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Author: Gulik, Laura van

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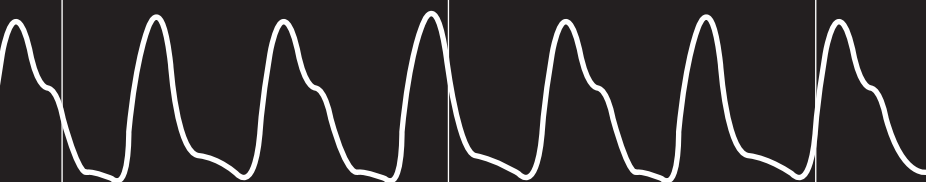
ECG

80



SpO₂

98%



ART

167
69



Pain?

PROCEDURAL PAIN DOES NOT RAISE PLASMA LEVELS OF CORTISOL OR CATECHOLAMINES IN ADULT INTENSIVE CARE PATIENTS AFTER CARDIAC SURGERY

CH. 5 section II



L. van Gulik^{1,2}, S.J.G.M. Ahlers^{2,3}, M. van Dijk³, P. Bruins¹, M.E. Meima⁴, Y.B. de Rijke⁵, H.S. Biemond-Moeniralam^{1,6}, D. Tibboel³, C.A.J. Knibbe^{2,3}

- 1 Department of Anaesthesiology, Intensive Care and Pain Management, St Antonius Hospital, Koekoekslaan 1, Nieuwegein, 3440 EM, The Netherlands
- 2 Department of Clinical Pharmacy, St Antonius Hospital, Koekoekslaan 1, Nieuwegein, 3440 EM, The Netherlands
- 3 Intensive Care, Erasmus Medical Centre, Sophia Children's Hospital, Dr Molewaterplein 60, Rotterdam, 3015 GJ, The Netherlands
- 4 Division of Vascular Medicine and Pharmacology, Erasmus MC, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands
- 5 Department of Clinical Chemistry, Erasmus Medical Centre, P.O. Box 2060, 3000 CB Rotterdam, The Netherlands
- 6 Department of Internal Medicine, St Antonius Hospital, Koekoekslaan 1, Nieuwegein, 3440 EM, The Netherlands

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Abstract

The gold standard for quantification of pain is a person's self-report. However, we need to have objective parameters for pain measurement when intensive care patients, for example, are not able to report pain themselves. An increase in pain is currently thought to coincide with an increase in stress hormones. This observational study investigated whether procedure-related pain is associated with an increase of plasma cortisol, adrenalin, and noradrenalin. In fifty-nine patients receiving intensive care after cardiac surgery cortisol, adrenalin, and noradrenalin plasma levels were measured immediately before and immediately after patients were being turned for washing, either or not combined with the removal of chest tubes. Numeric rating scale (NRS) scores were obtained before, during, and after the procedure. Unacceptably severe pain (NRS ≥ 4) was reported by 7 (12%), 26 (44%), and 9 (15%) of patients, before, during, and after the procedure respectively. There was no statistically significant association between NRS scores and change in cortisol, adrenaline, and noradrenaline plasma levels during the procedure. Despite current convictions that pain coincides with an increase in stress hormones, procedural pain was not associated with a significant increase in plasma stress hormone levels in patients having undergone cardiac surgery. Thus, plasma levels of cortisol, adrenalin and noradrenalin seem unsuitable for further research on measurement of procedural pain.

Introduction

Effective pain management promotes quality care in the intensive care unit(ICU). For example, studies showed reduced duration of mechanical ventilation[1,2], shorter ICU- and hospital-stay, lower 30-day mortality risk [2], and less use of opioids [2] after pain management programs had successfully brought down the incidence of pain. Pain levels are preferably established by the patient's self-report, but observational scales are needed to estimate pain levels in patients who are not capable of self-report due to sedation, critical illness, or neurologic diseases [3,4].

More objective parameters to measure pain have been sought for over fifty years [5]. Changes in heart rate, blood pressure, and respiratory rate have been used as surrogate markers, but especially in ICU patients, these parameters are influenced by disease severity and medication. Measuring skin conductance, which reflects sympathetic nervous system activity, showed higher sympathetic nervous system activity in adult patients with more postoperative pain [6]. The value of skin conductance measurements in intensive care patients remains debatable and only data in pediatric patients have been published [7]. Pain scales such as the behavioral pain scale (BPS)[3] are included in guidelines for analgesia in ICU patients, although they seem to underestimate pain [4]. Stress hormones, such as cortisol, adrenalin, and noradrenalin are potentially useful objective parameters of pain, as they are thought to be released systemically in a sympathetic stress response triggered by pain [8,9]. Although levels of these stress hormones have been related to various types of anesthesia [10] and depth of sedation [11] in cardiac surgery patients, they have never been studied in relation to procedural pain.

ICU patients who have undergone cardiac surgery are inevitably subjected to potentially painful procedures, such as posture change for washing and the removal of chest tubes [12,13]. Although they experienced major surgery assisted with cardiopulmonary bypass, most of them are able to report pain and pain intensity the morning after surgery. In the study reported here we investigated whether plasma levels of cortisol, adrenalin, and noradrenalin were associated with pain levels due to potentially painful procedures. If this should be the case, these parameters may be of additional value in research on the development of tools to measure pain in patients who are not able to communicate.

Methods

Design & patients

After approval by the local Ethics Committee of the St. Antonius Hospital, (VCMO, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands) (approval number R0715A, 7 November 2007, chairman dr. B.J.W.M. Rensing) and study registration at ClinicalTrials.gov (identifier NCT00558090), written informed consent was obtained from 117 patients before surgery. Patients participated in a double-blind, randomized controlled clinical trial on morphine for procedural pain after cardiac surgery, performed in a 30-bed mixed ICU in a teaching hospital in Nieuwegein, The Netherlands [14]. From these patients, 59 participated in the sub-study on stress hormones and procedural pain.

Study procedure

On the first postoperative day, patients received an intravenous bolus dose of morphine of either 2.5 or 7.5 mg thirty minutes before change of posture for washing combined with chest tube removal (32/59=54% of patients) or change of posture only (27/59=46% of patients) between 7.30 a.m. and 9.30 a.m. [14]. Arterial blood samples were taken from the arterial line directly before and after the procedure to determine the levels of cortisol and catecholamines.

Pain levels were recorded before, during, and after the procedure, if possible by the patients themselves on a numeric rating scale (NRS) from 0-10. Fifty patients (85%) were able to do this. Nurses assessed the pain for the other 9 patients (15%), who were still under residual sedation. The NRS has proven a reliable measure for the estimation of pain in ICU patients[4]. A NRS score ≥ 4 was considered to represent unacceptable pain [15] and served as a cut-off point for extra analgesia.

Analgesia was protocolized throughout the entire ICU stay, including paracetamol (acetaminophen) 1000 mg four times daily, morphine via continuous infusion, and intravenous morphine boluses as rescue medication. Pain was assessed at least three times a day, and around the procedure on the first postoperative day. Patient characteristics including the European System for Cardiac Operative Risk Evaluation (EuroSCORE) [16] and intraoperative features were registered, such as type of surgery and type of cardiopulmonary bypass (CPB; either conventional or minimal extracorporeal cardiopulmonary bypass (MECC)), and administration of steroids.

Biochemical analysis

Arterial blood samples were immediately stored on ice, centrifuged at 4° Celsius, and stored at -80° Celsius. Plasma (nor)adrenalin aliquots were assayed by reversed phase high performance liquid chromatography (RP-HPLC) with fluorimetric detection after solvent extraction and derivatization with 1,2-diphenylethylenediamine [17] with normal ranges for adrenalin and noradrenalin in awake healthy humans of <120 pg/mL and 100-600 pg/mL, respectively. Plasma cortisol was measured using a luminescence enzyme immunoassay with a normal range for awake healthy humans of 200-800 nmol/L at 9:00 AM (Immulite 2000, Siemens Healthcare Diagnostics, USA).

Statistical analysis

A power analysis with an overall $\alpha=0.05$ (two-tailed) and $\beta=0.20$ and an expected small correlation ($r=0.20$) between the changes in pain scores and changes in cortisol, adrenalin and noradrenalin plasma levels showed that at least 58 patients were needed. In this sub-study, 59 patients were randomly selected via the SPSS statistical package from the 117 patients included in the above-mentioned randomized controlled trial.

As we tested three times for significance (cortisol, adrenalin, and noradrenalin), we adjusted the α -level accordingly ($0.05/3=0.01666$).

Descriptive statistics of demographic and clinical variables are expressed as frequencies with percentages (%) or median with interquartile range (IQR). Statistical analyses were performed using IBM SPSS Statistics (version 19.0 for Windows; SPSS, Chicago, IL) and SAS (version 9.2, Cary, NC). To eliminate the potential influence of outliers and non-normal distribution of the data, robust regression analysis (procedure MM Estimation)[18] was performed in SAS to test the association between changes in NRS

scores (“during the procedure” compared to “before the procedure”) and change in log transformed values of cortisol, adrenalin, and noradrenalin plasma levels (“after the procedure” compared to “before the procedure”). This analysis was repeated adjusting for sex (male coded “0”, female coded “1”), age in years, dose of morphine (2.5 mg coded “0” or 7.5 mg code “1”), cardiopulmonary bypass with steroids (coded “0”) or without steroids (coded “1”), and the person who scored the pain (patient coded “0”, nurse coded “1”). Stress hormone plasma levels before the procedure were covariates in both analyses. Differences were considered significant at a *P* level of < 0.05 (two-tailed).

Results

Patients and data

Baseline demographic, intraoperative and procedural characteristics of patients are described in Table 1. The median age was 73 years and males predominated (n=46, 78%). Unacceptable pain during the procedure (NRS ≥ 4) was reported by 26 patients (44%).

Cortisol, adrenalin, and noradrenalin plasma levels before and after the potentially painful procedure

Median plasma levels of cortisol, adrenalin, and noradrenalin before the procedure were 161 nmol/L [IQR 51 to 572], 184 pg/mL [IQR 91 to 406], and 590 pg/mL [IQR 386 to 828], respectively. Values after the procedure were not statistically significantly different from before the procedure (211 nmol/L [IQR 61 to 677], 172 pg/mL [IQR 78 to 323], and 592 [IQR 402 to 891], respectively, *p*=0.26, 0.24, and 0.19).

Median cortisol and noradrenalin plasma levels before the procedure of patients who had been on conventional cardiopulmonary bypass CPB (using steroids) were significantly lower than those of patients who had been on minimal extracorporeal circulation (MECC) without the use of steroids (cortisol 88 nmol/L [IQR 43 to 180] vs. 737 nmol/L [IQR 337 to 1122] (*p*<0.001) and noradrenalin 520 pg/mL [IQR 335 to 705] vs. 810 pg/mL [IQR 521 to 1226] (*p*<0.01), respectively). Median adrenalin levels before the procedure were not statistically significantly different between the extracorporeal circuits (168 pg/mL [IQR 89 to 357] and 261 pg/mL [IQR 97 to 460], respectively, *p*=0.25).

Five patients had outlying plasma levels of adrenalin (up to 20 ng/mL) both before and after the procedure. This could not be explained by inotropes, previous use of monoamine oxidase- inhibitors, or otherwise. These patients were not hypertensive during the procedure.

Robust regression analysis of the relation between procedural related pain levels and changes in cortisol, adrenalin, and noradrenalin levels

The absolute changes of cortisol, adrenalin, and noradrenalin plasma levels “after” compared to “before” the procedure are shown in the scatter plots (Figure 1). The change in NRS “during” compared to “before” the procedure is shown on the x-axis. Robust regression analysis did not show a significant association between pain levels and a change in log transformed plasma levels of cortisol, adrenalin, and noradrenalin during the procedure with adjusted stress hormone levels before the procedure

Table 1: Patient characteristics (N=59)

Male, n (%)	46 (78%)
Age, years, median [IQR]	73 [66 to 77]
BMI, kg/m ² , median [IQR]	27 [24 to 29]
EuroSCORE, median [IQR]	7 [4 to 9]
CABG and valve surgery	21 (35%)
Aortic surgery	16 (27%)
CABG	11 (19%)
Valve surgery	11 (19%)
Preoperative steroids, n (%)	7 (12%)
Conventional CBP/ MECC, n (%)	38/21 (64/36%)
NRS $\geq$ 4	
Before the procedure	7 (12%)
During the procedure	26 (44%)
After the procedure	9 (15%)

Abbreviations: IQR=interquartile range, CABG= coronary artery bypass graft, EuroSCORE= European System for Cardiac Operative Risk Evaluation, CBP= Cardiopulmonary Bypass, MECC= Minimal extracorporeal circulation, NRS= numeric rating scale

Table 2: Robust regression model of the change of plasma cortisol, adrenalin, and noradrenalin levels in relation to the change in pain scores during the painful procedure as outcome

	Model 1			Model 2		
	Estimate ^c	95% CI	P value	Estimate ^c	95% CI	P value
Δ Cortisol^{a,b}	0.95	-2.40 to 4.29	0.58	1.88	-1.72 to 5.47	0.31
Δ Adrenalin^a	0.89	-1.25 to 3.02	0.42	1.92	-0.58 to 4.42	0.13
Δ Noradrenalin^a	0.41	-1.10 to 1.91	0.59	0.90	-1.40 to 3.21	0.44

Model 1: adjusted for cortisol/adrenalin/noradrenalin value before the procedure

Model 2: adjusted for cortisol/adrenalin/noradrenalin value before the procedure, sex (0=male, 1=female), age in years, 2.5 (coded 0) or 7.5 mg of morphine (coded 1), cardiopulmonary bypass with steroids (coded 0) or without steroids (coded 1), pain scored by patient (coded 0) or nurse (coded 1)

Δ cortisol/adrenalin/noradrenalin = change after the procedure compared to before the procedure

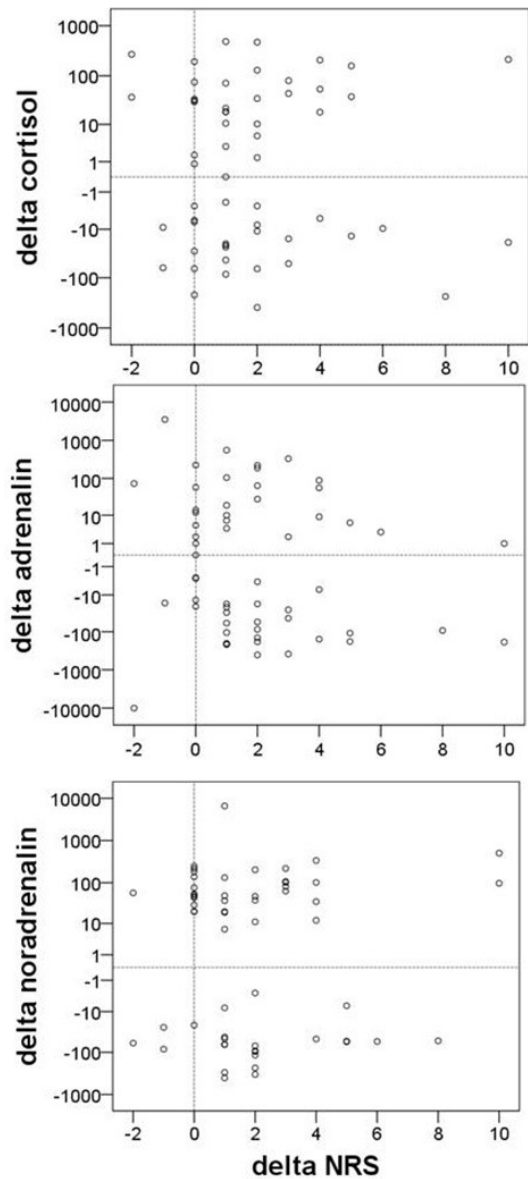
^a log transformed values were used

^b 2 values missing

^c estimates are unstandardized regression estimates

Abbreviations: CI; confidence interval

Figure 1: Change in plasma cortisol, adrenalin and noradrenalin levels versus the change in pain scores during an inevitable procedure.



delta cortisol/adrenalin/noradrenalin= change after the procedure compared to before the procedure in nmol/L(cortisol) or pg/mL ((nor)adrenalin); delta NRS (Numeric Rating Scale) = change in pain score during the procedure compared to before the procedure

(model 1, Table 2). After adjusting for stress hormone levels before the procedure, sex, age, morphine dosage, cardiopulmonary bypass with or without steroids, and person who scored the pain increased the unstandardized regression estimated, but not statistically significantly, with respective estimates of changes in cortisol ($B=1.88$ [-1.72 to 5.47]), adrenalin ($B=1.92$ [-0.58 to 4.42]), and noradrenalin ($B=0.90$ [-1.40 to 3.21]) (model 2, Table 2).

Discussion

Objective parameters to measure pain are essential to diagnose and treat pain in patients who are not able to report pain themselves. In this study, we correlated the change in plasma stress hormones before and after an inevitable potentially painful procedure with pain levels reported by patients during this procedure. This study shows that cortisol, adrenalin, and noradrenalin plasma levels were not significantly associated with procedural pain in ICU patients after cardiac surgery.

A sympathetic stress response with systemic release of stress hormones triggered by pain is widely suggested in literature [8,9]. However, studies in humans exploring the association between pain levels and stress hormones are rare. Ledowski et al [19] explored the association between postoperative pain and plasma (nor)adrenalin levels in 85 patients in the post-anesthetic care unit after minor surgery. Patients were repeatedly asked to rate their pain using the NRS. Plasma levels of (nor)adrenalin in samples taken each time the patient reported a decrease in pain and at discharge from the recovery room, did not correlate with NRS scores. The authors concluded that the severity of postoperative pain was not associated with the degree of sympathetic stress response after surgery. These authors studied postoperative patients without additional painful stimuli. From our own study, studying the stress response related to a potentially painful procedure, we draw the conclusion that even an increase in pain is not associated with an increase in levels of plasma cortisol and catecholamines.

Myles et al [20] found a significant association between serum levels of cortisol and pain levels at rest in ICU-patients 48 hours after cardiac surgery. The authors also compared cortisol levels between two regimens of postoperative analgesia: either continuous intravenous morphine adjusted by the nurse, or morphine via patient controlled analgesia. Cortisol levels did not differ between the analgesia regimens. It may well be that within 24 hours after surgery, the mixed effects of tissue trauma, surgical stress, hypothermia during surgery, etc. interfere with the effects of postoperative pain on cortisol and catecholamine levels. Furthermore, in the current study, the interval between measurements may have been too short to detect changes in cortisol levels, as procedural pain and not pain in rest was examined.

In a randomized trial comparing patients in the ICU after CABG, Hall et al [21] found an indication for higher levels of adrenalin, but not of noradrenalin and cortisol, in patients who had more pain. However, the randomization was aimed at different sedation levels, complicating pain measurement.

To our knowledge, only one study related pain during a short painful procedure to the change in stress hormones before and after a procedure. This was a study by Saarenmaa et al [22] in neonates, who received either alfentanil or placebo before tracheal suctioning. Neonates receiving alfentanil had significantly lower behavioural pain scores and significantly lower adrenalin levels; and there was a trend towards

lower levels of noradrenalin after the procedure. This study in neonates had to use subjective measurements of pain, however, and they had not undergone major surgery. Using the gold standard for pain measurement, that is: self-report, our study could not confirm an association between stress hormone levels and pain.

The patients included in this study participated in a clinical trial in which we evaluated pain levels around a procedure involving turning of the patient either or not combined with the removal of chest tubes. This setting provided a good opportunity to study patient's self-reported procedural pain in relation to stress hormones. Limitations of this study include the fact that previously used medication (steroids) were not uniform and that the type of surgery, surgical procedure, anesthesia, and type of cardiopulmonary bypass (with or without the use of steroids) differed. However, the absence of an association between pain and cortisol, adrenalin, or noradrenalin levels in these patients, reflecting the average population in our ICU, would render these markers not useful for diagnosing pain.

We conclude that plasma stress hormone levels are not suitable to replace or even support self-reported procedural pain. Moreover, the absence of change in or even a decrease in stress hormones during a painful procedure cannot be seen as a guarantee for the absence of pain. It would be worthwhile to explore other potential surrogate markers to measure pain in patients who cannot communicate. Plasma levels of cortisol, adrenalin, and noradrenalin are not suitable for measurement of procedural pain neither as an endpoint for therapeutic studies.

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