Procalcitonin in the post-operative burns patient.

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Declaration

I, Ludo Lorato Carol Masole (student no. 1927084), declare that this research report is my own, unaided work. This research report is being submitted for the Degree of Master of Medicine in Surgery at the University if the Witwatersrand, Johannesburg, South Africa. It has not been submitted before for any other degree or examination at any other University.

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On this 12th day of December 2023 in Johannesburg

Dedication

I dedicate this MMed to my family. My parents Mma-masire and Nkobi and daughter Nhlanhla have relentlessly supported me in all my endeavours. I give you thanks for always having belief in me and allowing me a chance to pursue my dreams.

Abstract

Background:

Infectious complications are common in hospitalized burns patients, with a high incidence contributing to significant morbidity and a high mortality. Serum Procalcitonin (PCT) has emerged as a biomarker to diagnose sepsis and infection. Following invasive bacterial infection PCT is detectable in peripheral blood. Levels of PCT more than 0.5µg/L are regarded as abnormal.

Objectives:

The aim of our study was to determine if there is a correlation between serum PCT post burn wound debridement and burn related sepsis. The primary objective is to determine serum PCT level threshold post burn wound debridement that correlates with a positive blood culture. Our secondary objective was to describe factors associated with elevated PCT post burn wound debridement.

Methods:

34 participants were recruited into the study from 1st November 2019 to 31st July 2020. Serum PCT levels were drawn on days 0, 1,2 and 3, day 0 being day of surgery. Blood cultures (BC) samples were drawn on days 0 and 3. Statistical analyses were performed to establish median serum PCT values and the interquartile range of the PCT level was reported for each day in µg/L. A two-sample Wilcoxon-Mann-Whitney test was performed to compare the PCT values with the blood culture result to establish if a correlation with a positive blood culture existed.

Results:

There were 33 patients on whom burn debridement procedures were done, and 1 patient demised before surgery. The median age was 35.5 years, and 61.8% were male. 4 patients were identified to have comorbidities. There was a trend to higher serum PCT values from day 0 to day 3. The median PCT on day 0 was 3.30 µg/L (IQR 0.78 – 15.10), compared to day 3 PCT which was 5.15µg/L (IQR 1.35 – 18.55). All median values for serum PCT for days 0 to 3 were above the threshold considered to be within normal limits regardless of BC positivity. There was a statistically significant difference in PCT level between positive and negative BC, with a *p-value* of *0.0087* for Day 3 serum PCT. The median serum PCT on day 0 and day 3 in the subgroup of patients with a negative BC was 1.8 and 0.91 respectively.

Conclusion:

Burns patients have a serum PCT that is higher than the threshold considered to be normal even in the absence of sepsis with both the burn injury itself and surgical debridement causing an induction of PCT. There is an association of a high serum PCT level with a positive blood culture in a burns patient post debridement surgery. In these patients interpretation should be performed cautiously to prevent unwarranted antibiotic exposure, a contributor of antibiotic resistance. Serum PCT level in burns patients with or without a positive blood culture is higher than the threshold considered positive in non-burns patients. A higher numerical threshold should be used for this cohort of patients, to aid in diagnosis of infectious complications to augment already existing criteria used to diagnose burn related sepsis. A cut off value could not be determined in this study due to the small sample size.

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List of abbreviations

ABA – American Burns Association

ABU – Adult Burns Unit

BC – blood culture

CHBAH – Chris Hani Baragwaneth Academic Hospital

CRP – C-reactive protein

IL-6 – interleukin-6

ISBI – International Society of Burn injury

LBP – lipopolysaccharide binding protein

LMIC – Low-to-middle income countries

NHLS – National Health Laboratory Services

PCT – procalcitonin

SOFA – Sequential Organ Failure Assessment

TBSA – total body surface area

WHO – World Health Organisation

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Chapter 1: Introduction

Background

A unique challenge in the management of hospitalized burn patients is the additional insult of wound debridement in a patient with a hyper inflammatory state (1,2). It is difficult to determine if elevated biomarkers of systemic inflammation in these patients are due to the trauma of wound debridement or sepsis. This is important as the local and systemic effects resulting from the burn injury weaken the entire immune system with consequent increased susceptibility to infection (3,4). Infectious complications are the most common in hospitalized burns patients, with the incidence of sepsis estimated to be 8-42.5% and a documented mortality of 28-85% within this subgroup of patients (1,5). In their retrospective study investigating bacterial sepsis in burns patients in South Africa, Wineberg and colleagues found that 47% of patients at Chris Hani Baragwaneth Academic Hospital burns unit had at least 1 positive blood culture (6). It is therefore paramount to identify and treat sepsis early to reduce mortality from burns related sepsis.

Literature review

Burn injury epidemiology

Burns are a major public health challenge in Sub-Saharan Africa, and a cause of significant morbidity and mortality. The Global Burden of Disease 2019 study identified more than 8 million new cases of burns globally, with a disproportionate impact on low-to-middle income countries(7). Burn prevention remains the cornerstone of reducing the burden of burn injury on a society. Prevention strategies in low-to-middle

income countries (LMIC) often are lacking, with little to no epidemiological data to direct a coordinated public health strategy to address this problem (8,9). Frequently the burden of communicable disease management takes priority(8). The mortality and morbidity benefit of establishing a dedicated burns unit has been demonstrated in several sub-Saharan countries such as Malawi(10) and South Africa(11). Ringo and Chilonga in their prospective cohort study reported a mortality of 26.8%, and highlighted the challenges of management of burns patient in Tanzania due to the lack of a burns unit in the country(12). Unfortunately, this is a challenge faced by many countries in sub–Saharan Africa.

Burn pathophysiology

Thermal burns cause injury to the skin leading to protein denaturation, cell membrane disruption and necrosis(13). Burn injuries are classified according to the cause of injury; flame, scald, contact, chemical and electrical(13). The Jackson model of burn injury describes three zones of injury. Zone of coagulation centrally, representing devitalised tissue; zone of hyperaemia most peripherally representing inflammation without structural damage; and zone of stasis in between the two representing an indeterminate area(13). This model purports to conceptualise how good initial burn management can affect progression of burn wound healing, by salvaging the indeterminate zone by preventing progression to necrosis(14). The depth of injury is of importance as it determines optimal treatment and prognosticates outcome. Burn injury is complex with both local and systemic effects. The larger the involved surface area of the burn, the more significant the systemic inflammatory process that occurs after a burn injury(2). Patients with larger burns often progress to a state of chronic

inflammation which can impair wound healing and alters the immune system, resulting in an increased susceptibility to infection and sepsis(2).

Biomarkers of sepsis

The burn inflammatory response results in a rapid production of serum inflammatory marker signalling the initial immune response. Measurement of some of these markers is used to detect sepsis in the post-surgical patient; these include C-reactive protein (CRP), interleukin-6 (IL-6) and lipopolysaccharide binding protein (LBP). CRP is one of the most used biomarkers of sepsis. Platt and colleagues demonstrated the utility of CRP in predicting infective complications in patients with colorectal malignancy undergoing curative resections(15). Similar results were obtained from a pooled meta-analysis investigating the performance of CRP in identifying infectious complications post major abdominal surgery(16). Despite its usefulness in such circumstances CRP has limitations. Non-infectious conditions such as trauma and malignancy can cause marked elevations in CRP. Similarly, IL-6 may be elevated in infectious conditions but share similar limitations as CRP(17). LBP appears to perform better in terms of predicting the presence of infection complications than both CRP and IL-6, and it has similar limitations as CRP and IL-6(15,17).

Procalcitonin and sepsis

Procalcitonin (PCT); a 116-amino acid pro-hormone produced by the parafollicular c-cells of the thyroid gland and certain neuro-endocrine glands has emerged as a promising biomarker for sepsis. Under normal physiological conditions PCT is not detectable in peripheral blood, however following trauma (including surgery), and invasive bacterial infection almost every cell in the body produces PCT which will be

detectable in peripheral blood(18,19). Peripheral blood levels of PCT in excess of 0.5ng/ml are regarded as abnormal(18). An elevated serum PCT is therefore used as a biomarker of sepsis. Use of serum PCT has been studied extensively in critically ill patients, in predicting sepsis, prognostication and guiding antibiotic stewardship(20,21). Additionally, PCT seems to outperform more traditional biomarkers such as CRP in early identification of sepsis in the severely burned patient(22).

Procalcitonin use in trauma and surgery

Procalcitonin elevation has been demonstrated in non-infectious states such as trauma and surgery. The degree of PCT elevation in the context of trauma is possibly dependent on the severity of the surgical trauma, suggesting a need for a higher threshold to be used in this group of patients to diagnose invasive bacterial infection(23–26). In their prospective study Mathur and colleagues demonstrated that while major trauma does cause serum PCT elevation, the PCT trend can be used as a surrogate marker in the early diagnosis of sepsis in the setting of major trauma(27); however burns patients were excluded in this study. Serial PCT measurements were further demonstrated to be useful in identifying patients at low risk for post-operative complications after major abdominal surgery in, thereby facilitating early discharge(28). Bouaicha and colleagues also noted a moderate level of induction in serum PCT in non-septic patients undergoing uncomplicated elective total hip replacement(26). Sharma and colleagues showed mild to moderate increases in measured serum PCT in two thirds of patients undergoing elective cardiac surgery with cardio-pulmonary by-pass(29). They concluded that a serum PCT more than 7ng/mL may assist in prognosis of post-operative mortality and infectious

complications in cardiac surgery patients and identify high risk groups that need closer observation. Similar conclusions were drawn by Varetto and colleagues in regards to elective abdominal aortic aneurysm repair(30). Liu et al investigated the effectiveness of PCT as biomarker in extensive burns and concluded that PCT is useful in prognostication and is an early harbinger of burn related sepsis (31). The impact of surgery on PCT levels was not considered in the Liu study. In the above studies, the higher threshold used for serum PCT level that correlated with clinical sepsis, was meant to mitigate the PCT induction effect caused by the surgery itself.

Justification of study

There is few data regarding the trend of serum PCT in the peri-operative burns patient with only one retrospective review identified in the literature(32). This study was however conducted in a high-income country, with no such data available from low-to-middle income countries (LMIC). With this study we can provide relevant and context appropriate data about the value of serum PCT in the burnt patient undergoing wound debridement surgery.

Aim

The aim of our study was to determine if there is a correlation between serum PCT post burn debridement and burn related sepsis.

Objectives

Primary objective:

- Determine serum PCT level threshold post burn wound debridement that correlates with a positive blood culture.

Secondary objective:

- Describe factors associated with elevated PCT post burn wound debridement.

Chapter 2: Methods

Study setting

The study was undertaken at Chris Hani Baragwaneth Academic Hospital (CHBAH), in the Adult Burns Unit (ABU), Johannesburg, South Africa, a middle-income country. This is a 22-bed Level-1 burn unit, which receives referrals from Gauteng as well as Free State, Mpumalanga, and Northwest provinces. For all patients, on admission, a panel of blood tests taken, which include a baseline serum pro-calcitonin. Those ABU patients requiring critical care have routine daily PCT levels taken, while daily testing is omitted in those not requiring critical care. In addition, a blood culture (BC) and PCT level are part of the panel of investigations taken if infectious complications or sepsis is suspected.

The ABU has a hospital infection prevention and control policy which is informed by guidelines recommended by the World Health Organization (WHO) and the International Society of Burn injury (ISBI) (33,34). In the ABU intensive care section each patient is nursed by a dedicated nurse, in a single isolation room. Before each admission a fogging machine is used to clean and disinfect the area. It is mandatory that nurses wear a plastic apron, gown, cap, gloves, and face mask when interacting with patients. There is an information chart at the entrance of the unit demonstrating hand hygiene, for which it is compulsory for each visitor to follow. An infection control steward is nominated on a weekly basis to ensure staff and visitor compliance to the unit infection control standards. Additionally, frequent in-house training is part of unit policy to reinforce infection control principles.

Inclusion and exclusion criteria

The population included in this study were patients aged 18 years and above with a total body percentage area (TBSA) burn of 15% or more and with an expected length of stay of more than 5 days. Consecutive patients admitted from 1st November 2019 to 31st July 2020, who were planned for surgical debridement were included in the study. Informed consent was obtained from the patient or their next of kin where the patient was unable to provide informed consent. Exclusion criteria was refusal or withdrawal of consent.

Study design

This was a prospective observational study. Convenience sampling was used for consecutive patients admitted during the study duration. 34 participants in total were enrolled into the study. A positive blood culture was used as a surrogate for burn sepsis in this study. The day of surgery was designated as day 0, then the first post-operative day as day 1 and so forth until day 3. A serum procalcitonin, reported in micrograms/litre(µg/L), was measured pre-operatively on the day of surgery, and on days 1, 2 and 3. A blood culture was performed on designated days 0 and day 3 in a sterile fashion. The procedure for collection of a sample for blood culture was to don a face mask and cap, and then an aseptic handwash was done using chlorhexidine soap. Sterile gloves and gown were worn. The site for collection was cleaned with betadine, allowed to dry and 10mls of blood collected, which was equally divided between 1 aerobic bottle and 1 anaerobic bottle as per ABU unit policy. Only the first surgical debridement was considered. All samples were analysed at the National Health Laboratory Services (NHLS). A quantitative serum PCT was measured using a Cobas® 8100 (*Roche*). The following thresholds in µg/L apply for serum PCT for this

assay: <0.5 systemic infection unlikely/localised infection, 0.5 – 2 systemic infection possible, 2 – 10 suggestive of systemic infection, >10 severe systemic infection/septic shock. The blood culture sample was run and analysed using BacT/ALERT 3D™ Microbial Detection System (bioMérieux, Duram, North Carolina, USA).

Data collection

Informed consent was obtained and signed by the patient or their next of kin. Data collected was entered into a Microsoft® Excel® spreadsheet. Each patient data collection sheet was de-identified and assigned a unique code. The demographic information collected included age, gender, and existing medical comorbidities. Variables data collected were burn depth, type, total body surface area (TBSA) burn, presence of inhalation injury, type of surgery performed, TBSA operated, day post burn, time on operating table as well as the use of prophylactic and/or treatment antibiotics. Blood culture results were recorded as either positive or negative for Day 1 and D3 respectively. The serum PCT value was recorded for each day as µg/L.

Ethics Approval

Ethics approval for this prospective observational study was obtained from the Human Research Ethics Committee (HREC) of the University of Witwatersrand. An application for ethical approval was submitted on 19 July 2019 and approval granted on 30 November 2019; Certificate No: M181119

Statistical analysis

Statistical analyses were performed using STATA© (version 16.1 suite of analysis software STATA© LLC; college station; Texas USA). Descriptive statistics are

presented as median (interquartile range - IQR) for continuous data and as frequencies for categorical data. The median value and interquartile range of the PCT level was reported for each day in µg/L. A two-sample Wilcoxon-Mann-Whitney test was performed to compare the PCT values on day 0 and day 3 with positivity of any blood culture, then specifically for a day 3 positive blood culture. A test for statistical significance was considered at a threshold p value of less than or equal to 0.05.

Chapter 3: Results

In total, 34 participants were recruited into the study from 1st November 2019 to 31st July 2020. One participant demised on the day of surgery. Of the 33 participants, 3 did not have pre-operative blood culture results as the specimens were rejected at the laboratory. Additionally, six day 3 blood culture results were not available due to clinician error in collection and/or labelling of specimens. The baseline characteristics of the study participants are illustrated in Table 1. Only 4 patients had reported co-morbidities. The types of comorbidities identified in our study were HIV infection, hypertension, type 2 diabetes mellitus and epilepsy. Inhalation injury was diagnosed on clinical suspicion.

Table 1: Characteristics of study participants

	Number (N = 34)	**Percentage (%)**
Gender		
Males	21	61.8
Females	13	38.2
Comorbidities		
Yes	4	11.8
No	30	88.2
Burn depth		
Partial	28	82.4
Deep	6	17.6
Burn type		
Electrical	4	12.0
Flame	25	73.3
Hot liquid/solid	5	14.7
Inhalation injury		
Yes	10	29.5
No	24	70.5

The median age of participants was 35.5years, with the majority being male. A total of 33 procedures were done. These were 26 surgical debridements without temporary skin substitute cover, and 7 surgical debridements with cover; 5 with porcine xenograft and 2 with xenograft plus Nanotrix™. The shortest time interval from burn injury occurring to first surgical debridement was 2 days, with the longest being 18 days. Haemodynamic instability and optimization for surgery were the reasons cited in patients where there was a long interval between burn injury and initial surgical debridement. The median day post burn injury for surgery was day 5 post-surgery. The burn wound total body surface area involved in the burn injury and operative parameters are as shown in Table 2.

Table 2: Operative burn parameters

Parameter	**Median**	**Interquartile Range**
TBSA %	34%	20-40%
TBSA % operated	20%	20-30%
Time on operating table	105 minutes	90-155 minutes

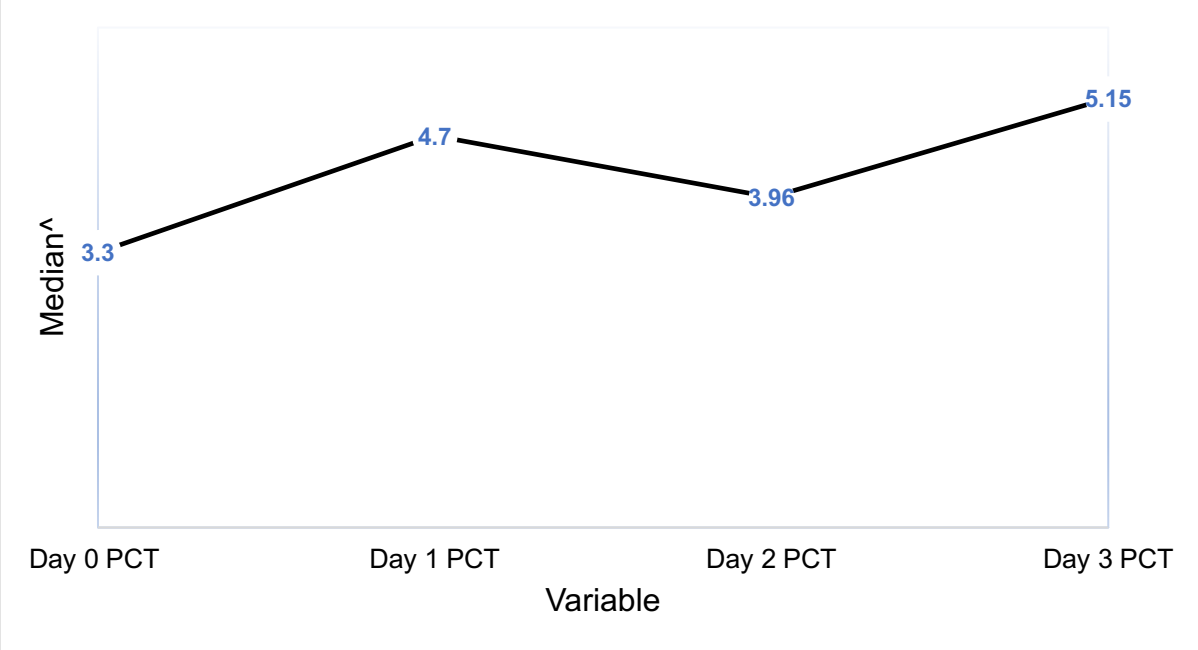
Gram-positive and gram-negative organisms were cultured for both the pre-operative (Day 0) and the post-operative (Day 3) blood cultures as illustrated in Table 3. For day 0 BC the most cultured organism was *Acinetobacter baumanii*, whilst that for day 3 BC was *Staphylococcus aureus*.

Table 3: Organisms identified on Blood cultures

Day 0 Blood culture	**Day 3 Blood culture**
Coagulase-negative staphylococci	*Staphylococcus aureus*
Proteus mirabilis	*Coagulase-negative staphylococci*
Pseudomonas aeruginosa	*Klebsiella pneumoniae*
Stenotrophomonas maltophilia	*Acitenobacter baumanii*
Streptococcus agalactiae	*Proteus mirabilis*
Klebsiella pneumoniae	*Enterococcus faecalis*
Enterobacter cloacae	*Pseudomonas aeruginosa*
Staphylococcus epidermidis	*Achromobacter xylosoxidas*
Enterococcus faecalis	
Escherichia coli	

There was a trend to higher serum PCT values from day 0 to day 3. The median PCT on day 0 was 3.30 (IQR 0.78 – 15.10), compared to day 3 PCT which was 5.15 (IQR 1.35 – 18.55) as demonstrated in figure 1. Median PCT for days 1 and 2 were also elevated above threshold, with IQR of 0.78 – 17.11 and 0.92 – 9.95 respectively. All median values for serum PCT for days 0 to 3 were above the threshold considered to be within normal limits, which is less than 0.05µg/L. These median values were also above 2.0µg/L, the threshold level indicating the possibility of systemic infection.

Figure 1:PCT values day 0 to day 3 ^=µg/L



A two-sample Wilcoxon-Mann-Whitney test was performed to compare the serum PCT level at day 0 and day 3 with the blood culture result (negative and positive). The blood culture result was for both day 0 and day 3. As shown in Table 4, this demonstrated a statistically significant difference in PCT level between positive and negative BC, with the *p-value* for day 0 being *0.0161* and day 3 serum PCT level being *0.0087* respectively. Table 4 demonstrates that the median serum PCT on day 0 and day 3 in the subgroup of patients with a negative BC was 1.8 and 0.91 respectively. Both values are above the normal serum PCT threshold of <0.5 µg/L. Serum PCT on both days 0 and 3 was above normal serum PCT threshold regardless of BC positivity.

Table 4: Serum PCT level compared to day 0 and day 3 blood culture results: ^=µg/L

Variable	**Positive Blood culture**	**Negative Blood culture**	***P-value***
PCT Day 0	N = 15	N = 15	0.0161
Median (IQR)^	8.47 (0.78 – 31.88)	1.8 (0.64 – 4.23)	
PCT Day 3	N = 18	N= 9	0.0087
Median (IQR)^	8.35 (2.83 – 23.14)	0.91(0.61 – 2.68)	

Chapter 4: Discussion

Serum PCT threshold in burns patients

This prospective study to investigate the value of serum PCT in the post-operative burns patient showed that the median serum PCT in burns patients is higher than the normal threshold, even in the absence of demonstrable sepsis. This is consistent with what has been reported in the literature (31,35). In our study, the median PCT was above threshold both pre-operatively and post operatively. This includes even the subgroup of patients with negative BC, suggesting the trauma of the burn injury itself causes an induction of PCT. If the current normal threshold for serum PCT is applied to diagnose burn sepsis, this may result in unnecessary exposure to antibiotics thereby encouraging antibiotic resistance. There has been a suggestion that a different threshold PCT for normal be used in burns and trauma patients(23–26,31), with no consensus as to what exactly this figure should be. In the pre-operative burns patient with a negative blood culture, the median serum PCT level in our study was 1.8μg/L. When the BC was positive the median PCT level was 8.47 and 8.35 on day 0 and day 3 respectively. This indicates that higher threshold could be used in burns and trauma patients.

Serum PCT and burn related sepsis

In our study sepsis was defined by blood culture positivity. A positive blood culture was defined by an identified organism, regardless of the identity of the micro-organism. This contrasts with clinical practice. In most units, including ours, the American Burns Association 2007 consensus definition for burn related sepsis is used. The ABA 2007 consensus takes into consideration many other clinical parameters which include the

following: temperature (>39° or <36.5° Celsius), progressive tachycardia >100 beats per minute, progressive tachypnoea (>25 breaths per minute in non-ventilated patients or minute ventilation >12 litres per minute in ventilated patients), thrombocytopaenia (<100,000 /microliter), hyperglycaemia in a non-diabetic patient and enteral feed intolerance(36). In addition, some organisms such as *Coagulase-negative staphylococci* are considered contaminants from the skin, unless other clinical parameters as defined in the ABA 2007 are also present. In our study, these other parameters were not factored into consideration as a positive blood was the sole parameter used to define sepsis. It is difficult to accurately diagnose burn related sepsis since criteria included by the ABA and other society guidelines are like the systemic inflammatory response syndrome (SIRS) related to the burn injury itself. A parameter such as serum PCT can be added to current definitions of sepsis to augment the accuracy of making the diagnosis.

A statistically significant association of high PCT and BC positivity on either day 0 or day 3 was observed in our study. This was more significant when correlated specifically with day 3 BC positivity and underscores the utility of serum PCT in identifying or suggesting sepsis in the burns patient. This has been suggested in several retrospective(6,31,32) and prospective(22) studies, as well as a meta-analysis(37). Conversely, some data suggests that serum PCT is not a precise indicator of sepsis at the time of diagnosis(38). In their retrospective review of severely burnt patients with suspected infection, Seoane et al found that PCT showed no discriminative value in differentiating between patients with or without sepsis. However, these studies did not take into consideration the impact that surgery has on PCT utility. Our study suggests that serum PCT can still be used in the patient who

has sustained a double hit of both burns injury and surgery. While it was a retrospective study, Cabral and colleagues in their 2018 study demonstrated that PCT can reliably identify sepsis in the burns patient undergoing surgery(32). They considered several surgeries primarily escharotomies, skin grafts and flaps as well as digit/limb amputations, and we considered only surgical debridement. An assumption can be made that our findings can be applicable to other surgery on burns patients as well. The Cabral study was retrospective and done in a high-income country setting, where the rate of burn related sepsis is far less than that found in low- and middle-income countries. The findings of our study are more applicable to the LMIC setting, as no prospective study examining this has to the best of our knowledge been conducted prior to ours.

The stronger statistical significance of high serum PCT in our study was evident in the post-operative burns patient who had a post operative positive blood culture. This is congruent with the findings of Cabral and colleagues(32), as they identified that the highest serum PCT values in their study were those who had pre-operative as well as post-operative sepsis. In addition, a single PCT value has limited value therefore serial measurements need to be done.

Our study suggests that sepsis be considered at a higher threshold for serum PCT in this group of patients. Several studies have attempted to determine this value with ranges of more than 1µg/L to 8.5µg/L (31,32,35), indicating the lack of consensus on this issue. The usefulness of a threshold is to identify low risk patients for possible early discharge(31), as well as a surrogate marker for prognostication of the development of infectious complications and risk of mortality(6,32,35). In our study

the median value for patients with negative blood cultures pre-operatively on day 0 and day 3 was 1.8 µg/L and 0.9 µg/L respectively. A recommendation for a threshold could not be made in our study due to the small sample size. A larger study could be done to definitively establish a serum PCT threshold that can be used. This threshold value can then be used in conjunction with other burn sepsis criteria to assist in diagnosis burns related sepsis.

Factors related to elevated serum PCT

Several factors have been suggested to correlate with elevated PCT levels. These include full thickness TBSA burns, burn index, the presence of severe inhalation injury as well as the Sequential Organ Failure Assessment (SOFA) score(31). We sought to identify if some of these factors, as well as the use of antibiotics, the extent of debridement, the time interval between burn injury and initial debridement surgery, the type of burn, and time spent on the operating table correlated with a high PCT level. We are however unable to comment as our small sample size lacked statistical power to identify such an association. The heterogeneity of data limited the ability to perform a trend analysis of the kinetics of PCT post debridement surgery.

Units that manage burn injuries use criteria outlined in the American Burns Association 2007 consensus definition of sepsis, or other clinical parameters rather than only BC positivity. Defining sepsis as a positive blood culture is a limitation of our study as it restricts the applicability of our findings in the non-research setting. In addition, for purposes of this study, a surveillance BC at day 0 was taken which was out of keeping with standard clinical practice in our unit of drawing BC specimens only when clinically indicated. This study may have classified patients with bacteraemia as having sepsis

even though they did not meet criteria for sepsis according to the 2007 ABA consensus definition.

To the best of our knowledge this is the first study of its kind conducted in a LMIC setting. The findings pave way for a larger, more robust study to confirm the utility of PCT in the burns patient who undergoes surgery in identifying infectious complications. A larger, prospective study may also determine a threshold that should be used in this specific group of patients.

Limitations

This study has several limitations. The study was performed in a specialised burn unit with strict admission criteria and was observational. This may have introduced selection bias. These findings may have limited applicability for burns patients that are not managed in a specialised burns unit, which is the case for several patients managed in our referral drainage area. Defining sepsis as a positive blood culture is a limitation of our study as it restricts the applicability of our findings in the non-research setting. In addition, for purposes of this study, a surveillance BC at day 0 was taken. This study may have classified patients with bacteraemia as having sepsis even though they did not meet criteria for sepsis according to the 2007 ABA consensus definition. The sample size was small, limiting ability of the study to establish a threshold value for serum PCT as well as identifying factors which correlate to elevated PCT levels in the study population. There are limited studies conducted in LMIC investigating the use of serum PCT in this population. This may be due to financial constraints. More studies, with larger sample sizes conducted in a prospective manner are required in this area.

Chapter 5: Conclusion

This prospective study demonstrates that burns patients have a higher-than-normal threshold serum PCT throughout the spectrum of their care. It also demonstrates the association of a high serum PCT level with a positive blood culture in a burns patient post debridement surgery. The usefulness of serum PCT in these patients has been demonstrated and that PCT is a serum biomarker that can be used in this specific group. Burn surgery itself causes an induction in PCT therefore in these patients interpretation of elevated serum PCT must be done with caution to prevent unwarranted antibiotic exposure, a contributor of antibiotic resistance. Serum PCT level in burns patients with or without a positive blood culture is higher than the threshold considered positive in other patients. A higher threshold should be used for this cohort of patients, to aid in diagnosis of infectious complications to augment already existing criteria used to diagnose burn related sepsis. A cut off value could not be determined due to the small sample size, and further studies need to be designed with enough statistical power to establish this value.

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Appendix

Approved Protocol

TITLE: PROCALCITONIN IN THE POST OPERATIVE BURNS PATIENT

Principal investigator

Dr Ludo Lorato Carol MASOLE

Student No: 1927084

MMed Surgery

Supervisors

Prof Adelin MUGANZA: MD, FCS(SA)

Dr Chikwe EDE: MBBS, DA(SA), FCS (SA), MMED (Wits)

INTRODUCTION

A burn injury is an insult that leads to a major systemic inflammatory response which has both beneficial and deleterious effects(2). Severe burn injuries require management in a specialized burn unit. The unique challenge in the management of hospitalized burn patients is the additional insult of wound debridement in a patient with a hyper inflammatory state (1,2). It is difficult to determine if elevated biomarkers of systemic inflammation in these patients are due to the trauma of wound debridement or due to sepsis.

Several biomarkers have been used to detect sepsis in the post-surgical patient. These biomarkers include C-reactive protein (CRP), interleukin-6 (IL-6) and lipopolysaccharide binding protein (LBP). C-reactive protein is the most commonly used biomarker of sepsis. Platt and colleagues demonstrated the utility of CRP in

predicting infective complications in patients with colorectal malignancy undergoing curative resections(15). Similar results were obtained from a pooled meta-analysis investigating the performance of CRP post major abdominal surgery(16). In spite of its usefulness in such circumstances CRP does have its limitations. Non-infectious diseases like trauma and malignancy can cause marked elevations in CRP. Similarly, IL-6 may also be elevated in infectious conditions. However it shares the same limitations as CRP(17). In addition LBP has the same limitations as CRP and IL-6, but appears to perform better at predicting infectious complications(17).

One of the most investigated biomarkers of sepsis is procalcitonin (PCT); a 116-amino acid pro-hormone produced by the parafollicular c-cells of the thyroid gland and certain neuro-endocrine glands. Under normal physiological conditions PCT is not detectable in peripheral blood. However, following trauma (including surgery), and invasive bacterial infection almost every cell in the body produces PCT which will be detectable in peripheral blood (18,19). Peripheral blood levels in excess of 0.5ng/ml are regarded as abnormal (18). Elevated PCT is therefore used as a biomarker of sepsis. Procalcitonin elevation has also been demonstrated to be elevated in non-infectious states such as surgery. The degree of PCT elevation in this context is dependent on the severity of the surgical trauma, suggesting a need for a higher threshold to be used in this group of patients (23–26).

Several studies have been conducted to measure the trend of serum PCT in different types of surgery and trauma. In their prospective study Mathur and colleagues demonstrated that while major trauma does cause serum PCT elevation, the serum PCT trend can be used as a surrogate marker in the early diagnosis of sepsis in the

setting of major trauma(27). Whilst patients with burn trauma were excluded from this study, they highlighted a need to use a higher threshold in these patients since major trauma caused an induction in patients who did not have sepsis. Sharma and colleagues showed mild to moderate increases in measured serum PCT in two thirds of patients undergoing elective cardiac surgery with cardio-pulmonary by-pass. However they concluded that a serum PCT >7ng/mL may assist in prognostication of patients and identify high-risk groups(29). Spoto and colleagues in their series of patients undergoing major elective abdominal surgery concluded that daily post-operative serum PCT measurements can aid in identifying low risk patients - enabling early discharge, early identification of infection and overall improved patient care in this group of patients(28). Similar conclusions were drawn by Varetto and colleagues in regards to elective abdominal aortic aneurysm repair(30). Bouaicha and colleagues also noted a moderate level induction in serum PCT in non-septic patients undergoing uncomplicated elective total hip replacement(26). In all these studies, higher thresholds were used to determine a significant serum PCT suggesting an induction in PCT caused by the surgery itself. There is a paucity of data regarding the trend of serum PCT in the post-operative burns patient.

The local and systemic effects resulting from the burn injury weaken the entire immune system with consequent susceptibility to infection(3,4). Infectious complications are the most common in hospitalised burns patients, with the incidence of sepsis estimated to be 8 - 42.5% and a documented mortality of 28-84% within this subgroup of patients(1,5). It is therefore paramount to identify and treat sepsis early in order to reduce mortality from burns related sepsis. There have been studies done to determine if serum PCT can be used as a predictor of sepsis and a prognostic marker

in burns patients, with promising results(39,40). Cabral and colleagues in a recent meta-analysis on the use of PCT in the diagnosis of sepsis in burns patients concluded that serum PCT may be useful in burns patients to discriminate those with sepsis, and suggested that serial rather than single measurements may be more useful(37). The impact of surgery on the serum PCT was not taken into account.

Serum PCT is a promising biomarker for the early identification of sepsis, but its performance in the setting of surgery in the burns patient has not been established. The major limitation possibly being that a major burn injury and surgery itself on the severely burnt patient may cause significant serum PCT elevations. If this is the case, such elevations may hinder early diagnosis of sepsis and consequently delay treatment. Data is lacking regarding the trend of PCT in the post-operative burns patient therefore it is not established if it is a useful marker of identifying sepsis in this particular group of patients. We hypothesize that the inflammatory response from the burn injury itself and surgery will cause a significant rise in serum PCT, thus it is not a reliable marker in this particular group of patients. We additionally hypothesize that a higher threshold serum PCT is required to predict sepsis post burn wound debridement.

AIMS

To determine if an elevated serum PCT post burn wound debridement suggests sepsis.

STUDY OBJECTIVES

Primary objective

- To determine factors that can predict an elevated serum PCT post burn wound debridement.

- To determine a threshold of serum PCT or trend of serum PCT that correlates with a positive blood culture. For this study sepsis will be defined as a positive blood culture.

Secondary objectives

- To describe the trend of serum PCT post burn wound debridement.

METHODS

Design

Prospective observational study.

Site of study

Chris Hani Baragwanath Academic Hospital (CHBAH) adult burns unit.

Study population

The study will be undertaken on adult patients aged 18 and above admitted to CHBAH adult burns Unit from 01 July 2019 – 3 September 2019 who undergo burn wound debridement. Data will be collected only for initial surgery that the consented participants undergo during their admission into the burns unit.

Sampling

Sample size and statistical rationale

The adult burns unit at CHBAH performs approximately 7-12 procedures per week. I estimate that 6 of these procedures will be wound debridement. Therefore, over the study period of three months, I will use a convenient sample of 60.

Inclusion criteria

- Adult patients aged 18 years and above admitted to CHBAH adult burns unit from 01 July 2019 to 30 September 2019 who had wound debridement.

- Patients with burns (irrespective of mechanism) involving a total body surface area of 15% or more.
- Patients undergoing surgery within 7 days of burn injury.
- Patients expected to have length of stay in the unit of more than 5 days.
- Patients who consent to be included in study

Exclusion criteria

- Withdrawal of consent.

Selection/recruitment of subjects

Informed consent will be obtained from patients who fit the inclusion criteria and have been admitted during the stated data collection period. Consecutive patients will be requested to participate, thus ensuring each patient has an equal chance at being included into the study. Consent will be sought to collect data for initial surgery.

Measuring tool/instrument

Participants meeting inclusion criteria who have given consent to participate in the study will have blood drawn for serum PCT and blood culture on the day of surgery and samples will be sent to the hospital National Health Laboratory Service (NHLS) laboratory for analysis. Serum PCT is a quantitative assay that gives a numeric result in ug/L. Further samples for serum PCT will be drawn on post-operative days 1, 2 and 3. An additional sample for blood culture will be drawn on post-operative day 3. Participants will be investigated and managed as per protocol existing in the adult burn unit without any deviation. The exception will be for additional blood samples as above. The decision for wound debridement will be made by the attending specialist.

Data collection

Data as per the attached data collection sheet (Appendix A) will be collected from the participants and the hospital record. Serum PCT results will be accessed via the NHLS Labtrack results electronic system. Permission to access the system will be obtained from NHLS.

Data analysis

Demographic data as per data collection sheet will be analysed as proportion, mean and median. The participants will be divided into 2 groups: positive blood culture as an intervention group and negative blood culture as a control group. A trend of serum PCT over time will be determined and formulated into a graph for trend analysis. An upward trend graph will be considered as elevated serum PCT. A linear logistic regression analysis will be performed to determine factors that are associated with elevated serum PCT and positive blood culture. Statistical significance will be considered reached if the p-value is <0.05.

Sources of Bias

- Selection bias – Including consecutive patients rather than at random may introduce selection bias.

- Lack of blinding – Investigators and participants are not blinded because it is difficult to blind participants to surgical interventions for ethical reasons. Lack of blinding in our study in unlikely to introduce bias because the outcomes measures in this study are objective.

ETHICS

The following ethical issues are raised by participation in the study:

- The intended study participants are vulnerable as they have undergone significant trauma from the burn injury, as well as being patients. During obtaining informed consent it will be emphasized that the information obtained is completely de-identified and that they are able to withdraw consent at any point of the study period.
- Some intended participants may not be able to provide consent for themselves due to the extent of their injury. Some may be on a mechanical ventilator or being given sedating pain-control drugs. In such instances consent will be sought from their next of kin. If the intended participant at a later stage is able to consent or would want to withdraw consent this will be allowed.
- All information obtained will be completely de-identified, with participants being allocated a unique code that will be known only to the investigators.
- The study does not change any usual care that is given to those that participate. By participating in the study, participants will not be in any way disadvantaged nor advantaged in the care provided to them by the treating physicians.

TIMING

	2018			2019					
	Jul-Oct	Nov	Dec	Jan-Apr	May-Jul	Aug	Sep	Oct	Dec
Literature review									
Preparing protocol									
Protocol assessment									
Ethics application									
Collecting data									
Data analysis									
Writing up - thesis									
Writing up - paper									

FUNDING

Funding for the study will be provided by the Adult Burns unit Research fund.

Estimated cost:

PCT assay – R349.87 each

60 patients, each with x4 PCT = R84 000.00

PROBLEMS

1. The study involves including consecutive participants, regardless of time or date of presentation, who meet inclusion criteria. This may make obtaining consent difficult if intended participants are admitted during weekends/holidays. The initial blood test in those that give informed consent needs to be drawn pre-operatively on the day of surgery, reducing the likelihood of any intended participants being missed.
2. We may need to change the timing of data collection pending ethics approval.

3. In the event that the intended number of procedures is not reached, the period of data collection may need to be increased.

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APPENDIX A

Data collection sheet

ID code	_____
Age *(years)*	_____
Gender	Male ☐ Female ☐
Co-morbidities *(tick all)*	Hypertension ☐ Diabetes ☐ Smoker ☐ HIV ☐ Other (please state) _____
TBSA *(%)*	_____
Burn depth (thickness)	Partial ☐ Deep☐ Mixed ☐
Burn type	Flame☐ Hot liquid/solid☐ Electrical☐ Chemical☐
Inhalation injury	Yes ☐ No ☐
Surgery performed	Debridement with cover ☐
	Cover type *(specify)* _____
	Debridement without cover ☐
TBSA operated *(%)*	_____
Time on operating table	_____ (minutes)
Day post burn	_____
Received antibiotics	Yes ☐ No ☐ If Yes Type: Pre-op Prophylactic ☐ Treatment ☐
Name of prophylactic antibiotic	_____
Name of treatment antibiotic/s	_____ Duration of treatment: _____ Days
Blood culture 1	Negative ☐ Positive ☐
	Organism identified:_____
Blood culture 2 (72hrs)	Negative ☐ Positive ☐

Organism identified:_____

PCT D1 _____μg/L

PCT D2 _____μg/L

PCT D3 _____μg/L

Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Ludo Masole

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M181119

NAME: (Principal Investigator)	Dr Ludo Masole
DEPARTMENT:	Surgery Chris Hani Baragwanath Academic Hospital Adult Burns Unit
PROJECT TITLE:	Procalcitonin in the post operative burns patient
DATE CONSIDERED:	30/11/2018
DECISION:	Approved uconditionally
CONDITIONS:	
SUPERVISOR:	Dr C.J. Ede and Prof R.A. Muganza
APPROVED BY:	Dr CB Penny, Chairperson HREC (Medical)
DATE OF APPROVAL:	19/09/2019

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **November** and will therefore be due in the month of **November** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

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I Ludo Lorato Carol Masole (Student number: 1927084) am a student registered for the degree of Master of Medicine (Surgery) in the academic year 4th.

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Definitions

1. Debridement – removal of necrotic or infected tissue to assist in wound healing. This can be done surgically or non-surgically(13).

2. Procalcitonin – a precursor peptide of the hormone calcitonin, involved in calcium haemostasis, produced in the c-cells of the thyroid and some neuroendocrine tissues(17).