/mm3 and RBCs detectable on Urine Routine examination.

Exclusion Criteria: Individuals with clinical, laboratory or radiological evidence suggesting infection at any other site were excluded from the study. People having any other disorder that could rise or falsely lower the Procalcitonin or CRP levels in blood were excluded from the study as well e.g., use of steroids or immunosuppressive mediation, immuno-compromised state etc. Patients allergic to first line empirical antibiotic i.e., Nitrofurantoin and pregnant women were excluded from the study as well.

After the diagnosis of urinary tract infection is confirmed and before the start of oral or parenteral antibiotic therapy, their serum and urine samples were taken for complete blood Picture, Urea and electrolytes, CRP Quantitative (CRP-Q), Serum Procalcitonin, pus cell count in urine and urine culture. During treatment of infection with the same first line empirical antibiotic therapy, daily serum and urine samples were taken for CRP-Q, Procalcitonin and pus cell count for first 5 days. Daily signs of clinical improvement or clinical deterioration was also recorded which included subjective scoring (zero to 10), vital signs charting etc. Those individuals who demonstrated any two or more of the following on third day of treatment were considered recovering from infection; 1) resolution of fever 2) improvement in Lower urinary tract symptoms 3) decrease of urine pus cell count 4) improvement in patient's self-score at day 3. While, those individuals who showed less than two of the above features were considered as not recovering from the infection.

Data was analyzed by using Statistical Package for Social Sciences (SPSS) 22.00. Quantitative data was represented using mean ± standard deviation and qualitative data was represented by using percentage and frequency. Paired Sample t test and independent sample were applied. The p-value of ≤ 0.05 was considered as statistically significant.

RESULTS

Two hundered individuals were included in the study. It comprised of 185(92.5%) females and 15(7.5%) males. Their mean age was 40.4±9.64 years. Out of these subjects, 179(89.5%) individuals recovered with the first line empirical antibiotic while 21(10.5%) did not respond to the same therapy when assessed on third day of first line antibiotic treatment. The frequency of sign and symptoms with which the patients presented to medical care, is compiled in Table-I.

Out of 200 urine cultures, 152(76.0%) showed growth. Organisms isolated in it are as shown in Table-II.

Table-I: Frequency of Sign and Symptoms of the Patients (n=200)

Sign and symptoms	n(%)
Fever	84(42.0%)
Dysuria	154(77.0%)
Frequency	159(79.5%)
Urgency	133(66.5%)
Hesitancy	45(22.5%)
Hematuria	44(22.0%)
Loin pain	13(6.5%)
Nausea/vomiting	13(6.5%)

Table-II: Organisms Isolated in Urine Cultures of Subjects (n=200)

Organisms Growth	n(%)
No growth	48(24.0%)
Escherichia Coli	85(42.5%)
klebsiella spp	25(12.5%)
Enterococcus	25(12.5%)
pseudomonas spp	8(4.0%)
Staph aureus	6(3.0%)
proteus	2(1.0%)
Acinetobacter	1(0.5%)

Among the subjects recovering from illness with treatment, the trend of Procalcitonin and CRP during the course of treatment were compared and compiled in theTable-III.

Table-III: Comparison of Procalcitonin and C-reactive protein (CRP) trend among the Patients responding to Treatment (n=179)

Parameters	Trends during Treatment in Recovered Patient		p-value
	On day Zero (Mean±SD) (n=179)	On day 3 (Mean±SD) (n=179)	
Serum Procalcitonin (ng/ml)	0.53±0.20	0.44±0.17	<0.001
Serum C-reactive protein (CRP) levels (mg/L)	74.4±24.9	61.97±21.6	<0.001

There was no significant difference in the percentage fall of Procalcitonin and CRP among the subjects who responded to treatment for urinary tract infection as shown in Table-IV.

Table-IV: Comparison of degree of Fall of Procalcitonin and C-reactive protein (CRP) in recovering Patients (n=179)

Parameters	Trends during treatment in recovered patient		p-value
	Procalcitonin (Mean±SD) (n=179)	C-reactive protein (CRP) (Mean±SD) (n=179)	
Percentage fall of markers in recovered patients (%)	16.01±8.4	15.96±8.58	0.382

DISCUSSION

The results of our research work show that majority of the urinary tract infections were detected in the females. Similar findings were observed in a study published in 2019 in by Zubair *et al.*, in which urinary tract infection was found in 87.95% ladies.[11] One study also found urinary tract infections more prevalent in females as compared to males in their study.[12] Another study found that multiple factors have been implicated in increased incidence of UTI in women including a short urethra.[13] The results also showed that 89.5 % of subjects responded to Ciprofloxacin therapy depicting that 10.5% of the total infected individuals included in the study were resistant to Ciprofloxacin. This finding was backed by the systemic review published in 2020 by Stalenhoef *et al.*, which showed 8.7-15% resistance to Ciprofloxacin when given for urinary tract infections.[14] However, the resistance was found higher in other studies. One study in 2022 reported a ciprofloxacin resistance of 22% in UTI which is higher than the findings in our study.[15] Another study reported 44% ciprofloxacin resistance to treatment for UTI in its research work published in 2021.[16] Another retrospective study revealed resistance to subject antibiotic as high as 84%.[17] Our Study found that there was a significant fall of CRP in our patients who responded to first line antibiotic therapy(*p*-value <0.001). Similar results were found in a study in which high CRP levels were found among patients suffering from urinary tract infection and its levels fell on effective treatment.[18]

There were certain limitations to our study as well. Renal insufficiency was not taken into account during the study as it can affect the serum levels of inflammatory markers in general and can increase Procalcitonin levels. Further studies are required to take these aspects into account as well.

CONCLUSION

Urinary tract infections are one of the common infections encountered in clinical practice. Laboratory investigations aid us in treating them. Procalcitonin and CRP are useful markers in predicting effective response to treatment of urinary tract infections. However, either marker has no superior role over another.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

UN & ARA: Data acquisition, data analysis, critical review, approval of the final version to be published.

BK & TS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

FN & MQ: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Byron JK. Urinary Tract Infection. Vet Clin North Am Small Anim Pract 2019; 49(2): 211-221. https://doi.org/10.1016/j.cvsm.2018.11.005

2. Neugent ML, Hulyalkar NV, Nguyen VH, Zimmern PE, De Nisco NJ. Advances in understanding the human urinary microbiome and its potential role in urinary tract infection. mBio 2020; 11(2): e00218-20. https://doi.org/10.1128/mbio.00218-20

3. Thomas-White KJ, Gao X, Lin H, Fok CS, Ghanayem K, Mueller ER, et al. Urinary microbes and postoperative urinary tract infection risk in urogynecologic surgical patients. Int Urogynecol J 2018; 29(12): 1797-1805. https://doi.org/10.1007/s00192-018-3767-3

4. Steinbach G, Bölke E, Grünert A, Orth K, Störck M. Procalcitonin in patients with acute and chronic renal insufficiency. Wien Klin Wochenschr 2004; 116(24): 849-853.

5. Choi JJ, McCarthy MW, Meltzer KK, Cornelius-Schecter A, Jabri A et al. The Diagnostic Accuracy Of Procalcitonin for Urinary Tract Infection in Hospitalized Older Adults: a Prospective Study. J Gen Intern Med 2022: 1-7.

6. Mattoo TK, Shaikh N, Nelson CP. Contemporary management of urinary tract infection in children. J Pediatr 2021; 147(2): e2020012138. https://doi.org/10.1542/peds.2020-012138

7. Abou-Heidar NF, Degheili JA, Yacoubian AA, Khauli RB. Management of urinary tract infection in women: A practical approach for everyday practice. Urol Ann 2019; 11(4): 339.

8. Gajdács M, Ábrók M, Lázár A, Burián K. Increasing relevance of Gram-positive cocci in urinary tract infections: a 10-year analysis of their prevalence and resistance trends. Sci Rep 2020; 10(1): 1-1.

9. Peñalver-Penedo R, Rupérez -Lucas M, Álvarez-Sala Walther LA, Torregrosa-Benavent A, Casas-Losada ML et al. MR-Proadrenomedullin as biomarker of renal damage in urinary tract infection in children. BMC Pediatr 2021; 21(1): 1-8.

10. Hamade B, Huang DT. Procalcitonin: where are we now?. Crit Care Clin 2020; 36(1): 23-40. https://doi.org/10.1016/j.ccc.2019.08.003

11. Zubair KU, Shah AH, Fawwad A, Sabir R, Butt A. Frequency of urinary tract infection and antibiotic sensitivity of uropathogens in patients with diabetes. Pak J Med Sci 2019; 35(6): 1664.

12. Baboudjian M, Gondran-Tellier B, Di Bisceglie M, Abdallah R, Michel F. The prognostic value of serum Procalcitonin in acute obstructive pyelonephritis. World J Urol 2021; 39(5): 1583-1589.

13. Tamadonfar KO, Omattage NS, Spaulding CN, Hultgren SJ. Reaching the End of the Line: Urinary Tract Infections. Microbiol Spectr 2019; 7(3): 10. https://doi.org/10.1128/microbiolspec.BAI-0014-2019

14. Stalenhoef JE, van Nieuwkoop C, Wilson DC, van-der Starre WE, van-der Reijden TJ. Procalcitonin, mid-regional proadrenomedullin and C-reactive protein in predicting treatment outcome in community-acquired febrile urinary tract infection. BMC Infect Dis 2019; 19(1): 1-10. https://doi.org/10.1186/s12879-019-3789-6

15. Kuil SD, Hidad S, Fischer JC, Harting J, Hertogh CM. Sensitivity of point-of-care testing C reactive protein and Procalcitonin to diagnose urinary tract infections in Dutch nursing homes: PROGRESS study protocol. BMJ Open 2019; 9(8): e031269. https://doi.org/10.1136/bmjopen-2019-031269

16. Rasoulinasab M, Shahcheraghi F, Feizabadi MM, Nikmanesh B, Hajihasani A, Aslani MM. Distribution of ciprofloxacin-resistance genes among ST131 and non-ST131 clones of Escherichia coli isolates with ESBL phenotypes isolated from women with urinary tract infection. Iran J Microbiol 2021; 13(3): 294. https://doi.org/10.18502/ijm.v13i3.6389

17. Gajdács M, Urbán E. Comparative epidemiology and resistance trends of proteae in urinary tract infections of inpatients and outpatients: a 10-year retrospective study. Antibiotics 2019; 8(3): 91.

18. AL-Khikani FH, Ayit AS. Correlation study between urinary tract bacterial infection and some acute inflammatory responses. Biomed Biotechnol Res J 2019; 3(4): 236. https://doi.org/10.4103/bbrj.bbrj_122_19

....