

Shift To The Left; An Indicator of Progression to Perforation in Acute Appendicitis

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Abstract

Background: Appendicitis is a surgical emergency and surgery is crucial for patients diagnosed with having acute appendicitis as any delay in surgery leads to perforation of the organ

Methods: 50 Patients with provisional diagnosis of acute appendicitis were included in the study. Pre-operative blood sample was analysed for neutrophil percentage. The patients were divided into two groups, each comprising of 25 patients on the basis of neutrophil percentage i.e. group A having neutrophils $\geq 75\%$ and group B having neutrophils $\leq 75\%$. Patients were then followed-up and per-operative findings and histopathology reports were noted for differentiating between perforated and inflamed appendices. SPSS version 22.0 was used for analysis and Pearson's Chi square test was applied at 5% level of significance. Relative risks along with 95% confidence intervals were also calculated.

Results: 15/25 (60%) patients in Group A developed perforation of appendix when compared to only 1/25 (4%) patient in Group B, who later developed perforation (Relative risk = 15.0, 95% confidence interval=2.1408 to 105.10, P value=0.00). No statistically significant association was observed between age and gender with perforation of appendix.

Conclusion: There is a highly significant statistical association of shift to the left of neutrophils with perforation of appendix.

Key Words: Shift to the left of neutrophils, perforated appendix.

Introduction

Acute abdominal pain in all age groups is usually associated with acute appendicitis. The life time risk of the disease is 7% and males are slightly more prone to develop it.¹ The incidence of the disease is 110-140 per 100,000 population.² Appendicitis is a surgical

emergency and surgery is crucial for patients diagnosed with having acute appendicitis as any delay in surgery can lead to perforation of the organ.^{3,4,5} Appendix may get inflamed due to obstruction by fecolith, gall stones or worms.¹ When appendix gets inflamed the attached peritoneum gets irritated and pain starts initially around the umbilicus (because of shared nerve supply) and then migrates to right iliac fossa.

The proposed mechanism of appendicitis is increased intraluminal pressure which is followed by venous congestion, these changes lead to ischemia of the wall of appendix resulting in perforation.¹

Careful history taking, examination and laboratory tests can lead to a provisional diagnosis of acute appendicitis.⁶ Perforated appendix can lead to peritonitis which increases the morbidity and mortality.¹ In a healthy individual neutrophils circulate as mature cells and their percentage is strictly regulated (around 61%). At the time of infection neutrophils are the first leucocytes to reach the site of infection which is a hallmark of acute inflammation. If the primary response doesn't restrict the infection, a great number of neutrophils are produced in the bone marrow and released in the blood hence shift to the left of neutrophils i.e. presence of immature neutrophils in the peripheral blood. Shift to the left of neutrophils has been part of the scoring systems devised for diagnosing acute appendicitis.^{6,7}

Findings of this study will be very helpful if shift to the left of neutrophils proves to be an efficient and accurate indicator and predictor of perforation. It can be a cost effective and easily accessible diagnostic and prognostic tool where MRI, CT scan, ultrasound and IV contrast media are not available, as in most of the resource deprived settings of our country. It can enlighten the healthcare providers of the anticipated risk of perforation and extent of urgency required in its prevention through timely intervention. The objective of the this study was to compare the risk of perforation of appendix in patients with shift to the

left i.e. neutrophil percentage of 75 % or more with patients having no shift to left i.e. neutrophil percentage of less than 75%.

Materials and Methods

This prospective cohort study was conducted at the department of Surgical Emergency Holy Family Hospital, Rawalpindi from January 2017 to March 2017. The Hospital is affiliated with Rawalpindi Medical University (RMU), Rawalpindi so Ethical approval was obtained from the Institutional research forum of RMU. All the patients presenting in emergency with acute pain in right iliac fossa with a provisional diagnosis of acute appendicitis were included in the study after informed written consent. All the patients with a history of appendectomy, recent infection, trauma, road traffic accident and malignancy were excluded. For all the patients fulfilling the selection criteria, socio-demographic profile was taken along with detailed history, physical examination and then pre-operative blood sample was taken to analyse neutrophil percentage using auto haematology analyser MINDRAY BC-3000PLUS. Based on the findings of the neutrophil percentage the patients were divided into group A with shift to the left of neutrophils (i.e. neutrophil percentage of 75 % or more) or group B with no shift to the left of neutrophils (i.e. neutrophil percentage of less than 75 %). All the information of the patient was recorded in the structured pro forma designed for this study.

Since no reference study was available on this topic so a pilot study of 30 patients (15 in group A with shift to left and 15 patients in group B with no shift to the left) was conducted. Its findings showed relative risk of 9.0 with 60 % patients developing perforation later in group A compared to 6.6 % in group B. Keeping level of confidence 95%, power of study 80%, and above mentioned anticipated values, minimally required sample size was calculated to be 14 in each group through World Health Organization's (WHO) sample size calculator software. Keeping in consideration any possible attrition rate, even though the follow up was only of few hours duration additional 5% patients were included in each study groups. Therefore the sample size came out to be 25 each group i.e. a total of 50 patients were studied. The sampling technique was systematic random sampling technique where based on number of patients with acute appendicitis per day, every third patient with shift to left of neutrophils was included in study and was allocated group A and similarly every third patient with no shift to left was included in group B.

Each patient in the study was then followed up till completion of the surgical process and histopathology of the surgical specimen. All the patients were prepared for surgery after inclusion in the study groups and were given standardized broad spectrum intra venous antibiotics that covered both gram negative and gram positive organisms. All the patients underwent open appendectomy, through an incision at Mc Burney's point. None of the patients were operated using laparoscopic technique. Peri-operative findings and histopathology reports were noted for differentiating between perforated and inflamed appendices. The diagnosis of inflamed appendix was made on the basis of microscopic findings and gross examination (wall appearance, inflammation and edema of the appendix) while the diagnosis of perforated appendix was noted on gross examination of the appendix.

Statistical package for the social sciences (SPSS) version 22.0 was used for data entry and statistical analysis, Descriptive statistics were calculated where the numerical variables were presented as median, mode, means and standard deviations while the categorical variables were presented as frequencies and percentages. Tests of normality (Kolmogorov-Smirnov, Shapiro-Wilk) were applied to check the normal distribution of age and neutrophil percentages, further on q-q plots were plotted to confirm the results of tests of normality. Independent sample t test at 5% level of significance was applied to check heterogeneity of study groups based on age and neutrophil percentage.

For comparison of proportion for patients with perforation in each study group Pearson's Chi square test was applied at 5% level of significance. A P-value of less than 0.05 was considered statistically significant. To compare the risk of perforation of study groups, Relative risks along with 95% confidence intervals were also calculated. Exclusion of value 1.00 from the 95% confidence intervals indicated the statistical significance of relative risks.

Results

This prospective cohort study included 50 patients, based on exposure, with 25 patients with shift to the left of neutrophils were placed in group A and equal number of patients were placed in group B without shift to the left of neutrophils.

The mean age of all 50 patients was 23.36 (± 11.53) years, mode 16 years and median 22.50, where the youngest patients was 5 years of age and the eldest was 50 years old. The mean age of patients in group A

was 22.68 (±12.99) years while it was 24.04 (±10.08) years in group B. On comparison of mean ages of both study groups a non-statistically significant difference with p-value of 0.71, determined the homogeneity of groups based on age. When patients were categorized as those up to 25 years of age or above, then 10 patients in each study group were above 25 years and 15 patients in both study groups were up to 25 years, so groups was homogeneous based on age categories too.

Amongst 50 patients included in the study, 27 (54%) were males and 23 (46%) were females

Table I: Relation of different variables with morphology of appendix, P-value and relative risk

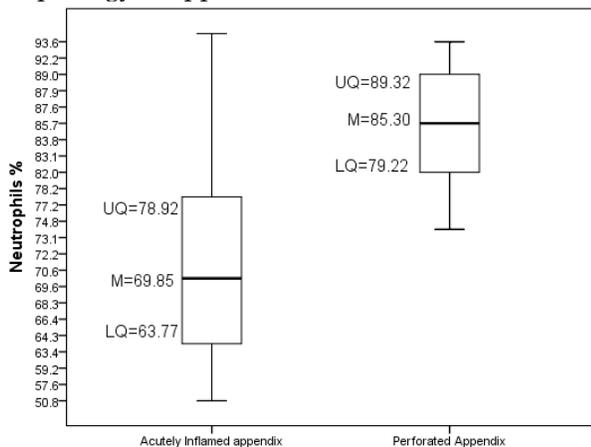
VARIABLE		PERFORATION f (%)	INFLAMED f (%)	P-value	RELATIVE RISK (95% confidence interval)
AGE	< 25 years	7(35%)	13(65%)	0.71	1.166 (0.5192 to 2.621)
	>25 years	9(30%)	21(70%)		
GENDER	Male	11(40.7%)	16(59.3%)	0.17	1.8741 (0.7627 to 4.6050)
	Female	5(21.7%)	18(78.3%)		
STUDY GROUPS	Group A*	15(60%)	10(40%)	0.00***	15.00 (2.1408 to 105.10)
	Group B**	1(4%)	24(96%)		

*Group A: patients with shift to the left i.e. neutrophil percentage ≥ 75%

**Group B: patients with no shift to the left i.e. neutrophil percentage < 75%

*** Highly Statistically Significant

Figure I: Neutrophil Count and per-operative morphology of appendix.



For acutely inflamed appendix:

M = Median

UQ = Upper Quartile = 75% percentile

LQ = Lower Quartile = 25% percentile

When the gender distribution was compared in both study groups, 16 (59.3%) patients in group A were males compared to 9 females(39.1%) while in group B 11(40.7%) were males and 14 (60.9%) were females A

p-value of 0.17 showed that this difference was not statistically significant and both the study groups were heterogeneous based on gender too. Table I

The mean of neutrophil percentages of all 50 patients was 75.57(±11.31), with a multiple-mode of 58.7 and median 75.10. The lowest percentage of neutrophils was 50.8% whereas the highest percentage was 93.8%.

The mean of neutrophil percentage was 85.17(±5.25) in group A and 65.97 (±6.47) in group B and on comparison of both study groups a statistically highly significant difference with p-value of 0.00, determined the heterogeneity of groups based on exposure to shift to the left of neutrophils. (Figure I)

Discussion

The world is advancing towards management of appendicitis with antibiotics.⁸⁻¹⁰ This has indeed given surgeons a variety of treatment options but surgical management in advanced stage of disease remains the first choice.^{3,4,5} Surgical literature states that the incidence of perforation in acute appendicitis is estimated to be 20-30 % in overall population but this percentage markedly increases to 32-72% in elderly.^{5,11,12}

Neutrophilia is a hallmark of acute inflammation and has been part of the systems devised for the diagnosis of acute appendicitis. The involvement of neutrophilia in acute appendicitis paved the path for our study¹¹, establishing relationship between shift to the left of neutrophils and the perforation of appendix.

When a patient with perforated appendix presents in emergency of any hospital, the signs and symptoms are not typical. In a suspected case of perforated appendix spiral CT scan and contrast IV media are recommended.^{13,14,15} In such a situation if these tests are not available, the perforated appendix can be missed and a negative laparotomy is done.⁵ Laparoscopic appendectomy is a surgical procedure which comes hand in hand with open appendectomy. Laparoscopic appendectomy has an advantage over open appendectomy especially in wound size, pain, wound infection and early discharge from the hospital.¹⁶ This technique is slowly being adapted in our setup.

The Chi square test was applied for shift to the left and perforation of appendix and the value came out to be 18.015 with P-value of less than 0.00, the sensitivity of shift to the left is 0.93, the specificity is 0.70, positive predictive value is 0.60 and negative predictive is 0.96, positive likelihood ratio 3.19 was and negative likelihood ratio was 0.09.

Among the patients having perforated appendix 15 had shift to the left (93.75%) and 1 did not have shift to left (6.25%) which is in accordance to other studies¹² and among the patients with inflamed appendix 10 had shift to the left (29.4%) and 24 had no shift to the left (70.6%). The mean age, the most affected age group (13-40 years) and the gender distribution of the disease were all in accordance to previously conducted studies.^{2,6} Perforated appendix was unrelated to age but was more common among males, this can be justified by a comparison of life time risk of developing acute appendicitis in males and females which is 8.6% and 6.7% respectively.^{2,17-19}

There is a greater percentage of neutrophils among the patients having perforated appendices as compared to the patient having inflamed appendices. The mean value of neutrophils in patients with perforated appendix which is 85.2% may be used as a standard for predicting the perforation in setting where MRI, spiral CT scan, ultra-sonogram and IV contrast media are not available.

This study did not incorporate the duration since initiation of the symptoms of appendicitis, so we recommend large scale studies with insight into role of duration of delay in the association of shift to left and perforation. We used the percentage of neutrophils, but to broaden the scope of the study CRP, leukocyte count and leukocyte to neutrophil ratio is also recommended in future studies.

Conclusion

There is a highly significant statistically association of shift to the left of neutrophils with perforation of appendix. However no association of perforation with age and gender of the patient was observed. With the advancements of medical science, MRI, CT scan, ultrasound and IV contrast media can help in diagnosis of perforation but where they are not available a simple laboratory indicator i.e. shift to the left of neutrophils may be used as an indicator of perforation.

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