ORIGINAL ARTICLE

Analgesia and endocrine surgical stress:
Effect of two analgesia protocols on cortisol and prolactin levels during abdominal aortic aneurysm endovascular repair

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Abstract

OBJECTIVES: Endovascular abdominal aortic aneurysm (AAA) repair was performed with local anaesthesia and intravenous analgesia. The objective of the study was to evaluate how two analgesia protocols affected stress response, measured as cortisol, 17-OH progesterone (17OHP) and prolactin (PRL) concentration during the procedure.

METHODS: 44 patients undergoing elective AAA endovascular repair were included to either receive regular boluses of fentanyl midazolam or remifentanil continuous infusion, analgesia was monitored by Visual Analogue Scale (VAS) measurement; cortisol, 17OHP and PRL were sampled preoperatively, at skin incision, endovascular prosthesis release and skin suture.

RESULTS: 42 patients were included. Mean VAS values were lower in the remifentanil group 0.50±0.68 vs 1.48±1.20, p=0.002 at incision, 0.24±0.58 vs 1.45±1.18, p<0.001 prosthesis release, 0.51±0.90 vs 1.73±1.45, p=0.002 suture. No statistically significant difference was found among cortisol and 17OHP levels; PRL was significantly lower in the fentanyl-midazolam group (23.83±16.92 ng/ml vs 40.81±22.45 p=0.009 at prosthesis release and 28.23±15.05 vs 41.37±14.54, p=0.007 at suture).

CONCLUSIONS: Although statistically significant VAS difference had a limited clinical impact due to its small entity. The group that experienced less pain showed a more intense PRL response, while cortisol and 17OHP did not reach statistical significance.

INTRODUCTION

An aging population is becoming the usual setting of surgery and in particular vascular procedures are peculiar of the elderly. General anesthesia is a mandatory choice in most aortic interventions, often characterized by severe and even fatal complications. Endovascular abdominal aortic aneurysm (AAA) repair is an alternative to open surgery that can be safely performed under conscious sedation with local anesthesia, which are better tolerated by patients.

In fact vascular pathologies often affect the body as a whole impacting on stress reaction.

Cortisol is a core mediator of stress response. The activation of hypothalamic-pituitary-adrenal axis (HPA) is influenced by various agents both psychological and physical such as anxiety and pain (Lightman 2008), its effect is cortisol release into the bloodstream (Matousek *et al.* 2010) in order to better react to what is perceived as a possible threat. Elevated prolactin (PRL) levels are generally associated with lactation or endocrine pathologies in males; however there is evidence that stress (Tomei *et al.* 2006) can raise its plasma concentration. 17-OH progesterone (17OHP) (Lindh *et al.* 1992) is a cortisol precursor derived from progesterone that has, alongside well-known effects on reproductive system, several actions as a modulator of inflammatory response, coagulation and smooth muscle tone.

Exploring the impact of intravenous analgesia on stress response in the frail equilibrium of the elderly undergoing endovascular abdominal aortic surgery with preserved conscience can give new insight on endocrine systemic reaction pathways, that go beyond the usual clinical parameters.

The aim of the study was to evaluate how two analgesia protocols affect stress response (Marana *et al.* 2008), measured as cortisol, 17OHP and PRL serum concentration at fixed times during the operation.

MATERIAL AND METHODS

Following approval by the institutional ethics committee the study, subsidized by University of Modena and Reggio Emilia research funds, was conducted on 44 consecutive patients undergoing elective AAA endovascular repair, after having obtained proper written consent. Exclusion criteria were non collaboration by the patient, age under 18, pregnancy, emergency surgery, allergy to one of the drugs used, intraoperatory change of anesthetic technique.

Data for this study were derived from a subgroup of patients participating a randomized controlled trial for the evaluation of two analgesia protocols during endovascular aortic procedures (Bonfreschi *et al.* 2009).

Surgery was performed by University of Modena and Reggio Emilia Vascular Surgery team.

Abdominal aortic endoprostheses were introduced via femoral arteries with high bore catheters in order to exclude the aneurism sack and preserve the adjoining vessels. Local anesthesia was performed with 7 mg/kg mepivacaine, a rapidly acting local anesthetic, divided between the sites of catheter introduction.

Using a computer-generated list (OpenOffice 2.0), patients were randomized into two groups, to receive remifentanil or fentanyl-midazolam (Ledowski *et al.* 2005; Winterhalter *et al.* 2008).

Just before entering the operating room, the patients were randomly assigned to one of the two treatment groups by opening a sealed envelope.

During AAA endovascular repair, patients blindly received one of the two treatments. In the remifentanil group, infusion (0.03 μg/kg/min) was started approximately 5 minutes before skin incision. The infusion rate was increased in steps of 0.02 μg/kg/min each time VAS, a pain measurement tool, was greater than 4, considered the threshold for rescue medication. A period of more than 5 minutes between two steps was required. In the fentanyl-midazolam group, intravenous doses of fentanyl and midazolam (1–3 μg/kg and 0.05–0.1 mg/kg respectively) were administered approximately 5 minutes before skin incision and repeated, up to the maximum allowed dose, as long as the reported pain score was greater than 4. A period of more than 5 minutes between two boluses was required.

Blood samples were collected by a catheter previously inserted into the radial artery, after local anesthesia of the puncture site with lidocaine 2% 2 ml local injection, to dose serum cortisol, 17OHP and PRL levels. Samples were collected at the patient arrival in the induction room (T0) (about 30 minutes before skin incision), 15 minutes after skin incision (T1), at main body prosthesis release (T2) (about 60 minutes after skin incision), at skin suture (T3) (about 90 minutes after skin incision). The timing for sample collection was strictly dependent on the phase of the operation. In fact ŦthesŦe moments were chosen as most surgical stimuli are concentrated in T1, T2, T3. All procedures were completed before 2 pm. Mean values VAS were calculated during time intervals T0–T1, T1–T2, T2–T3.

All samples were analyzed by Modena Policlinico Teaching Hospital Endocrinology Laboratory. Plasma cortisol, PRL, 17OHP were determined by radioimmuno-assay (Radim, Pomezia, Rome, Italy) (Genazzani *et al.* 2002). Based on two quality control samples the average within- and between-assay coefficients of variation were 3.8% and 9.3%.

Statistics

Mean age, sex and American Society of Anesthesiologists (ASA) physical status were recorded for each group, data were expressed as means (SD) and numbers (percentages). Comparison of two means was performed using the Student's *t*-test.

Mean VAS values were calculated for both groups, data were expressed as means (SD). Comparison of two means was performed using the Wilcoxon Rank Sum test.

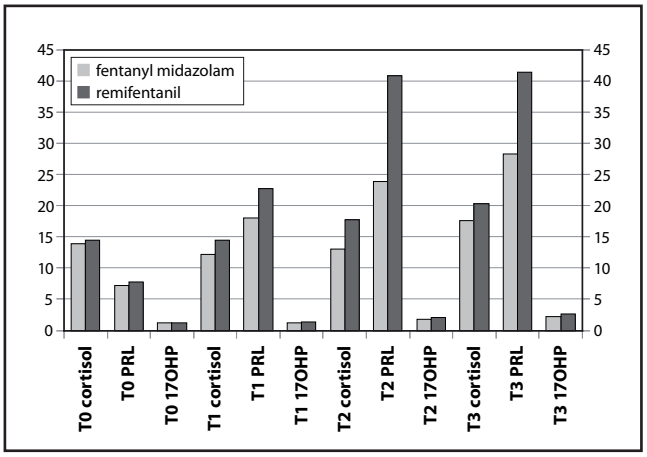

Fig. 1. Serum cortisol (µg/dl), 17-OH progesterone (17OHP, ng/ml) and prolactin (PRL, ng/ml) basal preoperative levels (T0), 15 minutes after skin incision (T1), at endovascular prosthesis release (T2), at skin suture (T3).

Mean cortisol, 17OHP and PRL were calculated for both groups variation at T1, T2, T3, data were expressed as mean (SD). Comparison of two means was performed using one-way analysis of variance (ANOVA).

A *p*-value of <0.05 was considered significant. Statistical analysis was performed on a personal computer using STATA (10.0) software.

RESULTS

A total of 44 patients were investigated, 2 subjects were excluded due to blood sample deterioration. The study groups were similar with respect to age, sex, American Society of Anesthesiologists (ASA) physical status (Table 1).

Mean VAS values for the T0–T1, T1–T2, T2–T3 intervals are summarized in Table 2.

One-way ANOVA was used to compare cortisol, 17OHP and PRL serum concentration in remifentanil and fentanyl-midazolam group (Table 3, Figure 1). Bartlett's test for equal variances was positive in both groups.

DISCUSSION

Endovascular surgery is a less invasive treatment for potentially lethal pathologies such as AAA. The level of analgesia and sedation required for the procedure can be effectively achieved without abolishing conscience. Moreover patient's collaboration is needed to aid the surgeons work. However this experience can elicit a stress reaction.

Groups were similar according to age, sex, ASA physical status. Mean VAS values were statistically lower in remifentanil group, as already noted (Bonfreschi *et al.* 2009). In both groups, pain level was suitable to guarantee an adequate analgesia, safely complete the procedure and favor patients' collaboration throughout the operation.

Cortisol is a well-known stress mediator secreted in response to psychological and physical stimuli perceived as dangerous by the subject – its increase is a sign of HPA activation (Michaud *et al.* 2008). This mechanism's importance is fundamental in fight-or-flight reaction but its role inside the operating room has not been clearly explained. The reaction it produces, how-

Tab. 1. Study groups age (years), sex (number of males), American Society of Anesthesiologists (ASA) physical status. Age and ASA physical staus are expressed as means ± standard deviation.

Groups	Age	Sex	ASA physical status
Fentanyl midazolam	71.50±6.00	20 males (100%)	3.04±0.21
Remifentanil	73.23±8.20	22 males (100%)	3.05±0.22

Tab. 2. Mean Visual Analogue Scale (VAS) values at T0-T1, T1-T2, T2-T3 intervals by treatment group. Induction room (T0), 15 minutes after skin incision (T1), at endovascular prosthesis release (T2), at skin suture (T3).

Groups	Fentanyl midazolam	Remifentanil	
	Mean (SD)	Mean (SD)	*p*-value
VAS at T0-T1	1.48±1.20	0.50±0.68	0.0024 *
VAS at T1-T2	1.45±1.18	0.24±0.58	0.0003 *
VAS at T2-T3	1.73±1.45	0.51±0.90	0.0019 *

Tab. 3. Average serum cortisol (mg/dl), 17-OH progesterone (17OHP, ng/ml) , prolactin (PRL, ng/ml) concentration one-way analysis of variance of basal preoperative levels (T0), 15 minutes after skin incision (T1), at endovascular prosthesis release (T2), at skin suture (T3) in the remifentanil and fentanyl midazolam groups.

	Mediator	Remifentanil	Fentanyl midazolam	*p*-value
T0	Cortisol	14.53±5.25	13.89±4.29	0.6687
	PRL	7.82±3.28	7.20±3.53	0.5593
	17OHP	1.27±0.65	1.26±0.74	0.9768
T1	Cortisol	14.49±5.67	12.15±3.88	0.1308
	PRL	22.77±15.52	18.00±14.95	0.3180
	17OHP	1.16±0.95	1.40±1.32	0.5221
T2	Cortisol	17.75±7.99	12.99±7.22	0.0500
	PRL	40.81±22.45	23.83±16.92	0.0090 *
	17OHP	1.77±2.23	2.07±1.67	0.6388
T3	Cortisol	20.34±10.56	17.63±8.97	0.3779
	PRL	41.37±14.53	28.23±15.05	0.0064 *
	17OHP	2.23±1.63	2.69±2.24	0.4635

ever, gain relevance in the context of an elderly patient, whose functional reserves are considerably reduced.

Consequently two analgesia protocols were confronted to assess their impact on stress reaction. These models show a potentially direct effect of therapy on cortisol (only marginally significant at T2) and PRL increase. In fact, from the data collected no statistically significant correlation could be found between analgesia protocol and 17OHP.

Interestingly remifentanil does not seem to impact on cortisol, with the exception of the above noted effect at T2, differently than fentanyl-midazolam, which, on the other hand reduces PRL release. The phenomenon could be explained by an increased gabaergic central activity (Genazzani *et al.* 2000) mediated by benzodiazepines, with inhibition of PRL secretion resulting in a higher reaction threshold – response is thus blunted not abolished. In males PRL rises, apart from some very specific pathologies, during emotional stress, benzodiazepines are well-known anxiolytics: their action is logically linked to PRL variation. Their effect on the elderly patient can lead to paradoxical reactions so their use can be controversial during procedures that may benefit from patients' collaboration.

Stress response seemed to be disjoint from pain management, also because both groups experienced very limited noxious stimuli, it should consequently be evaluated if further therapeutical effort has to be implemented to reduce this endocrine reaction, increasing pharmacological pressure, or if remifentanil, a potent opioid selective agonist, is capable of guaranteeing alone an adequate level of analgesia and sedation to safely perform AAA endovascular repair.

Most anesthesiology efforts are oriented towards surgical stress reduction, due to well-known (Baldini & Carli 2009) detrimental effects for the patient, however only those alterations impacting on treatment quality should be addressed, as, in the perspective of a minimally invasive anesthesia, every intervention has to be carefully weighted (Goldstein & Kopin 2007).

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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