Available online at www.sciencedirect.com

ScienceDirect

EJSO 42 (2016) 234–243

EJSO the Journal of Cancer Surgery

www.ejso.com

Procalcitonin levels predict infectious complications and response to treatment in patients undergoing cytoreductive surgery for peritoneal malignancy

K. Saeed [a,b,*], A.P. Dale [a], E. Leung [c], T. Cusack [a], F. Mohamed [c], G. Lockyer [a], S. Arnaudov [c], A. Wade [d], B. Moran [c], G. Lewis [a], M. Dryden [a,b], T. Cecil [c], J.A. Cepeda [e]

[a] *Department of Microbiology, Hampshire Hospitals NHS Foundation Trusts (Basingstoke and Winchester), Royal Hampshire County Hospital, Romsey Road, Winchester, SO22 5DG, UK*

[b] *University of Southampton Medical School, Tremona Road, Southampton, SO16 6YD, UK*

[c] *Department of Surgery and Pseudomixoma Surgery, Hampshire Hospitals NHS Foundation Trusts, Basingstoke and North Hampshire Hospital, Aldermaston Road, Basingstoke, RG24 9NA, UK*

[d] *Department of Intensive Care Unit, Hampshire Hospitals NHS Foundation Trusts, Basingstoke and North Hampshire Hospital, Aldermaston Road, Basingstoke, RG24 9NA, UK*

[e] *Department of Microbiology, Kingston Hospital NHS Foundation Trust, Kingston Upon Thames, Surrey, KT2 7QB, UK*

Accepted 16 October 2015
Available online 29 October 2015

Abstract

Background: Cytoreductive-surgery for peritoneal-malignancy (PM) involves extensive intra-abdominal surgery and a massive post-operative systemic–inflammatory-response (SIRS). It is often challenging to differentiate SIRS that are solely surgery-associated from those of post-operative infections. White-Cell-Counts (WCC) and C-Reactive-Protein (CRP) are routinely used as markers for infection, but are non-specific and their elevation is often delayed in PM cases. Other markers need to be evaluated to assist early identification/prediction of post-operative infections.

Methodology: Prospective evaluation of serum procalcitonin (PCT), CRP and WCC in 50 patients pre-operatively (Day0), and on post-operative days (POD) 1, 3 & 6, following cytoreductive-surgery with or without splenectomy.

Results: Day0 PCT, CRP and WCC values were within normal limits, but increasing physiologically in post-operative period without infection, with noticeable higher PCT in splenectomized patients. In our cohort post-operative infections were diagnosed in 14 patients, often within 48 h. There was a trend for faster rise in serum PCT on POD1 compared to CRP and WCC, and faster PCT decline following appropriate therapy on POD3 and POD6 when infected cases were clinically resolving while WCC and CRP continued to rise, particularly in non-spelenectomised patients. The AUC on POD1 was significantly higher for PCT (0.689) *vs.* WCC (0.476) and CRP (0.477) ($p = 0.04$). Sensitivity, specificity, positive-predictive-value and negative-predictive-values for PCT ranged between (57%–100%), (22%–74%), (33%–47%) & (81%–100%), for CRP (28%–78%), (5.5%–86%), (18%–44.4%) & (40%–75.5%) and for WCC (14%–26.5%), (65.5–80.5%), (22%–25%), (67%–70%) respectively.

Conclusion: PCT, like WCC and CRP, needs to be interpreted with extreme cautions in the context of infections post-cytoreductive-surgery and should only be used in association with other clinical and investigational findings.

Keywords: Cytoreductive surgery; Peritoneal malignancy; Procalcitonin

Introduction

Cytoreductive surgery for peritoneal malignancy (PM) is associated with extensive tissue resection and a prolonged

* Corresponding author. Department of microbiology, Hampshire Hospitals NHS Foundation Trusts (Basingstoke and Winchester), Royal Hampshire county Hospital, Romsey Road, Winchester, SO22 5DG, UK. Tel.: +44 1962825927.

E-mail address: kordosaeed@nhs.net (K. Saeed).

http://dx.doi.org/10.1016/j.ejso.2015.10.004
0748-7983/

operating time. Splenectomy is often performed and, in the majority of cases, blood transfusions are common and hyperthermic intraperitoneal chemotherapy (HIPEC) is generally administered.[1] Early post-operative supportive therapy is invariably delivered in the intensive care unit (ICU) for an average of two days. The systemic inflammatory response mounted following this extensive surgery is substantial and often manifests as the systemic inflammatory response syndrome (SIRS). SIRS can also occur as a consequence of post-operative infection or sepsis. In these cases, early recognition is paramount and enables prompt administration of broad-spectrum antibiotic therapy and, if required, further surgical procedures to achieve source control. In many cases, the inability to distinguish between the causes of SIRS in this patient group makes the diagnosis of post-operative infection particularly challenging.

Currently used inflammatory markers of systemic inflammation e.g. white cell count (WCC) and C-Reactive protein (CRP), which are routinely used as surrogate markers for infection are of limited use in this group of patients. In our experience, these markers are non-specific for bacterial infection in PM cases and elevations may lag behind clinically significant events. Furthermore, in patients with underlying medical conditions, e.g. liver disease or immunosuppression, the WCC and CRP may remain low despite the presence of infection. Conversely, following surgical procedures, WCC and CRP levels may be high in the absence of infection.[2–9] Consequently, the use of these markers may result in either under or over-diagnosis of post-operative infections which may be associated with a delay in appropriate management, or the inappropriate administration of antibiotics. Minimising the inappropriate use of antibiotics is important and significantly reduces the risk of complications including the potential selection of multi-drug-resistant bacteria and *Clostridium difficile*-associated diarrhoea.

Procalcitonin (PCT), another biomarker, has been found to have an important role in the diagnosis of bacterial infection.[10] PCT is a prohormone of calcitonin, normally produced by thyroid gland C-cells in response to hypocalcaemia. Under normal conditions, very low concentrations of PCT in serum (<0.1 μg/L) are observed.[11] In infection, the inflammatory process induces extra-thyroid production of PCT, levels of which increase after 3–4 h, peaking at around 6 h with a plateau of up to 24 h.[12] PCT is an appealing biomarker as, not only is it a more sensitive and specific marker of bacterial infections compared with WCC and CRP, but it also rises earlier in the course of bacterial infection.[13–20] Studies have shown that the use of PCT can significantly reduce unnecessary antibiotic use by identifying patients with non-infective (bacterial) aetiologies allowing the early cessation of antibiotics.[21] There is a body of controlled studies,[13–20,22] mostly in medical patients, that support the role of PCT in diagnosing bacterial infections as a useful antimicrobial stewardship tool.

Current evidence relating to the use of PCT measurements in surgical patients is limited but encouraging and, in the main, demonstrates that there is a transient "physiologic" PCT rise following surgery in general,[11,23–26] though, the available evidence also suggests that PCT is a more accurate predictor of major anastomotic leak after elective colorectal resection than WCC and CRP.[27] However, Meisner et al. suggested that "physiologic" post-operative induction of PCT largely depends on the type of surgery. For example, while intestinal surgery and other major operations often result in a post-operative PCT increase, in the majority of patients undergoing relatively minor surgery, involving primarily aseptic surgical procedures, the PCT remains normal.[28] This led the authors to conclude that PCT should be used post-operatively for the diagnosis of infection only when the range of PCT concentrations during the normal course of specific surgery types is considered and when PCT concentrations are sequentially assessed.[28] To our knowledge, there are no published data relating to PCT dynamics and their associated clinical usefulness in PM patients undergoing cytoreductive surgery.

Our aim was to study the dynamics of serum PCT in this group of patients to: firstly establish baseline measurements for PCT in this group and observe its dynamics in the immediate post-operative period; and secondly to find out about the potential diagnostic ability of PCT in early infectious complications, compared to CRP and WCC, post cytoreductive surgery for PM, by determining area under the curve (AUC) as well as sensitivity, specificity, positive and negative predictive values. Additionally potential variations in PCT dynamics in splenectomised versus non-splenectomised patients undergoing cytoreductive surgery was evaluated.

Methods

Study design and participants

Non-interventional, single-centre prospective study at Basingstoke and North Hampshire Hospital/Hampshire Hospitals NHS Foundation Trust one of the two major National PM centers in the UK.

From February 2014 to February 2015 serum samples were obtained on the immediate pre-operative day (Day 0), and then on Day 1 (POD1), Day 3 (POD3) and Day 6 (POD6) post-operatively, from fifty adult patients undergoing extensive cytoreductive surgery for PM. Patients younger than 18 years, pregnant patients, or those who refused consent, were excluded.

The samples were transferred to the microbiology department, initially stored at −20 °C, and tested in batches for PCT based on our previously published methodology (18). Simultaneous CRP and WCC were measured as part of routine clinical care. As this was a non-interventional study, and PCT measurements were not performed in