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ORIGINAL ARTICLE

Robotic assisted radical prostatectomy accelerates postoperative stress recovery: Final results of a contemporary prospective study assessing pathophysiology of cortisol peri-operative kinetics in prostate cancer surgery



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Stress system

Abstract *Objective:* To investigate the effects of prostate cancer (PCa) surgery on the stress system and to identify potential independent factors associating with stress recovery. *Methods:* The design of the study was prospective and PCa surgery included robot assisted radical prostatectomy (RARP) or retropubic radical prostatectomy (RRP). Between February 2013 to December 2014, 315 consecutive patients were evaluated. The effects of PCa surgery on the stress system were measured by cortisol serum levels before and after surgery on post-operative day (POD) 0, 1, 3, 5 and 45. Cortisol variations in the population and subpopulation

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Hypothalamus
–pituitary–adrenal
axis;
Cortisol hormone

(RARP vs. RRP) of patients were investigated by statistical methods. Factors associating with stress recovery were assessed by simple linear regression (SLR) and multiple linear regression (MLR) analysis.

Results: RARP was performed in 75.9% of cases. In the patient population, there were wide serum cortisol perioperative variations. PCa surgery triggered the stress system which immediately (POD 0) responded by cortisol overproduction which induced the negative feedback mechanism that started on POD 1, continued on POD 3, was still ongoing on POD 5 and completely settled on POD 45 (stress recovery). In the subpopulation of patients, significantly lower cortisol serum levels were detected on POD 3–5 in RARP cases in whom cortisol levels were close to preoperative levels (stress recovery) on POD 5. Independent predictive factors of serum cortisol on POD 5 (stress recovery) were preoperative cortisol ($p = 0.02$), cortisol levels on POD 3 ($p < 0.0001$) and RARP ($p = 0.03$) in which the association was negative (stress recovery faster than RRP).

Conclusion: Our study shows that PCa surgery immediately (POD 0) triggers the stress system which respond by overproduction of cortisol which induces the negative feedback mechanism that starts on POD 1, is still ongoing on POD 5, but is completely settled on POD 45. Moreover, after surgical trauma, our study gives evidence that the RARP procedure associates with stress recovery faster than RRP. Further confirmatory studies are required.

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1. Introduction

Prostate cancer (PCa) is the second most frequent solid tumor after lung cancer in adult males [1] and associates with a mortality rate of 1.2% [2]. Radical prostatectomy (RP) is the most performed procedure for treating clinically localized PCa in men who have life expectancy more than 10 years, associates with extended lymph node dissection (LND) in high risk patients [3], and aims to eradicate cancer disease, to preserve urinary continence, and potency as well [3,4]. RP may be performed by the open retropubic approach (RRP) or by minimally invasive laparoscopic techniques which include the laparoscopic RP (LRP) and robot assisted RP (RARP) techniques [3–5]. Actually, RARP is increasingly displacing RRP all over the world [3,4], and associates with lesser blood loss than RRP. However, post-operative complications related to RARP and RRP appear similar. Although there are no prospective randomized trials comparing RRP vs. RARP, experts consider RARP a valuable therapeutic option for treating clinically localized PCa [5].

It has been shown that major surgery trauma induces profound immunological dysfunction [6] by triggering the stress system which is represented by the hypothalamic–pituitary–adrenal (HPA) axis [7–9]. The HPA axis is a neuroendocrine system that regulates the circulating levels of glucocorticoid hormones (mainly cortisol) that are important for homeostasis and play a critical role in stress response [7–9].

The hormones of the stress system include the corticotrophin-releasing hormone (CRH) which is released by the hypothalamus, the adrenocorticotrophic hormone (ACTH) which is produced by the pituitary and cortisol which is the main glucocorticoid hormone secreted by the adrenals. Approximately, 95% of plasma cortisol is bound to proteins that include the cortisol binding globulin (CBG, 95%) and albumin (10%–15%); moreover, the remaining 5% is

unbound, free to cross cell membranes and binds to glucocorticoid and mineralocorticoid receptors [9].

Major surgery is a significant challenge to homeostasis because it alters the steady state of neuroendocrine systems of which the most pivotal is the HPA axis [9]. Clinical models and studies investigating on the stress system after major surgery are actually unknown. Although it has been shown that RARP is less invasive than RRP [10], studies dealing with the effects of RARP and RRP related to the stress system are missing. Actually, the pathophysiology of the HPA axis after PCa surgery is an unexplored field because we are missing clinical models which are important for progressing and improving care. The present study explores the pathophysiology of the stress system by RARP and RRP as well as complications related to the HPA axis by the two procedures.

2. Patients and methods

The study relates to a period that ranges from February 2013 to October 2014 and includes 315 consecutive patients who underwent RP by RARP or RRP.

Exclusion criteria were as follows: (i) sarcoma of the prostate, (ii) preceding focal therapies, (iii) androgen blockade, (iv) history of glucocorticoid medications or adrenal surgery. The choice of the procedure, RARP or RRP, was based on a joint decision by urologists and patients who were sharply informed and provided written consent to surgery as well as to the use of their data. Robot assisted RP was delivered by the three-arm da Vinci Robot System (Intuitive Surgical, Inc, Sunnyvale, CA, USA) and performed by two experienced surgeons who were experienced in both techniques. The approach was transperitoneal with prostatic dissection in all cases [11]. RRP was performed by experienced surgeons according to the Walsh technique [12]. According to the D'Amico class risk classification [13], LND was planned in all high risk

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