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Procalcitonin Ratio of Post-Operative Day 1 and Day 2 Procalcitonin Values to Predict the Surgical Outcome in Severe Necrotizing Soft Tissue Infections

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Abstract

Introduction: Necrotizing soft tissue infections are fulminant and life threatening bacterial infections which affects the fascia and subcutaneous tissue. The progression of disease is in hours and early diagnosis is difficult as the infection advances below the surface and cutaneous manifestations do not match the severity of the underlying disease. In this study we aim to calculate an optimum cut off Procalcitonin (PCT) ratio which determines the success and failure of surgical treatment offered.

Methods: Study group comprised of 38 patients with various forms of Necrotizing Soft Tissue Infections (NSTIs) who were offered major surgical debridement within the 1st 24 h under anesthesia. Intra operative specimens were sent for microbial culture and antibiotic sensitivity and for histopathological examination.

PCT levels on post-surgery day 1 and day 2 were measured after every major surgical debridement. Based on these values a PCT ratio value day 1/day 2 was developed which is used to assess the progress of disease and the adequacy of the 1st debridement and to facilitate the decision process of re-operations and major amputations.

Results and Conclusion: The calculated optimal PCT cut off ratio, which was 1.19 in our study, is able to distinguish between the successful and unsuccessful surgical eradication of the infection in NSTI's with a high sensitivity of 91% and specificity of 97%.

Keywords: Severe necrotizing soft tissue infections; Optimal cutoff procalcitonin ratio; Major surgical debridement; Focus eradication

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Introduction

The term Necrotizing fascitis was first coined by Wilson [1]. Other terms, such as "complicated skin and skin structure infections" and "acute bacterial skin and skin structure infections" are also in vogue. Joseph Jones of The United States in 1871, coined the term Hospital Gangrene when he reported 2,642 cases with a mortality of 46% [2]. Etiological factors like trauma, intravenous drug abuse and insulin injection administration, cutaneous infections, bites of animals and insects, entero-cutaneous fistulas with high output, Streptococcal pharyngeal infection [3], surgical site infections, percutaneous insertion of intravenous catheters, and idiopathic causes have been described. Simon et al. [4] stated that usage of Non-Steroidal Anti-Inflammatory Drugs (NSAID) causes NSTIs.

The disease progress very rapidly at a rate as fast as 1inch per hour. Therefore early diagnosis which is difficult is a must to make appropriate decisions regarding the treatment [5]. Most widely accepted laboratory risk indicator for NSTI's is LIRENEC Score by Wong and colleagues, a score >6 has a high correlation with NSTI's with 92% PPV and 96% NPV [6].

Freischlaq et al. [7] observed that if surgical management was delayed for more than 24 h after recognition of infection, it resulted in higher mortality rates up to 70%, whereas 36% mortality was noted when operations were performed in less than 24 h. However, despite aggressive initial surgical treatment, the possibility of the limb amputation is up to 20% [8] as surgical control of the infectious source is often not achieved. Malangoni et al. in 2001 suggested several hematological values at the time of admission to the hospital to predict mortality, such as serum lactate [1,9]

and sodium levels [9]. Anaya et al. [10] suggested WBC count, serum creatinine and hematocrit levels along with clinical parameters such as age, heart rate and temperature can be used to predict mortality as well as amputation possibility in case of infected limbs.

Criteria in deciding whether additional radical treatment such as proximal extension of amputation is required or not are not available and this decision is only based on clinical scenario and the surgeon's experience. Procalcitonin (PCT) a precursor of Calcitonin produced in the C-cells of thyroid gland is a biomarker for diagnosis of bacterial infection whose levels help in the assessment of severity & prognosis of the disease and also facilitates the therapeutic decision as compared to other biomarkers. It helps to differentiate bacterial infection leading to sepsis from other causes of systemic non-infectious inflammatory reaction where in the levels of PCT are usually lower Pro calcitonin has a long half-life of 25 h to 35 h [11], which is not altered by renal failure or by continuous veno-venous hemo-diafiltration, thereby helpful for diagnostic purposes in patients with impaired renal function. Patients with localized infections or infections without systemic manifestations cause very negligible or no increase in serum PCT levels and this can be interpreted that infection is not fulminant. Therefore we should understand that PCT cannot be used as a marker of infection [5]. Novotny et al. [12] identified an optimal cut off level of the PCT (Procalcitonin) ratio of 1.03 on postoperative day 1 to day 2 in intra-abdominal sepsis with a sensitivity of 95%. Friederich et al. [13], in their study, calculated the optimum PCT ratio to be 1.14 on postoperative day 1 to day 2 in various NSTI's.

This study aims to make a similar attempt to develop one such tool to aid in deciding the need for further surgical intervention by calculating the optimal Procalcitonin ratio in NSTI's.

Materials and Methods

This is a prospective observational study with the approval of Institutional Ethics Committee involving 38 patients who were clinically diagnosed with various forms of NSTI's and were admitted for treatment in the department of surgery at our Institution from September 2013 to July 2015 after taking informed consent. Inclusion criteria were all cases of NSTI's of limbs, Fournier gangrene, Meleney's abdomen with clinical and lab criteria of sepsis and NSTI's. Blood investigations like complete blood picture, renal function tests, liver function tests, serum C- Reactive Protein levels, chest X-ray and electrocardiography were performed before surgery. All patients were offered emergency major surgical debridement within 1st 24 h under anesthesia. Intraoperative specimens were sent for microbial culture and antibiotic sensitivity and for Histopathological Examination (HPE) and clinical diagnosis of NSTI's was confirmed with HPE report. Patients who did not give consent for surgery and who did not meet sepsis criteria were excluded from the study. Preoperative variables are illustrated in Table 1.

PCT levels on postoperative day 1 and day 2 were measured after every major surgical debridement for which venous samples of blood were used and PCT levels were measured using an Immunoluminometric Assay (Liason, BRAHMS AG, Henningsdorf, Germany) as per manufacturer's instructions. PCT ratio was calculated post day 1 level over day 2 postoperative PCT level. Major surgical procedures include amputations, disarticulations and radical debridement with resection of necrotic and infected soft tissue. Minor surgical procedures included antiseptic dressing without resections and usage of chemical debriding agents like papaine ointments, hydrogen peroxide, EUSOL (Edinburgh University Solution). For this study, the successful surgical eradication of the septic focus was defined as negative results on microbiological examination of the swab from the wound and by the absence of visible slough in all further operations and no reappearance of local infectious signs and no systemic features of inflammation.

Statistical analysis was performed using the STATA software (version 12.0; College Station, TX: StataCorp LP). The optimum cut off value of PCT ratio which differentiates whether a surgery is successful or not was calculated using Youden index and Receiver Operating Characteristics (ROC) curve. Box plot was used to show the distribution of data. Sensitivity and specificity were calculated by receiver operating curve analysis. P value at less than 0.05 was considered significant.

Results

Patients at the time of admission presented with several signs and symptoms like erythema (most common presentation in up to 95% of study population), tenderness beyond erythema, swelling, crepitus and skin necrosis, induration, edema, bullae, fever and shock. Most common organisms isolated were *Streptococcus* Group B and *Staphylococcus aureus* (MRSA strain). Other organisms that were isolated were *Pseudomonas*, *Clostridial species*, *Klebsiella* and *E. coli*. Mean duration of hospital stay was 41 days, of which patients received a critical care for a mean period of 20.6 days. An average of 8.4 operations were performed per patient. Eradication of infection was achieved by performing an average of 1 major operation per patient (Table 2).

Table 1: Preoperative Data.

Age		
Mean age of incidence	50.6 years	47.30%
Peak age of incidence	40-60 years	
Sex		
Males	33	86.80%
Females	5	13.10%
Site of infection		
Upper limb	2	5.20%
Lower limb	18	47.30%
Meleny's gangrene	4	10.50%
Fournier's gangrene	14	36.80%
Etiology		
Trauma	18/38	47.30%
Chronic ulcer	9/38	23.60%
Postoperative	1/38	2.60%
Idiopathic	10/38	26.30%
Relative risk of co-morbidities		
Diabetes	1.37	
Obesity (BMI>30)	0.15	
Steroid usage	0.08	
HIV	0.02	
Smoking	0.46	
Alcohol	0.58	
Intra venous drug abuse	0.02	

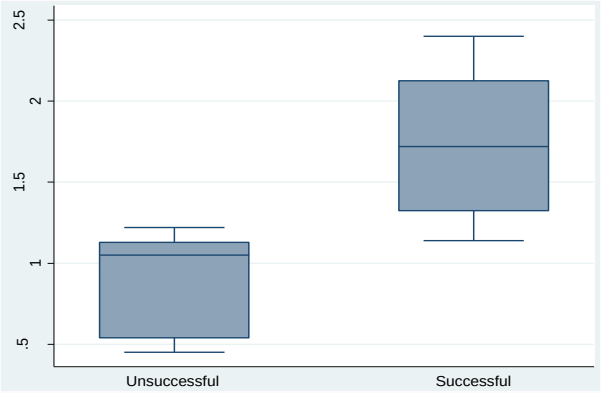

Figure 1: Box plot suggestive of distribution of PCT ratios.

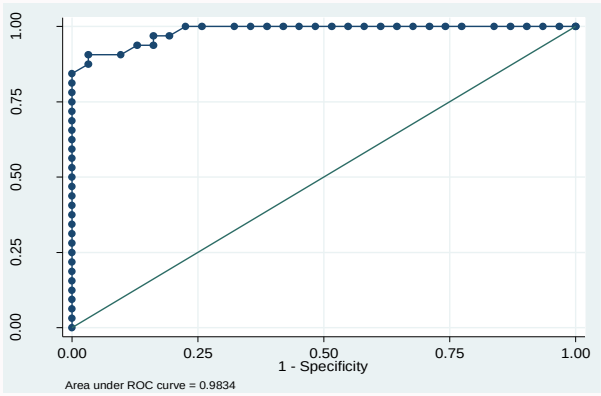

Figure 2: Receiver Operating Characteristic curve.

The probability significance level was set at less than 0.05. The mean PCT ratio of 32 successful surgical procedures was1.72 ± 0.4152 and the mean PCT ratio of 31 unsuccessful surgeries was 0.883 ± 0.30. The distribution of PCT ratio values is demonstrated by Box Plot (Figure 1).

A cut off PCT ratio value of 1.19 was identified to predict whether the surgical debridement offered has successfully eradicated the source of infection or not with sensitivity of 91% and specificity of 97%. Area under ROC is 0.98 suggestive that the cutoff PCT ratio value of 1.19 has 98% probability of differentiating a successful from an unsuccessful surgery (Figure 2).

Discussion

Incidence of NSTI's has not been associated with any age or sex predilection. In our study, the mean age of incidence was 50.6 years and a maximum incidence noted in 4th and 5th decades. Friederich et al. [13], in their study, recorded mean age as 58.5 years and maximum incidence in the 6th decade. Anaya et al. [10], in their study recorded a mean age of 45.6 years and maximum incidence in 5th and 6th decades. Novotny et al. [12], in their study of intra-abdominal sepsis, recorded the mean age to be 66 years. In our study, the most common etiology was found to be trauma which was also common in the studies conducted by Friederich et al. [13] (most common was idiopathic) and Anaya et al [10]. Post-operative infections were the least common cause in our study, which differs with the findings of the study conducted by McHenry et al. [14] where it was the most common etiological factor causing NSTI's. This low incidence of NSTI's due to post-operative etiology in our study could be due to the increased usage of more effective higher generation antibiotics and improved aseptic conditions over the past two decades. The most common site of infection in our study was lower limb which was consistent with the findings in the studies conducted by Friederich et al. [13] and Anaya et al. [10]. Perineum (FG) was found to be the second most common site of occurrence of NSTI's in all the studies reviewed. Upper limb involvement in our study was least significant. However, the occurrence of upper limb involvement, though less common, occurred in a significant number of patients in the western studies which could be due to high rate of I.V drug abuse in the western countries compared to India. The most common co-morbid condition associated with NSTI's in our study was Diabetes (57.8%) with a relative risk of 1.37. Diabetes was found to be a common co-morbidity in the studies conducted by Friederich et al. [13] (45%) and Anaya et al. [10] (19.2%).

Table 2: Operative data.

Eradication of focus	32/38	84.20%
Amputations	20/12	60%
Upper limb	1	5%
Lower limb	11	55%
Mortality	9/38	23.60%
Sepsis related	6	15.70%
Non-sepsis complications	3	7.90%
Number of operations	320	
Major	**63**	
Successful (focus eradication+)	32	
Unsuccessful (focus eradication -)	31	
Minor	**257**	
Type of infection and organisms		
Mono – microbial	**24/38**	**63.10%**
Streptococcus group B	6	25%
Streptococcus group A	1	4.10%
Staph aureus MRSA	6	25%
Staph aureus non MRSA	3	12.50%
Pseudomonas	4	16.60%
Clostridial Species	2	8.30%
Klebsiella Species	2	8.30%
Poly–microbial	**14/38**	**36.90%**
Streptococcus group A	2	14.20%
Streptococcus group B	7	50%
Staphylococcus aureus	10	17.40%
Enterococcus	5	35.70%
E. coli	1	7.14%
Klebsiella	8	57.14%
Anaerobes	3	21.40%

In our study, debrided tissue on culture revealed mono-microbial infections to be more common (63.1%) with *Streptococcus* Group A (25%) being the most common organism followed by *Staph aureus* MRSA strain (24%). Poly-microbial infections contributed 36.9%. The average no. of organisms in poly-microbial infections was 3 organisms per patient. Friedrich et al. [13], in their study, found mono-microbial infections to be more common contributing 58%

with *Staph aureus* (41%) being the most common organism isolated. Poly-microbial infections (42%) averaged 2.5 organisms per patient. In the study conducted by Anaya et al. [10], Poly-microbial infections were more common amounting to 57%. McHenry et al. [14], in their study, recorded poly-microbial infections to be more common amounting to 69%. In our study, limb amputation rate was up to 60%. Friederich et al. [13], in their study, recorded an amputation rate of 71%. In the study conducted by Anaya et al. [10], it was 26%. McHenry et al. [14] recorded 18.4% amputation rate. The factors useful in predicting limb loss were not properly evaluated in our study. Anaya et al. [10], in their study, defined predictors of limb loss as Shock at the time of admission, pre-existing heart disease, Clostridial infection, raised WBC count and IV drug abuse. In our study, the mortality was calculated to be 23.6% with a mean survival of 19.2 days. In Friederich et al. [13], mortality calculated as 29% with a mean survival of 18 days. In the study by Anaya et al. [10], the mortality was calculated as 16.9%. McHenry et al. [14] calculated mortality as 29%. Elliot et al. [9] calculated 25.3% mortality rate and suggested the following factors to be associated with increased mortality: Older age of the patient, female sex, extent of infection, and delay in performing first major surgical debridement, increased serum creatinine, increased blood lactate levels and Diabetes mellitus when associated with renal dysfunction. Focus eradication in our study was successfully achieved in 32 out of 38 cases constituting 84.2%. Novotny et al. [12], in their study, achieved successful focus eradication in 81.7%. Friederich et al. [13] achieved a successful focus eradication of 84%.

In our study, the optimum PCT ratio was calculated as 1.19, with a sensitivity of 91%, specificity of 97%. Friederich et al. [13], in their study, calculated the optimum PCT ratio to be 1.14, with sensitivity of 83.3% and specificity of 71.4%. Novotny et al. [12], in their study concerning intra-abdominal sepsis, calculated the optimum PCT ratio to be 1.03, with sensitivity of 95% and specificity of 63%.

Conclusion

The calculated optimal PCT cut off ratio, which was 1.19 in our study, is of help to make decisions regarding further surgical management as it distinguishes between the success and failure of surgical eradication of the infectious focus in NSTI's and is to be used only as an adjunct to the clinical diagnosis and opinion, and good clinical assessment and surgical judgment still plays pivotal role to make decisions regarding further surgical management. However prospective studies and Randomized Controlled Trials involving a large study group to assess the validity of this PCT ratio are required. However, patients with NSTI's in sepsis will benefit from the above method.

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