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Original Article

Role of High Altitude in Thrombosis of Appendicular Artery and Pathogenesis of Acute Appendicitis

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ABSTRACT

Objective: To determine the role of high altitude in thrombosis of appendicular artery and pathogenesis of acute appendicitis.
Study Design: Cross Sectional study
Place and Duration of Study: Forward Treatment Centre, Goma, Pakistan from June 2020 - May 2024.
Methodology: A total of 86 patients undergoing open appendectomy at high altitude, were enrolled in the study. All patients underwent open appendectomy. Standard operating procedures were followed. Appendix and mesoappendix were examined and intraoperative findings were recorded. Appendix specimens were sent for histo-pathological examination. Patients who had more than 01 month stay at high altitude at time of development of acute appendicitis were considered as "Exposed" to High Altitude whereas patients with less than 01 month stay at high altitude were considered as "Not Exposed". Outcomes were evaluated in terms of post operative fever, surgical site infection or organ space infection. Operative time and length of Hospital stay recorded
Results: Eighty six patients were included in the study ranging from 18–52 years. There were 17(19.7%) females and 69(80.2%) males. Seventy one (81.3%) were Exposed to high altitude & 16(18.6%) were Not Exposed to High Altitude. The mean total operative time was 47.53±11.46 minutes. The hospital stay ranged from 02 to 05 days. Fecolith was found in 45(52.3%) cases and inflammatory pathology was found in 29(33.7%) cases. Six cases (6.9%) were found to have thrombosis of appendicular artery. Odds Ratio of appendicular artery thrombosis in comparison to high altitude exposure is 1.154.
Conclusion: Faecolith was the most common cause of acute appendicitis at high altitude. However, Extended exposure of high altitude can incite thrombosis of appendicular artery and development of acute appendicitis. Exposure to high altitude is an autonomous contributing factor in etiology and pathogenesis of acute appendicitis.

Keywords: Appendicular Artery Thrombosis, High Altitude, Open Appendectomy, Pathogenesis

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INTRODUCTION

Globally, Acute Appendicitis is the most prevailing cause of acute abdomen, for which emergency surgery is performed. It is an articulated public health problem having an annual incidence of around 96.5 to 100 cases per 100,000 individuals.[1] The acknowledgement of acute appendicitis as a clinical disease is traced to Reginald Fitz, who submitted a paper in the first meeting of Association of American Physicians in 1886 bearing the title of 'Perforating inflammation of the vermiform appendix'. According to the data of Western Europe, the collective incidence of appendicitis is approximated to be around 151 cases per 100,000 persons.[2] It is an acute inflammation of vermiform appendix, which presents with peri-umbilical abdominal pain, anorexia, nausea, vomiting or fever. One local study published in 2021, on population sample of Rawalakot, found that most common symptom of acute appendicitis in local Pakistani population is abdominal pain, vomiting & fever.[3]

Undeterred by the fact that it is a fairly common disease, its etiology and pathogenesis still continue to persist in scientific argument till date.[4] The two most commonly endorsed etiologies in pathogenesis of acute appendicitis are obstructive and inflammatory etiologies. Obstruction of appendix can arise from fecolith, lymphoid hyperplasia or a tumor. Few viruses, bacteria and parasites are associated with inflammation of appendix. The influence of seasonal variations, environmental temperature, dietary habits and role of air pollution on incidence of acute appendicitis has also been analyzed.[5]

Hypoxia at high altitude has been enormously presented in literature as a rational risk factor in precipitation of venous as well as arterial thrombosis.[6] Increase in Viscosity of blood, decline in fibrinolytic capacity, hypercoagluable state and inflammatory activation of the endothelium are postulated as

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probable reasons for high altitude induced thrombosis.[7] The causation of arteriovenous thrombosis at high altitude is multifactorial and can elicit a life threatening arterio-venous thrombosis, demanding intensive life support.[8] Hypoxic stress at high altitudes can induce increased intestinal permeability, increase in bacterial translocation along gut lumen, intestinal barrier dysfunction and damage to microvasculature in any segment of Gastrointestinal Tract.[9]

There is very scant data available on the role of high altitude in causing appendicular artery thrombosis and acute appendicitis. One study was published in 2022, which analyzed the impact of high altitude in thrombosis of appendicular artery or its branches and acute appendicitis at an altitude of 11,800 feet above sea level.[10] No such study is conducted on local population of Pakistan. This study was conducted at an altitude of 11,000 feet above sea level and aimed to determine the role of high altitude in thrombosis of appendicular artery and pathogenesis of acute appendicitis in a subset of Pakistani population.

METHODOLOGY

This cross sectional study was carried out on patients of acute appendicitis who underwent emergency open appendectomy at Forward Treatment Centre, Goma at a high altitude of 11,000 feet above mean sea level. This study was conducted from 1st Jun 2020 to 31st May 2024, over a span of 48 months after approval of Ethical review board committee (IRB Certificate Number 04/IRB/144, dated 30 May 2020). Sample size was calculated using WHO sample size calculator, with 95% confidence level, Absolute precision required as 0.05, the anticipated incidence/ rate of Acute Appendicitis as 6%.[11-12] The total sample size came out to be 86 cases. Informed Consent was taken from all the participants of the study.

Inclusion Criteria: Patients of age 18-52 years of either gender, having ASA class 1 and 2 with diagnosis of acute appendicitis who were staying at high altitude and underwent emergency open appendectomy were included in the study.

Exclusion Criteria: ASA 3, 4 & 5 patients, pediatric & pregnant patients, patients who had clinical or radiological suspicion of appendiceal mass and those patients with unclear diagnosis or those requiring CT Scan Abdomen for further diagnosis were excluded.

A pre-operative ultrasound abdomen was done in all cases to rule out any concomitant pathology. All patients received a single dose of ceftriaxone intravenously at the time of induction of anaestheisa. All cases were administered general anaestheisa. All selected patients underwent open appendectomy. Standard operating procedures were followed. Appendix and mesoappendix were examined and intraoperative findings were recorded. All retrieved appendix specimens were subsequently sent for histo-pathological examination.

Demographic data, smoking status, the type of incision, operative time, hospital stay, surgical complications, intra operative findings, histo-pathological evaluation of specimens and readmission were analyzed. Patients who had more than 01 month stay at high altitude at time of development of acute appendicitis were considered as "Exposed" to High Altitude. Patients who had less than 01 month stay at high altitude were considered as "Not Exposed" to High Altitude. Outcomes were evaluated in terms of post operative fever, surgical site infection or organ space infection. Operative time was estimated in minutes, commencing from time of incision to the completion of operation. Hospital stay was numbered in days beginning from the day of operation till discharge of patient. The skin stitches were removed on 10th post-operative day.

Sampling Technique was non-probability convenient sampling. Data confidentiality was maintained. Statistical analysis was carried out with using Statistical Package for the social sciences (SPSS) version 26.0. Descriptive statistics were applied to represent Qualitative and Quantitative variables. The quantitative variables which included age of patients and operation time were interpreted by calculating Mean and Standard Deviation. Qualitative variables like gender, high altitude exposure, etiology of appendicitis, and complications were expressed as frequency percentages. Odds Ratio analysis was done by using cross tabulation for patients having thrombosis of appendicular artery in comparison to exposure.

RESULTS

Out of total 86 patients, 69(80.2%) were males and 17(19.7%) were females. Minimum and maximum ages were 18 and 52 years and mean age was 25.33±7.69 years. 14(16.2%) were smokers and 72(83.7%) were nonsmokers. Seventy patients (81.3%) had more than a month stay at high altitude and were

considered "Exposed" to high altitude. 16 patients (18.6%) had less than a month stay at high altitude and were considered as "Non Exposed" patients. The mean total operation time was 47.53±11.46 minutes. The hospital stay ranged from 02 to 05 days. Obstructive pathology & fecolith was found in 45 cases (52.3%). Inflammatory pathology was found in 29 cases (33.7%). Six cases (6.9%) were found to have a thrombotic pathology with visible thrombosis of appendicular artery. In the remaining 06 cases (6.9%) no identifiable pathology was found during per operative assessment. Odds Ratio of appendicular artery thrombosis in comparison to high altitude exposure is 1.154. The value is statistically significant. These results are summarized in Tables I and II.

Table-I: Pathogenesis of Acute Appendicitis at High Altitude (n=86)

PATHOGENSIS	Group (n=86)
Obstructive (Faecolith)	45(52.3%)
Inflammatory	29(33.7%)
Thrombotic	6(6.9%)
No Gross Pathology	6(6.9%)

Table-II: Comparison of Thrombosis of Appendicular Artery among Exposed and Non Exposed patients (n=86)

		Thrombosis		Odds Ratio for Exposure	95 % Confidence Interval
		No Thrombosis	Thrombosis		
Exposure	Non Exposed	15(17.4%)	1(1.1%)		
	Exposed	65(75.5%)	5(5.8 %)		
Total		80(93.0%)	6(6.9%)	1.154	(0.125-10.616)

Out of total 86 patients, 37 patients (43.1%) had complicated appendicitis (Perforation, gangrenous appendicitis) while 49 patients (56.9%) had simple appendicitis. Two patients (2.3%) developed surgical site infection. Wound infections were superficial in all cases and responded to conservative measures. Three cases (3.4%) developed post operative fever. However, workup did not reveal any abdominal collection. Fever responded to IV antibiotics. Seven patients (8.14%) developed post operative nausea and vomiting, which improved on 2nd or 3rd post operative day. These results have been summarized in Table-III.

Table-III: Post operative Complications of Acute Appendicitis at High Altitude (n=86)

COMPLICATIONS	Frequency (%)
Wound Infection	2(2.3%)
Fever	3(3.4%)
Nausea / Vomiting	7(8.1%)
Total	12(13.9%)

Two patients (2.3%) were readmitted for post operative fever and pain. However, workup did not reveal any intra-abdominal collection or organ space infection. Patients responded to IV antibiotics and were managed conservatively. There was 0% mortality in this study.

DISCUSSION

In our study, 06 cases (6.9%) were found to have a thrombotic pathology with visible thrombosis of appendicular artery or its branches within mesoappendix before ligation of mesoappendix. Out of these 06 cases having thrombotic pathology, 05 patients had stay at high altitude more than a month and 01 patient with thrombotic pathology had a stay of less than 01 month at high altitude. Acute appendicitis is the most frequent cause of acute abdomen and is prevalent throughout the world as a universal surgical emergency.[11] Regardless of the fact, that it is the most common cause of acute abdomen; acute appendicitis continues to be a bothersome diagnosis because it is essentially a clinical diagnosis which has diverse clinical spectrums. There is always an evolving debate among general surgeons regarding the pathogenesis, diagnosis, surgical or non surgical treatment and optimal timings for surgical intervention in acute appendicitis.[12] Fecolith is one of the risk factors and it has clinical association with complicated appendicitis.[13] Another important cause of acute appendicitis is an infective agent, which initiates an inflammatory response. Seasonal variation in the incidence of acute appendicitis has also been observed, with more cases occurring between May and August in northern Europe.

The etiology and pathogenesis of acute appendicitis has been discussed extensively in literature. However, the role of high altitude in causing acute appendicitis has been rarely analyzed or discussed. High Altitude is defined as a height greater than 2400 meters (8000 feet) above sea level. According to a study, approximately 81.6 Million people live at altitude greater than 2500 meters (8200 feet) above sea level.[14] However, there is only one study conducted in India on the impact of high

altitude in causing thrombosis of appendicular artery and acute appendicitis at the height of 11800 feet above sea level. No such study has been conducted on local population of Pakistan. High Altitude presents a distinctive challenge, in which an exaggerated physiological compensation may bring about pathological fallouts, such as thrombotic events. The oxygen levels continue to decline with every gain in altitude. The higher the altitude, the higher will be the oxidative stress. This oxidative stress prevails throughout the duration; an individual remains exposed to high altitude and reduces only upon return of the individual to the sea level. Exposure to hypoxia modifies several signaling pathways, like production of reactive oxygen species. These reactive oxygen species are known to activate important adaptive responses.[15] The incidence of thrombotic events at High altitudes is several times higher than the individuals residing at sea level.[16] Thrombotic events at High Altitude can incite serious morbidity and mortality even in normal healthy individuals.

Presence of polycythaemia, increased blood viscosity, stasis of blood, Red blood cell and platelet adhesiveness are all responsible for causing thrombosis in vessels.[17] Gastrointestinal symptoms are time and again communicated during the ascents to high altitude of greater than 2,500 meters. Hypoxia-induced oxidative stress is attributed to the formation of as peptic ulcers mostly in duodenum. Hypoxic stress can result in thrombosis of mesenteric vessels and can also damage intestinal microvasculature.[18]

In our study, we performed open appendectomy under General Anaestheisa using Gridiron or Lanz incisions. Per operative findings were noted especially presence of fecolith, thrombosis of appendicular artery in mesoappendix. The finding of thrombosis was noticed before the ligation of the mesoappendix to avoid any contribution of surgical handling in thrombosis. All appendectomy specimens were sent for histopathologic analysis. Mean operative time was 47.53±11.46 minutes. Mean hospital stay was 2.86±0.97 days. Fecolith and obstructive pathology was the most common etiology and was found in 45 cases (52.3%). Mei Sze Lee et al (2023)19 observed that fecolith was found in 34% patients of acute appendicitis and fecolith was associated with more than threefold increase in development of complicated appendicitis. Inadequate hydration and resultant constipation at high altitude can be attributed to increased finding of fecolith at high altitude. In our study we noticed 29 cases (33.7%) were of inflammatory or catarrhal type.

In our study, 06 cases (6.9%) were found to have a thrombotic pathology with visible thrombosis of appendicular artery or its branches within mesoappendix before ligation of mesoappendix. Out of these 06 cases having thrombotic pathology, 05 patients had stay at high altitude more than a month and 01 patient with thrombotic pathology had a stay of less than 01 month at high altitude. In the only study available in literature on impact of high altitude in thrombosis of appendicular artery at an altitude of 11,800 feet. Zenith et al (2022)10 reported that 27 Cases (15.7 %) were found to have a thrombotic pathology of acute appendicitis at high altitude. Our finding of 6.9% patients having thrombotic pathology at high altitude was although less than the study conducted in India, but is statistically significant. Odds Ratio of appendicular artery thrombosis in comparison to high altitude exposure is 1.154 in our study. The value is suggestive of lines for further research in finding odds of association of high altitude exposure and thrombosis of appendicular artery. The appendicular artery being an end artery, in the background of pro-thrombotic state at high altitude, provides an ideal environment for precipitation of thrombosis.

In our study, superficial surgical site infection occurred in two cases (2.32%). However, it responded to local wound exploration and IV antibiotics. No patient in our study developed organ space infection or any intra abdominal collection. Patrick Téoule et al (2020)20 reported the complication rate and wound infection rate of 2.1%, which are similar to the results of our study. Three patients (3.4%) patients developed post operative fever. Seven patients (8.0%) patients developed post operative nausea and vomiting. There was No mortality in this study.

According to our experience in this study, we found that faecolith was the most common cause of acute appendicitis at high altitude. Therefore, it can be suggested that maintaining adequate hydration at high altitude can decline in number of appendicitis due to obstructive pathology (fecolith). It is pertinent to mention that, clinically significant percentage of people developed thrombosis of appendicular artery, which resulted in acute appendicitis. As a result, we can draw the conclusion that thrombosis of appendicular artery is an important and independent etiologic factor in causing acute appendicitis at high altitude.

LIMITATIONS OF STUDY

Our study is a single hospital based study which is a peripheral hospital located at high altitude of 11,000 feet above sea level. There was non availability of CT Angiography for pre operative confirmation of thrombosis of appendicular artery in suspected patients. However, data from our study provides the basis for further research.

CONCLUSION

Faecolith was the most common cause of acute appendicitis at high altitude, However, the appendicular artery being an end artery, in the background of pro-thrombotic state at high altitude, provides an ideal environment for precipitation of thrombosis. Extended exposure of high altitude can incite thrombosis of appendicular artery and development of acute appendicitis.

Authors' Contribution

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

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

AM & FZ: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

BR & TJ: Data acquisition, critical review, 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.

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