Combination of remifentanil with isoflurane or propofol: effect on the surgical stress response

S. Azemati, M. Savai, M. B. Khosravi, E. Allahyari and F. Jahanmiri

Abstract: Background: Hormonal and metabolic changes following surgery are markers of the stress response to surgery. We compared hemodynamic parameters and stress response markers (glucose, cortisol, and C-reactive protein) in two groups of patients receiving either propofol or isoflurane combined with remifentanil for maintenance of anesthesia.

Methods: We randomly assigned 100 women (ASA I-II) scheduled for diagnostic gynecologic laparoscopy to receive either isoflurane (0.8% end-tidal) or propofol (100 mg/kg/min) in addition to remifentanil (0.25 mg/kg/min). Heart rate and mean arterial pressure were recorded after induction, 30 seconds after intubation, at four time points after incision, and 60 min after surgery. Serum C-reactive protein, cortisol and glucose concentrations were measured before induction, one hour after incision, and one hour after surgery.

Results: After induction, heart rate decreased significantly from baseline in both groups, and remained below baseline until the end of surgery. Mean arterial pressure also decreased significantly in both groups. C-reactive protein levels were not significantly different between groups. In the propofol group, cortisol decreased significantly one hour after incision, but increased in the isoflurane group. Glucose increased significantly in both groups, but was significantly lower in the propofol group one hour after the incision and one hour after surgery.

Conclusion: An anesthetic regimen combining propofol and remifentanil attenuates two indicators of the stress response more efficiently than a isoflurane – remifentanil combination.

Key words: Anesthesia; propofol; isoflurane; remifentanil; surgery; glucose; cortisol; stress response.

Introduction

Surgical stress results in metabolic and endocrine responses. The combination of autonomic, hormonal and catabolic changes that accompany surgery has been called the surgical stress response (1). This is part of a wide range of neuroendocrine, immunological and hematological changes which follow injury or trauma, called systemic reaction to injury (2). Sympathetic nervous system activation results in catecholamine secretion from the adrenal medulla and in the release of noradrenaline that is responsible for the resultant increase in blood pressure and tachycardia (2).

In response to surgical injury, the secretion of anterior pituitary hormones such as the adrenocorticotropic hormone (ACTH) increases. This leads to a rapid increase in cortisol secretion (2), which in turn promotes glycogenolysis and gluconeogenesis. As a result, blood glucose concentration increases. The glucose response to surgical injury is one of the indicators of the stress response. Surgical trauma also elicits the synthesis and release of acute phase proteins such as C-reactive protein (CRP) (3).

Much interest has centered on modifying the stress response in order to improve the potential benefits of surgery (2). Some reports have compared the effect of propofol combined with an opiate on the stress response and the effect of isoflurane alone, but few studies have compared the stress response when propofol or isoflurane are combined with remifentanil (4). We therefore compared hemodynamic parameters, CRP, cortisol and glucose as indicators of stress response in patients who received propofol or isoflurane, two widely-used anesthetic medications, in combination with remifentanil, a potent µ-opiate receptor agonist.

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Sources of support: This study was supported by Shiraz Anesthesiology and Critical Care Research Center, Department of Anesthesia affiliated to Shiraz University of Medical Sciences, Shiraz, Iran.

© Acta Anaesthesiologica Belgica, 2013, 64, n° 1
Methods

Following approval by the Ethics Committee of the Shiraz University of Medical Sciences, and written informed consent of participants, 100 women, with an ASA physical status I or II and aged between 16 and 50 years, were recruited for this prospective, randomized, semi-open study. All were scheduled for a diagnostic gynecologic laparoscopy. The attending anesthetist and anesthesia technician were aware of the allocated treatment, but the nurse who collected the blood samples, the anesthesia technician who recorded the hemodynamic data, the patients and the laboratory technicians were not.

Patients with cardiovascular, renal, liver, endocrine or hormonal disease, a body mass index (BMI) equal to or higher than 30 kg/m², using any cardia or hormonal medication, or having hypersensitivity to the anesthetic agents used in this study were excluded. Recruited patients were randomized using a computer-generated random list. Each patient was attributed a sealed envelope prescribing to receive either propofol (Group P, n = 50) or isoflurane (Group I, n = 50) for anaesthesia maintenance.

None of the patients received any premedication. Upon arrival in the operating room, heart rate (HR) and mean arterial pressure (MAP) (automated non-invasive monitor, Datex-Ohmeda Helsinki, Finland) were recorded, and this recording served as the baseline value (T0). After the insertion of an intravenous catheter, the nurse obtained blood samples for the baseline measurements of CRP, cortisol and glucose levels (P0).

Following the intravenous infusion of a fixed volume of a Ringer lactate solution (5 mL/kg), and a pre-oxygenation with 6 L/min of oxygen through a face mask, patients received intravenous midazolam (0.03 mg/kg) and remifentanil (1 mg/kg). Anesthesia was induced using intravenous sodium thiopental (4 mg/kg) and atracurium (0.5 mg/kg) to facilitate tracheal intubation. After intubation, the lungs were mechanically ventilated using an oxygen-air mixture. Ventilation was adjusted to keep the end-tidal CO₂ (ETCO₂) partial pressure between 32 and 35 mmHg. To maintain anesthesia, patients in Group I received isoflurane at a constant 0.8% end-tidal concentration, and patients in Group P received propofol at a constant rate of 100 mg/kg/min. Both groups also received a remifentanil infusion at a rate of 0.25 mg/kg/min. This rate was adjusted every 5 minutes to maintain MAP and HR within a 20% range above or below the baseline value. Body temperature was maintained within normal limits using a warming device. Throughout surgery, patients were placed in a 10° head-down position. For laparoscopy, CO₂ was insufflated to obtain a maximal 14 mmHg intra-abdominal pressure. At the end of surgery, all anesthetic agents were discontinued. To reverse neuromuscular blockade, neostigmine 0.05 mg/kg and atropine 0.02 mg/kg were administered. When acceptable spontaneous ventilation was restored, the endotracheal tube was removed and the patient was transferred to the post-anesthesia care unit.

Heart rate and MAP were recorded after induction of anesthesia (T1), 30 seconds after intubation (T2), 1, 15, 30 and 60 minutes after surgical incision (T3-T6), and 60 minutes after the end of surgery (T7). Blood samples for CRP, cortisol and glucose level measurements were collected at three time points: immediately after inserting the intravenous access (baseline value, P0), 60 minutes after surgical incision (P1), and 60 minutes after the end of surgery (P2).

Blood samples for CRP, cortisol and glucose determinations were centrifuged at 3000 rpm for 5 minutes to obtain clear serum. For the first two analyses, samples were frozen at -20 °C for up to 2 weeks. C-reactive protein was determined by a latex agglutination test, which allows a qualitative and semi-quantitative dosage (Humatex CRP, Human Gesellschaft für Biochemie und Diagnostica, Wiesbaden, Germany). The results are reported as negative, 6 or 12 µg/L. Cortisol was measured by enzyme-linked immuno-analysis with a RADIM automatic microplate reader (KS18EW, RADIM Iberica, Barcelona, Spain). Glucose was measured with the Elitech Glucose Pap SL kit (SEPPIM, Sees, France).

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Science (SPSS v. 15) for MS Windows®. Sample size was based on a pilot study including 20 patients where cortisol level was measured at the equivalent of time P1. The mean cortisol level in that group of patients was 20.35 ± 14.56 µg/dL (mean ± SD). Considering a relevant difference of 10 µg/dL, and α threshold of 0.05, we calculated that 50 patients in each group would lead to a power higher than 80%. Data were expressed as mean ± SD or counts (%), unless otherwise indicated. Data were compared to their baseline value and between groups using a mixed-design ANOVA, and least significant difference (LSD) test for post hoc comparisons. For CRP values, the proportion of patients with changes (increase or de-
remifentanil with isoflurane or propofol and surgical stress response

Results

Groups were comparable in terms of age (30 ± 5 and 30 ± 7 years in Group I and P, respectively), weight (66 ± 10 and 66 ± 10 kg, respectively) or duration of the surgical procedure (40 ± 13 and 42 ± 12 minutes, respectively). Baseline HR and MAP values did not show any statistically significant differences between groups (Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic characteristics and duration of surgery in 100 women with ASA physical status I or II who underwent diagnostic gynecologic laparoscopy in Shiraz, Iran</th>
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</thead>
<tbody>
<tr>
<td></td>
<td><strong>Group I (n = 50)</strong></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>29.8 ± 5.3</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.3 ± 10.7</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>40 ± 13</td>
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</table>

Group I: Isoflurane + remifentanil.
Group P: Propofol + remifentanil.
Values are expressed as mean ± SD.

Heart rate

The baseline HR was 93 ± 13 in Group I and 93 ± 13 in group P. It decreased significantly (78 ± 12 and 82 ± 13) after induction of anesthesia (P < 0.001), and this decrease persisted up to the end of the study period in group I (P < 0.05). In Group P, heart rate showed a significant decrease (P < 0.001), except for the recording performed 30 seconds after intubation (T2). The evolution of heart rate during the study period in both groups was parallel (Fig. 1).

Mean Arterial Pressure

MAP decreased significantly after induction of anesthesia in both groups and remained lower than baseline throughout the study period. These values were lower in group I than in group P but this intergroup difference was only significant 1 minute after surgical incision (T3) (P < 0.05) (Fig. 2).

Inflammatory response

Before induction of anesthesia, 43 patients (86%) in group I and 44 (88%) in group P had negative CRP values. The CRP value did not show any change in 45 patients in each group (90%). It decreased in 3% of Group I patients and 4% of Group P patients. It raised in 2% of Group I patients and 1% of Group P patients, but the difference was not statistically significant.
groups of patients having received two different general anesthesia regimens, isoflurane or propofol, while both receiving remifentanil to insure anti-nociception.

**Hemodynamic indicators**

Isoflurane alone, through the baroreceptor reflex, causes tachycardia, whereas sevoflurane or propofol have much less marked effects on HR (7, 8). In most studies that compared propofol with the volatile anesthetic agent isoflurane (9, 10, 11) and sevoflurane (10, 12, 13), average HR in the propofol group was lower than in the volatile agent group. In the present study, we used the same dose of remifentanil to maintain anesthesia in women given isoflurane or propofol, and found slightly increased HR in our propofol group but with a global evolution through the course of surgery that was parallel to the one of our isoflurane group. Our hemodynamic findings are similar to those of Ledowski et al. (14) and Fredman et al. (15), who compared total intravenous anesthesia with propofol-remifentanil, and balanced anesthesia with sevoflurane-remifentanil. They concluded that HR was lower in the sevoflurane group. In a study by Wilhelm et al. with methods similar to ours, HR was lower in the isoflurane group (4). In both their study and the present one, the cause for lower HR appears to be the use of remifentanil.

**Endocrine response**

**Cortisol**

Cortisol levels at baseline (P0) were similar in both groups (25.5 ± 14 µg/dL in Group I and 25.2 ± 15 in Group P). In Group I, cortisol increased one hour after incision (P1) and one hour after the end of surgery (P2) (26.9 ± 14 and 27.9 ± 16, respectively), but neither of these changes was statistically significant (P > 0.05). In group P, cortisol significantly decreased at P1 (P < 0.02). At P2, it was still lower than the baseline value, although the difference was not significant (Fig. 3).

**Glucose**

Baseline glucose was 82.9 ± 12 mg/dL in Group I and 82.8 ± 1 mg/dL in Group P. In both groups, serum glucose increased significantly (p < 0.05). Glucose in group P was significantly lower than in group I at P1 (P < 0.02) and P2 (P < 0.001) (Fig. 4).

**DISCUSSION**

The stress response to surgery is characterized by the increased release of catabolic and immunosuppressive pituitary hormones (2). This response may be influenced by several factors such as severity and duration of the surgical trauma, surgical technique, patient age, or anesthetic technique (5, 6). We compared stress responses between two
nerve endings (2). Some anesthetic agents can blunt this secretion. In our study, MAP decreased significantly after the induction of anesthesia and remained lower throughout the study period in both groups. This result is similar to that of Wilhelm et al. (4), who reported a decrease in BP with remifentanil-isoflurane (-17%) and with remifentanil-propofol (-13%), and a higher blood pressure (5-8 mmHg) with remifentanil-propofol five minutes after intubation. Our observations are similar to the findings by Ledowski et al. (14) that there is no difference in MAP between patients receiving propofol or sevoflurane in combination with remifentanil (0.25 mg/kg/min). Contrarily, Ozkan et al. (10) found that blood pressure decreased significantly in their total intravenous anesthesia group after induction of general anesthesia, whereas it increased in patients given isoflurane or sevoflurane. Those discrepancies may be due to several factors, including, among others, intravascular volume status, dosages, different drug combinations, and patient population.

C-reactive protein

We used a semi-quantitative method to measure CRP, and found no significant difference in either group compared to baseline. The acute phase reaction and serum concentration of CRP reflect the amount of tissue damage (16). Because laparoscopic surgery causes less tissue injury than conventional procedures, the increase in biochemical markers of inflammation such as CRP is not as great (2, 17). Some reports have compared stress and inflammatory hormone release between laparoscopy and laparotomy. Yuen et al. (18) compared metabolic and inflammatory responses after laparoscopic and abdominal hysterectomy, and found lower stress responses in the former. This result contrasts with those of Ellstrom et al. (19), who reported no significant difference in CRP and cortisol concentration. Joris et al. (20) and Kristiansson et al. (3) reported lower values of plasma glucose and CRP in laparoscopic compared to laparotomic cholecystectomy. In our patients who underwent gynecologic laparoscopy, and assuming that tissue damage is lower in this surgical procedure, the concentration of CRP remained so low that neither isoflurane nor propofol caused any changes.

Cortisol and glucose

We observed a significant decrease in cortisol in the propofol group one hour after incision compared to baseline and compared to the isoflurane group. Cortisol remained lower in the propofol group than in the isoflurane group one hour after incision and one hour after the end of surgery. A surgical procedure activates the hypothalamic pituitary and sympathetic systems, increasing the release of stress hormones such as cortisol and catecholamines (2). Cortisol promotes glycogenolysis and gluconeogenesis, and activates glucose utilization, resulting in hyperglycemia. Factors that can influence the endocrine metabolic response include the severity of surgical trauma and tissue damage, patient age, gender, duration of the procedure, and surgical and anesthetic technique (5, 6). Glucose increased in both groups of women in the present study, although the increase in the propofol group was significantly lower than in the isoflurane group.

Other studies have used different drugs for total intravenous anesthesia, and different volatile anesthetic agents. They reported variable results. Demirbilek et al. compared endocrine responses in patients given remifentanil-propofol or alfentanil-propofol for abdominal hysterectomy (21). They found no significant differences in plasma cortisol or glucose. Monk et al., who used propofol (50 mg/kg.min) and alfentanil for retro-pubic dissection surgery, reported a significant increase in plasma cortisol (22). Others have used higher doses of alfentanil with propofol, and found increased (23) and decreased (24) cortisol levels. Castillo et al. compared cortisol levels in two groups of balanced anesthesia with isoflurane and propofol infusion, and reported a higher cortisol concentration in the latter group (25). Marana et al. investigated the effect of propofol with remifentanil as compared to sevoflurane alone on hormone levels in patients who underwent laparoscopic surgery for benign ovarian cyst (26, 27). They found higher levels of norepinephrine, epinephrine, growth hormone, ACTH and cortisol in the total intravenous anesthesia group. Another study reported similar peri-operative cortisol responses with propofol-remifentanil or sevoflurane-nitrous oxide (13). Brockmann et al., who used propofol at 4 mg/kg.h in conjunction with remifentanil or sufentanil, found significant decreases in plasma cortisol during retinal surgery when propofol-remifentanil was used (28). We used a higher infusion dose of propofol (100mg/kg.min) and observed a significant decrease of cortisol in that group at one hour. At that time, cortisol was lower than at baseline in the propofol group, but higher than at baseline in the isoflurane group. Adams et al. found lower cortisol levels when propofol and fentanyl were used together (11).
We think the main difference between the result of our study and the other ones is the method of anesthesia. None of the above-mentioned studies used remifentanil to maintain anesthesia in combination with isoflurane or propofol. Opiates can suppress stress hormone release through an inhibition of pituitary and hypothalamic hormone secretion (2). Co-administration of remifentanil was aimed at equalizing the influence of the two anesthetic techniques on stress hormones. In other words, this method increased the comparability of the two groups. Moreover, our sample size of 100 women (50 in each group) was larger than in similar studies. All our patients underwent the same type of surgery, i.e., diagnostic gynecologic laparoscopy, in contrast to other studies in which the study groups included patients who underwent different procedures. Such a study controls for as many confounding factors as possible.

Our study is flawed by the following limitation. Indeed, it was performed on patients benefiting from a diagnostic laparoscopic procedure. This kind of operation is accompanied by a very moderate surgical stress. This might be the cause of the absence of any significant changes in CRP.

Conclusion

Both isoflurane and propofol combined with remifentanil provided good hemodynamic stability. There was a significant reduction in plasma cortisol one hour after the operation with the propofol-remifentanil combination and a non-significant increase with the isoflurane-remifentanil one. Although glucose increased in women who received both kinds of anesthesia, the increase was significantly lower with propofol than isoflurane. We conclude that a propofol-remifentanil combination limits cortisol release and attenuates postsurgical hyperglycemia, two indicators of the stress response. We suggest that the use of this combination could be beneficial for surgical outcomes, but this would deserve further investigations.

Acknowledgements

We thank SH Tabatabai for help with the statistical analysis, the Clinical Laboratories of Namazee and Zeinabiyeh Hospitals in Shiraz for performing the blood tests, and K. Shashok (AuthorAID in the Eastern Mediterranean) for help with the English and organization of the manuscript.

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