Relationship between blood remifentanil concentration and stress hormone levels during pneumoperitoneum in patients undergoing laparoscopic cholecystectomy

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Abstract. – OBJECTIVE: The effect of remifentanil on stress response to surgery is unclear. However, there are not clinical studies investigating the relationship between blood remifentanil concentrations and stress hormones. Therefore, the aim of the present study was to assess the association between blood remifentanil concentrations measured after pneumoperitoneum and cortisol (CORT) or prolactin (PRL) ratio (intraoperative/preoperative value), in patients undergoing laparoscopic cholecystectomy.

PATIENTS AND METHODS: Patients did not receive any pre-anesthetic medication. Anesthesia induction was standardized. Anesthesia maintenance was performed with inhaled sevoflurane at age-adjusted 1.0 minimum alveolar concentration and intravenous remifentanil at infusion rate ranging from 0.1 to 0.4 mcg/kg/min. Blood samples were withdrawn before anesthesia induction and 5 min after achieving a pneumoperitoneum pressure of 12 mmHg. Correlation analyses were performed to evaluate the relationship between measured blood remifentanil concentrations, CORT or PRL ratio (intraoperative/preoperative value) and remifentanil dose delivered by the pump.

RESULTS: A significant inverse correlation was found between CORT ratio and measured blood remifentanil concentration (p=0.03) or planned remifentanil dose (p=0.04). No correlations were found between blood remifentanil concentration and PRL ratio (p=0.83).

CONCLUSIONS: Our data suggest that the CORT response to surgical stress is more efficiently counteracted by increased blood remifentanil concentration.

Key Words

Remifentanil, Cortisol, Prolactin, Stress, Pneumoperitoneum, General anesthesia.

Introduction

It has been demonstrated that laparoscopic surgery may produce a moderate stress response although this approach is considered as minimally invasive[1]. Intravenously administered remifentanil, combined with general anesthetics, provides stable hemodynamic during laparoscopic surgery[2,3]. Previous studies regarding remifentanil effect on stress response in laparoscopic surgery are conflicting. Some authors reported remifentanil dose-independent stress hormone variations in response to pneumoperitoneum, whereas other studies demonstrated reduced hormone release only at high doses[1,4]. In this regard, it may be suggested that remifentanil, as other opioids, could mitigate stress response activation in a dose-dependent manner[5,6]. Currently, there are not clinical studies investigating the relationship between blood concentrations of remifentanil and stress hormones during surgery. In this scenario, the aim of the present study was to assess the association between blood remifentanil concentration measured after pneumoperitoneum and stress hormones (cortisol and prolactin) ratio (intraoperative/preoperative value), in patients undergoing laparoscopic cholecystectomy. Also, we investigated the relationship between blood remifentanil concentration and the remifentanil dose delivered by pump.

Patients and Methods

After local Ethics Committee approval and patients' informed consent, 30 adult patients with an American Society of Anesthesiologists phy-

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sical status I, scheduled for laparoscopic cholecystectomy, were recruited. Exclusion criteria were: age >70 years; Body Mass Index >30 kg/m^2; chronic use of medications. In the pre-anesthetic room, blood samples were collected to measure the baseline levels of cortisol (CORT) and prolactin (PRL). Patients did not receive any pre-anesthetic medication, whereas anesthesia induction was standardized using propofol 2 mg/kg, remifentanil 0.25 mcg/kg/min and cisatracurium 0.15 mg/kg. Anesthesia maintenance was performed with inhaled sevoflurane at 1.0 age-adjusted minimum alveolar concentration and intravenous remifentanil at infusion rate ranging from 0.1 to 0.4 mcg/kg/min, to maintain non-invasive mean arterial pressure and heart rate within a range of 20% more or less than the basal values. Intravenous paracetamol 1 g and morphine 0.06 mg/kg were administered to patients and local anesthetic infiltration (ropivacaine 4.75%) of trocar insertion sites was performed at the end of surgery, accordingly to local multimodal analgesia protocol. The same surgeon performed all the procedures by using Hasson's open access technique. Intraoperative blood samples were collected 5 min after achieving a pneumoperitoneum pressure of 12 mmHg (carbon-dioxide flow rate of 1.2 L/min) to assess both remifentanil blood concentration and intraoperative levels of stress hormones. Blood samples were stored in capped vacutainer tubes at low temperatures, -20°C and -80°C for stress hormone and remifentanil evaluations respectively. Samples were analyzed within a maximum period of 90 days from surgery. To prevent remifentanil degradation, collection tubes containing EDTA whole blood were placed in ice water immediately after sampling. CORT and PRL serum levels were measured by using a chemiluminescence assay developed for the Abbott Architect i1000sr immunologic analyzer (Abbott Laboratories, Chicago, IL, USA). Remifentanil concentrations were measured via a laboratory-developed assay, according to the following protocol. Briefly, 1 mL aliquots of samples, containing an internal standard (alfentanil), were mixed with 2 ml acetonitrile. After centrifugation, the supernatant was evaporated and reconstituted with 1 ml buffer phosphate 0.1 M at pH=8,5. A liquid/liquid extraction with dichloromethane was performed. After evaporation of the solvent, the dry extracts were reconstituted with 25 mL ethyl acetate and analyzed by GC/MS (gas chromatography/mass spectrometry) technology. A focus GC couplet with DSQ operative in electron impact mode (70eV) was employed. An Equity 5 capillary column, 30 m·0.25 mm·0.25 mm film thickness, was used for 1 min isotherm at 70°C with further 15°C/min linear increment up to 290°C (5 min final isotherm). The acquisition in selected ion monitoring mode was performed by choosing 3 ions for remifentanil (m/z 227-303-319), and internal standard (alfentanil m/z 289-268-222). Bispectral index (BIS; BIS Vista™ monitoring system, Aspect Medical System Inc., Norwood, MA, USA) and cardiovascular parameters (non-invasive blood pressure and heart rate) were recorded throughout anesthesia.

Statistical Analysis

Correlation analyses were performed to assess the relationship between measured blood remifentanil concentration, planned remifentanil dose (delivered by pump) and CORT or PRL ratio (intraoperative/preoperative value) and between planned and measured remifentanil concentration. $p<0.05$ was considered statistically significant. All the analyses were performed using the Statistical Version 10.0 software (StatSoft, Tulsa, OK, USA).

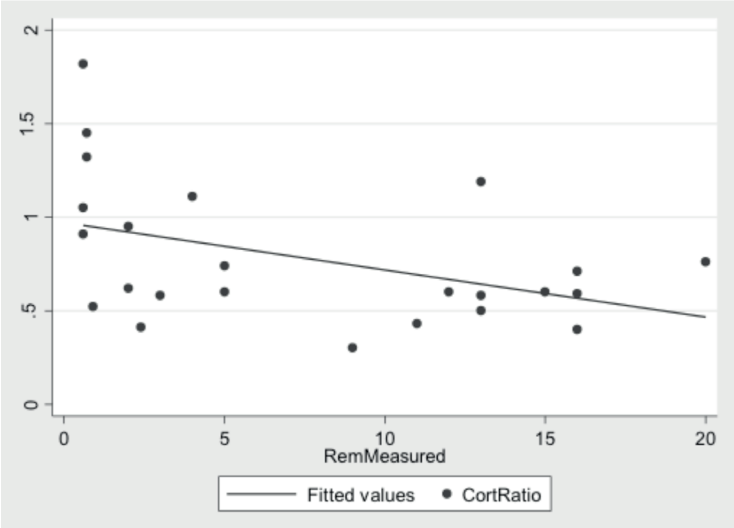
Results

Out of the 30 patients originally enrolled in the study, only 24 patients (mean age: 48.7±12.9 years; gender (M/F): 11/13; weight: 73.6±12.4 kg) with completed case report form were included in the final analysis (Table I). 6 patients were excluded for the following reasons: one patient did meet the exclusion criteria; another patient due to clotted blood withdrawal and 4 patients due to the abnormal values of remifentanil blood concentrations (i.e. out of validated range, 0.1-20 ng/ml). A significant inverse correlation was found between CORT ratio and measured blood remifentanil

Table I. Values are calculated from five consecutive readings, each one registered every minute after establishment of pneumoperitoneum.

	Patients (n=24)
BIS value	43.2±6.5
Heart rate	63.8±8.8
Systolic pressure	109±8.3
Diastolic pressure	66±5.1

Figure 1. Scatterplot showing an inverse correlation between remifentanil measured concentration and CORT ratio.



concentration (Pearson's r=-0.45; p=0.03) or planned remifentanil dose (Pearson's r=-0.42; p=0.04) (Figure 1). On the other hand, no correlation was found between blood remifentanil concentration and PRL ratio (Pearson's r=-0.05; p=0.83). Also, we observed a significant correlation between planned remifentanil dose (delivered by pump) and blood remifentanil concentration (Pearson's r=0.72; p=0.0001).

Discussion

The main result of this study was that CORT ratio (intraoperative/preoperative blood levels) was lower in patients showing higher remifentanil blood concentrations, thus indicating that surgical stress was counteracted more efficiently. Previous studies regarding the effect of remifentanil on stress response in laparoscopic surgery are conflicting, including not clear evidence on dose-dependent hormonal response to pneumoperitoneum[1-4]. It is essential to blunt stress hormone secretion to prevent adverse postoperative events, including cognitive and psychological complications[7-9]. The physiological feedback mechanism that leads to the inhibition of adrenocorticotropic hormone synthesis due to increased CORT concentration is disrupted during surgery[6]. Therefore, the anesthetic drugs are essential to prevent an excessive hypothalamic-pituitary-adrenal (HPA) axis activation in response to surgical trauma. From this work, it emerges that remifentanil can mitigate cortisol response in a dose-dependent manner. On the other hand, most of the anesthetic drugs, including opioids, have been found to stimulate PRL release during anaesthesia[10]. It has been demonstrated that patients undergoing endovascular abdominal aortic aneurysm experienced less pain but showed a more intense PRL response in the remifentanil group when compared to the midazolam-fentanyl group[11]. However, in our study, no relationship was found between blood remifentanil concentration and PRL release. Our findings also show a significant correlation between remifentanil blood concentration and target infusion concentration, albeit the methodology used to assess remifentanil blood level needs additional validation data to meet the Food and Drug Administration requirements for pharmacokinetic studies.

Conclusions

CORT response to surgical stress seemed to be more efficiently counteracted by increased blood remifentanil concentration in patients undergoing laparoscopic cholecystectomy. Despite the small size of the analyzed sample, this study may contribute to understanding the complex interaction between the effects of surgical stimulus and remifentanil on stress response.

Conflict of Interest

The authors declared no conflict of interest.

References

1) Watanabe K, Kashiwagi K, Kamiyama T, Yamamoto M, Fukunaga M, Inada E, Kamiyama Y. High-dose remifentanil suppresses stress response associated with pneumoperitoneum during laparoscopic colectomy. J Anesth 2014; 28: 334-340.
2) Aceto P, Perilli V, Lai C, Sacco T, Modesti C, Luca E, De Santis P, Sollazzi L, Antonelli M. Minimum alveolar concentration threshold of sevoflurane for postoperative dream recall. Minerva Anestesiol 2015; 81: 1201-1209.
3) Aceto P, Lai C, Perilli V, Dello Russo C, Federico B, Navarra P, Proietti R, Sollazzi L. Stress-related biomarkers of dream recall and implicit memory under anaesthesia. Anaesthesia 2013; 68: 1141-1147.
4) Myre K, Raeder J, Rostrup M, Buanes T, Stokland O. Catecholamine release during laparoscopic fundoplication with high and low doses of remifentanil. Acta Anaesthesiol Scand 2003; 47: 267-273.
5) Desborough JP. The stress response to trauma and surgery. Br J Anaesth 2000; 85: 109-117.
6) Aceto P, Lai C, Dello Russo C, Perilli V, Navarra P, Sollazzi L. Stress response to surgery, anesthetics role and impact on cognition. J Anesth Clin Res 2015; 6: 539.
7) Aceto P, Perilli V, Lai C, Sacco T, Ancona P, Gasperin E, Sollazzi L. Update on post-traumatic stress syndrome after anesthesia. Eur Rev Med Pharmacol Sci 2013; 17: 1730-1737.
8) Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Montanini S, Danelli G, Nuzzi M, Mentegazzi F, Torri G, Martani C, Spreafico E, Fierro G, Pugliese F, De Cosmo G, Aceto P, Servillo G, Monaco F. Monitoring cerebral oxygen saturation in elderly patients undergoing general abdominal surgery: a prospective cohort study. Eur J Anaesthesiol 2007; 24: 59-65.
9) Zhi XL, Li CY, Xue M, Hu Y, Ji Y. Changes in cognitive function due to combined propofol and remifentanil treatment are associated with phosphorylation of Tau in the hippocampus, abnormal total water and calcium contents of the brain, and elevated serum S100β levels. Eur Rev Med Pharmacol Sci 2016; 20: 2156-2162.
10) Mujagic Z, Cicko E, Verag-Brozovic V, Prašo M. Serum level of cortisol and prolactin in patients treated under total intravenous anesthesia with propofol-fentanyl and under balanced anesthesia with isoflurane-fentanyl. Cent Eur J Med 2008; 3: 459-463.
11) Barbieri A, Giuliani E, Genazzani A, Baraldi E, Ferrari A, D'Amico R, Coppi G. Analgesia and endocrine surgical stress: effect of two analgesia protocols on cortisol and prolactin levels during abdominal aortic aneurysm endovascular repair. Neuro Endocrinol Lett 2011; 32: 526-529.