# Evaluation of stress-related hormones after surgery

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**Summary**

*Introduction:* Improvements in instrumentation, optics, video cameras and technology have brought laparoscopy to the point at which many surgical procedures that once could be performed only by laparotomy are now successfully performed endoscopically.

*Patients and Method:* Twenty women undergoing surgery by laparotomy (11 patients) or laparoscopy (9 patients) were evaluated prospectively. Concentrations of adrenaline, noradrenaline, cortisol, prolactin, and ACTH were measured. Statistical analysis was performed by using the Friedman Two-way ANOVA, Kruskal-Wallis 1-way ANOVA and Mann-Whitney U - Wilcoxon Rank Sum W Test.

*Results:* By comparing the means of all serum levels of ACTH, cortisol and prolactin between the laparoscopy and the laparotomy group, significant differences of ACTH ($p<0.0001$), prolactin ($p=0.0164$) and cortisol ($p<0.0001$) were found. Furthermore, statistically significant differences ($p<0.05$) of the serum levels of noradrenaline and adrenaline between the laparoscopy and the laparotomy group were observed.

*Discussion:* While laparoscopic surgery causes less activation of stress-related hormones laparotomy results in a much more obvious response to all hormones evaluated, particularly catecholamine and ACTH production. This is probably related to the major tissue trauma.

*Key words:* Laparoscopy; Laparotomy. Stress; ACTH; Prolactin; Adrenaline; Noradrenaline; Cortisol.

## Introduction

Improvements in instrumentation, optics, video cameras and technology have brought laparoscopy to the point at which many surgical procedures that once could be performed only by laparotomy are now successfully performed endoscopically. One of the most relevant differences between laparotomy and laparoscopy is the type of injury to the intraabdominal environment. Although operative laparoscopy is undoubtedly less invasive, peritoneal trauma is still likely to occur. Furthermore, insufflation of peritoneal cavity may be responsible for peritoneal neuronal stimulation, which may activate a stress condition. The surgical injury caused by laparoscopy or laparotomy could be analyzed by evaluating variations in patterns of endocrine stress markers. It was previously reported that the only difference between the two techniques is the rise of ß-endorphines, markers of pain response, after surgery by laparotomy. Evaluation of other hormones such as adrenaline, noradrenaline, dopamine, cortisol and prolactin failed to show any statistically significant difference [1].

## Patients and Methods

Prospectively, 20 women undergoing surgery for either uterine leiomyomas, chronic pelvic discomfort or desire for definitive contraception by laparotomy (11 patients) or laparoscopy (9 patients) were evaluated. All patients were healthy, free of intercurrent disease, without endocrine disorders; none of them received drugs before this study. Additional patient characteristics are shown in Table 1.

Women were assigned to laparotomy or laparoscopy depending on the gynecological diagnosis. The procedure was discussed the day before with the patients who consented to the operation. All patients received premedication with either dikaliumclorazepat (20 - 30 mg) or flunitrazepam (1 - 1.5 mg) at 7 a.m. before surgery was started. The operations were started approximately at the same time between 8:00 and 8:30 a.m. to avoid the secretion of hormones such as cortisol, which is dependent on a circadian rhythm.

Since anesthetic drugs may influence hormonal secretion (2], the anesthetic procedure was similar in the two groups. General anesthesia was induced by propofol (laparoscopy: 8 patients, 1.11 - 2.04 mg/kg, mean: 1.58 mg/kg; laparotomy: 9 patients, 1.31 - 1.90 mg/kg, mean: 1.49 mg/kg) or etomidate (laparoscopy: 1 patient, 0.28 mg/kg; laparotomy: 2 patients, 0.29 - 0.30 mg/kg, mean: 0.295 mg/kg). Endotracheal intubation was performed after muscle relaxation with vecuroniumbromid (laparoscopy: 8 patients, 0.04 - 0.08 mg/kg, mean: 0.0625 mg/kg; laparotomy: 7 patients, 0.05 - 0.066 mg/kg, mean: 0.061 mg/kg), pancuroniumbromid (laparotomy: 4 patients, 0.057 - 0.07 mg/kg, mean: 0.06 mg/kg) or alcuroniumbromid (laparoscopy: 1 patient, 0.102 mg/kg) and administration of sufentanil (laparoscopy: 8 patients, 0.25 - 0.05 µg/kg, mean: 0.39 µg/kg; laparotomy: 11 patients, 0.32 - 0.48 µg/kg, mean: 0.37 µg/kg) or alfentanil (laparoscopy: 1 patient, 0.029 mg/kg). All patients were ventilated mechanically by CATO servo-ventilator (Dräger, Germany). Anesthesia was maintained as total intravenous anesthesia (TIVA) with nitrogene oxide ($N_2O$) and oxygen ($O_2$) 2:1 minimal alveolar concentration (MAC); further $N_2O/O_2$ administration was tailored to the surgical stimulation on the basis of the patient's response in terms of heart rate and blood pressure. During surgery anesthesiologic values were measured by PM 8040 (Dräger, Germany). A balanced electrolyte solution (Ringer's lactate and normal saline) was administered at a constant rate of 6 ml/kg/hour. Postoperatively, the solution was

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Table 1. — *Patient characteristics*

| | Laparoscopy | Laparotomy | |
|---|---|---|---|
| Mean (±SD) age (years): | 37.2 (28 - 62) | 53.4 (35 - 60) | n.s. |
| Mean (±SD) body weight (kg): | 65.4 (51 - 90) | 67.7 (52 - 76) | n.s. |
| Mean (±SD) operating time (min): | 23.6 (16 - 31) | 77.0 (49 - 116) | p<0.05 |

n.s. = not significant

reduced to 2 ml/kg/hour. Laparoscopy was performed by using a transumbilical 10-mm laparoscope connected to a video-camera with high-resolution monitor. The two 5-mm canulas were introduced suprapubically as accessory instruments (Karl Storz GmbH, Tuttlingen, Germany). Laparoscopic surgery was performed according to accepted techniques [3]. Postoperative analgesia with morphine 0.15 mg/kg intravenously was administered to all women directly after operation. No additional analgesia was performed during the study. Pain scores were measured by using the visual analogue scale (VAS; 0=no pain, 10=most pain) as described previously [4, 5].

Venous samples were collected at fixed times as demonstrated in Table 2. The samples were transferred to precooled tubes containing EDTA and 50µl glutathione solution, immediately centrifugated at +4°C and plasma stored at −80°C until analysis.

Concentrations of noradrenaline, adrenaline, cortisol, prolactin and ACTH were measured by commercially available radioimmunassay test kits. Statistical analysis was performed by the Friedman Two-way ANOVA, Kruskal-Wallis 1-way ANOVA and Mann-Whitney U - Wilcoxon Rank Sum W Test. The level of significance was set at probability below 0.05. All results are expressed as means ±SD.

## Results

The two groups were similar regarding the mean age and body weight (Table 1). The operative time was statistically significantly ($p<0.05$) longer in the laparotomy group than in the laparoscopy group. No anesthesiologic or surgical complications occurred. No patient required a blood transfusion.

In the laparoscopy group, there were no statistically significant changes in serum levels of ACTH ($p=0.5065$), cortisol ($p=0.3265$) and prolactin ($p=0.2740$) (Table 3) nor in diastolic blood pressure ($p=0.1388$), pain score ($p=0.8591$) and pulse rate ($p=0.190$) after surgery. Only the systolic blood pressure showed significant changes during observation ($p=0.0032$). The lowest value was 5 minutes after application of morphine (RRS=103.33 mmHg) and the highest just before application (RRS=118.33 mmHg) (Table 4).

In the laparotomy group there were only statistically significant changes in the serum levels of prolactin ($p=0.094$; maximum before application of morphine at T0: 141.20 ng/ml; minimum 120 minutes after application: 72.00 ng/ml), while the serum levels of ACTH ($p=0.8085$) and cortisol ($p=0.8295$) showed no significant changes after surgery (Table 5). A highly significant increase in the pain score was observed ($p<0.0001$; minimum at T1: 3.00; maximum at T8: 6.82), while the diastolic ($p=0.0671$) and systolic ($p=0.0543$) blood pressure showed only slightly significant changes (Table 6).

By comparing the means of all serum levels of ACTH, cortisol and prolactin between the laparoscopy and the laparotomy group, there were significant differences of ACTH ($p<0.0001$), prolactin ($p=0.0164$) and cortisol ($p<0.0001$). At each measurement time statistically significant differences were obvious between both groups.

Furthermore, statistically highly significant differences ($p<0.005$) of the serum levels of noradrenaline at T4 and T6 between the laparoscopy and the laparotomy group were observed, while there were slightly less statistically significant differences ($p<0.05$) of noradrenaline at T8 and of adrenaline at all (Table 7).

## Discussion

Trauma and surgery profoundly affect the circulating concentrations of stress hormones and their metabolites, and may thereby directly or indirectly influence recovery. This endocrine and metabolic response to surgery

Table 2. — *Design of the study*

| Time of collecting samples | Collections | Clinical parameters |
|---|---|---|
| T0: end of the operatiopn | ACTH, C, PRL | RRD, RRS, P, PSC |
| AM: application of morphine 0.15 mg/kg | | |
| T1: 5 minutes after application | ACTH, C, PRL | RRD, RRS, P, PSC |
| T2: 10 minutes after application | ACTH, C, PRL | RRD, RRS, P, PSC |
| T3: 20 minutes after application | ACTH, C, PRL | RRD, RRS, P, PSC |
| T4: 30 minutes after application | ACTH, C, PRL, A, NA | RRD, RRS, P, PSC |
| T5: 45 minutes after application | ACTH, C, PRL | RRD, RRS, P, PSC |
| T6: 60 minutes after application | ACTH, C, PRL, A, NA | RRD, RRS, P, PSC |
| T7: 90 minutes after application | ACTH, C, PRL | RRD, RRS, P, PSC |
| T8: 120 minutes after application | ACTH, C, PRL, NA | RRD, RRS, P, PSC |

A: adrenaline, NA: noradrenaline, C: cortisol, PRL: prolactin, ACTH: adrenocorticotrope hormone, RRD: diastolic blood pressure, RRS: systolic blood pressure, P: pulse rate, PSC: pain score.

Table 3. — *Mean (±SD) plasma values of stress-related hormones in women undergoing laparoscopy*

| | ACTH (pg/ml) | Cortisol (μg/ml) | Prolactin (ng/ml) |
|---|---|---|---|
| T0: | 94.57 (SD:±93.74); a1 | 15.88 (SD:±11.58); b1 | 156.00 (SD:±43.96); c1 |
| T1: | 65.86 (SD:±66.59); a2 | 17.50 (SD:±10.99); b2 | 153.38 (SD:±49.27); c2 |
| T2: | 60.57 (SD:±65.14); a3 | 16.50 (SD:±11.12); b3 | 145.13 (SD:±48.59); c3 |
| T3: | 44.71 (SD:±46.29); a4 | 15.38 (SD:±10.45); b4 | 147.00 (SD:±53.55); c4 |
| T4: | 40.14 (SD:±44.08); a5 | 14.50 (SD:± 9.81); b5 | 138.38 (SD:±52.57); c5 |
| T5: | 35.33 (SD:±40.79); a6 | 14.25 (SD:±10.22); b6 | 135.63 (SD:±54.87); c6 |
| T6: | 44.00 (SD:±59.58); a7 | 12.88 (SD:± 8.76); b7 | 125.00 (SD:±50.71); c7 |
| T7: | 37.71 (SD:±33.61); a8 | 10.88 (SD:± 7.68); b8 | 105.38 (SD:±46.31); c8 |
| T8: | 42.57 (SD:±76.07); a9 | 9.88 (SD:± 7.24); b9 | 103.25 (SD:±46.90); c9 |
| | p=0.5065 (Kruskal-Wallis 1-way ANOVA) | p=0.3265 | p=0.2740 |

Table 4. — *Clinical data of women undergoing laparoscopy*

| | RRS (mmHg) | RRD (mmHg) | PSC | P (beats/minute) |
|---|---|---|---|---|
| T0: | 118.33 (SD:±11.07) | 68.22 (SD:±7.31) | 1.78 (SD:±3.23) | 68.11 (SD:± 9.52) |
| T1: | 103.33 (SD:± 7.16) | 62.56 (SD:±9.67) | 0.89 (SD:±1.96) | 67.33 (SD:±10.52) |
| T2: | 108.89 (SD:±13.31) | 63.89 (SD:±9.66) | 0.44 (SD:±1.01) | 64.89 (SD:±13.09) |
| T3: | 108.44 (SD:±12.50) | 65.11 (SD:±9.36) | 0.44 (SD:±0.73) | 67.67 (SD:±12.02) |
| T4: | 107.22 (SD:± 7.63) | 68.56 (SD:±8.11) | 0.67 (SD:±0.87) | 64.22 (SD:± 8.04) |
| T5: | 111.56 (SD:±10.30) | 70.22 (SD:±8.83) | 0.67 (SD:±0.87) | 66.33 (SD:±11.96) |
| T6: | 109.22 (SD:±11.54) | 67.00 (SD:±7.98) | 0.44 (SD:±0.73) | 63.67 (SD:±11.07) |
| T7: | 114.56 (SD:±12.77) | 67.22 (SD:±6.94) | 0.44 (SD:±0.73) | 66.89 (SD:±10.83) |
| T8: | 112.00 (SD:± 9.60) | 67.67 (SD:±7.65) | 0.56 (SD:±0.73) | 72.00 (SD:±14.79) |
| | p=0.0032 (Friedman Two-way ANOVA) | p=0.1388 | p=0.8591 | p=0.190 |

Table 5. — *Mean (±SD) plasma values of stress-related hormones in women undergoing laparotomy*

| | ACTH (pg/ml) | Cortisol (μg/ml) | Prolactin (ng/ml) |
|---|---|---|---|
| T0: | 585.80 (SD:±459.77); a1 | 26.90 (SD:± 9.45); b1 | 141.20 (SD:±37.46); c1 |
| T1: | 513.70 (SD:±400.10): a2 | 27.60 (SD:±10.63); b2 | 134.20 (SD:±39.89); c2 |
| T2: | 462.40 (SD:±416.24): a3 | 27.80 (SD:± 9.85): b3 | 131.30 (SD:±41.47); c3 |
| T3: | 489.22 (SD:±454.03); a4 | 27.70 (SD:±10.08); b4 | 126.20 (SD:±42.21); c4 |
| T4: | 452.70 (SD:±459.81); a5 | 28.40 (SD:± 9.64); b5 | 117.60 (SD:±41.69); c5 |
| T5: | 473.70 (SD:±412.81); a6 | 28.20 (SD:±10.76); b6 | 114.70 (SD:±48.20); c6 |
| T6: | 539.40 (SD:±441.51); a7 | 28.10 (SD:±10.74); b7 | 93.40 (SD:±53.14); c7 |
| T7: | 598.40 (SD:±388.72); a8 | 31.50 (SD:±10.11); b8 | 104.60 (SD:±52.26); c8 |
| T8: | 614.20 (SD:±344.09); a9 | 31.20 (SD:±11.72); b9 | 72.00 (SD:±18.86); c9 |
| | p=0.8085 (Kruskal-Wallis 1-way ANOVA) | p=0.8295 | p=0.0094 |
| | a1: p=0.0057 | b1: p=0.503 | c1: p=0.3231 |
| | a2: p=0.0018 | b2: p=0.617 | c2: p=0.3655 |
| | a3: p=0.0032 | b3: p=0.406 | c3: p=0.5025 |
| | a4: p=0.0062 | b4: p=0.405 | c4: p=0.3713 |
| | a5: p=0.0046 | b5: p=0.0086 | c5: p=0.3274 |
| | a6: p=0.0034 | b6: p=0.0144 | c6: p=0.3056 |
| | a7: p=0.0024 | b7: p=0.0051 | c7: p=0.1424 |
| | a8: p=0.0062 | b8: p=0.0010 | c8: p=0.6560 |
| | a9: p=0.0018 | b9: p=0.0014 | c9: p=0.0999 |
| | a: p<0.001 | b: p<0.001 | c: p=0.0164 |
| | (Mann-Whitney U - Wilcoxon Rank Sum W Test) | | |

as a stressful stimulus is influenced by the magnitude of the trauma and conditioned by several factors such as anxiety, hemorrhage, infection and pain [6-8]. The hypothalamus receives afferent neural and humoral signals from the injured area and integrates this input to provide an adequate response [8]. This endocrine metabolic response including pituitary and sympathetic stimulation may be responsible for intraoperative morbidity such as cardiocirculatory effects [6, 9, 10].

Improvements in anesthetic and operative techniques were recommended to obtain stress-free surgical conditions [9]. Regardless of the anesthetic used it is impor-

Table 6. — *Clinical data of women undergoing laparotomy*

| | RRS (mmHg) | RRD (mmHg) | PSC | P (beats/minute) |
|---|---|---|---|---|
| T0: | 140.45 (SD:±22.06) | 82.64 (SD:±15.03) | 4.00 (SD:±2.14) | 67.18 (SD:±11.19) |
| T1: | 137.27 (SD:±24.89) | 77.09 (SD:±10.32) | 3.00 (SD:±1.67) | 67.36 (SD:±10.29) |
| T2: | 132.55 (SD:±22.41) | 77.00 (SD:± 8.90) | 3.09 (SD:±1.51) | 67.64 (SD:± 9.33) |
| T3: | 134.45 (SD:±19.70) | 77.91 (SD:±11.23) | 3.27 (SD:±1.35) | 68.27 (SD:± 9.00) |
| T4: | 135.82 (SD:±20.15) | 78.27 (SD:±10.66) | 3.45 (SD:±1.63) | 68.27 (SD:±10.11) |
| T5: | 132.18 (SD:±18.64) | 77.09 (SD:± 9.06) | 4.18 (SD:±1.94) | 68.73 (SD:± 7.62) |
| T6: | 135.36 (SD:±22.34) | 78.18 (SD:±10.51) | 4.73 (SD:±2.10) | 70.91 (SD:±69.64) |
| T7: | 131.00 (SD:±16.27) | 74.73 (SD:±11.17) | 5.45 (SD:±2.21) | 69.64 (SD:± 8.41) |
| T8: | 128.27 (SD:±18.33) | 73.00 (SD:±11.25) | 6.82 (SD:±2.09) | 73.55 (SD:±10.04) |
| | p=0.0543 (Friedman Two-way ANOVA) | p=0.0671 | p=0.0001 | p=0.3438 |

Table 7. — *Means (±SD) of noradrenaline and adrenaline secretion of patients undergoing laparotomy and laparoscopy*

| | LAPAROSCOPY | | LAPARATOMY | |
|---|---|---|---|---|
| | noradrenaline (pg/ml) | adrenaline (pg/ml) | noradrenaline (pg/ml) | adrenaline (pg/ml) |
| T4: | 435.31 (SD:±209.57)[a] | 154.56 (SD:±149.34)[c] | 1104.31 (SD:±496.37)[a] | 356.68 (SD:±157.48)[c] |
| T6: | 463.88 (SD:±160.73)[a] | 161.00 (SD:±113.95)[c] | 1006.77 (SD:±400.85)[a] | 335.82 (SD:±148.18)[c] |
| T8: | 448.44 (SD:±139.87)[b] | – | 984.23 (SD:±513.71)[b] | – |

t-test for independent samples
[a]: p<0.005
[b]: p<0.05
[c]: p<0.05

tant to improve surgical techniques when considering the extent of trauma able to stimulate the stress hormones [11]. The place value of laparoscopic surgery is increasingly important in the field of surgery. Although the advantages seem to be obvious, it is interesting to quantify the parameters of operative stress and to compare laparoscopic surgery with conventional surgery. Therefore we analyzed the stress markers usually considered in the literature.

Adrenocorticotropic hormone is a sensitive indicator of stress and correlates with the severity of surgical trauma. Its secretion is blocked by spinal anesthesia [12], while it is released in a concomitant pattern with ß-endorphine due to the common precursor proopiomelanocortin [13]. Compared with laparoscopy, we found significantly higher values of ACTH after laparotomy indicating that laparotomy is a much more severe surgical trauma. In both groups, no statistically significant changes of ACTH secretion were observed after postoperative morphine application. Nevertheless, in the laparotomy group ACTH decreased directly after morphine application, while it increased 45 minutes after morphine administration concomitant with the pain score.

The increase in plasma cortisol concentrations was correlated to the severity of surgical trauma, probably secondary to a previous increase of ACTH [7]. It has been described that an adrenocortical response could be stimulated directly by substances released at the site of injury [14]. Thus, the small dissociation between ACTH and cortisol profiles could be explained since we did not detect a significant change in plasma cortisol concentrations after morphine administration. Morphine application in a therapeutical dosage does not seem to influence cortisol secretion postoperatively.

Increased PRL values are detected in patients undergoing major surgical procedures [15]. But it has been reported that PRL rises even during laparoscopy [16]. The mechanism of stress relating PRL secretion is difficult to explain, but metabolic effects seem to be of minor relevance [17]. Thus, elevation of PRL was noted after induction of anesthesia. Drugs such as fentanyl seem to be responsible for a significant rise [18]. In our study, a slightly, statistically significant higher PRL secretion was detected in the laparoscopy group compared with the laparotomy group. After morphine application, we found a statistically significant decrease of PRL secretion in the laparotomy group indicating that the opioid application which results in a cessation of postoperative pain influences PRL secretion more effectively than the surgical approach does.

The dissociation of noradrenaline and adrenaline release observed previously [19] may be explained by a dual origin. Circulating adrenaline is secreted by the adrenal medulla, whereas plasma noradrenaline is released primarily form sympathetic nerve endings [6]. The adrenergic response is related to the extent of surgical injury [8] and is due to afferent signals originating from the site of trauma [6]. This activation can be influenced by anesthetic agents [3]. The anesthetic drugs we used do not seem to influence catecholamine stimulation [20]. In previous studies it could be demonstrated that surgical stress increased catecholamine secretion. Failure to document significant changes in catecholamine release after surgery was due to measurements with insensitive and nonspecific methods in the beginning. In our study, catecholamine secretion showed a remarkable difference between the two surgical approaches. In the laparoscopic group, the catecholamine secretion was statistically significantly less increased compared to the laparotomy group.

Our findings indicate, that laparoscopic surgery causes less activation of stress-related hormones. Laparotomy results in a much more obvious response of all hormones evaluated, particularly catecholamine and ACTH production. This is propably related to the major tissue trauma. The effects of pneumoperitoneum induction during laparoscopy seem to be negligible. On the contrary, abdominal wall injury, exploration of the abdomen and manipulation of the bowel during laparotomy cause an increased and prolonged release of stress-related hormones. A more prolonged catabolic status might be the consequence. Whenever possible, laparoscopy should be performed for the treatment of pelvic benign disease, as it causes a lower stress response and possibly a shorter recovery time.

## Conclusion

Laparoscopic surgery causes less activation of stress-related hormones. Laparotomy results in a much more obvious response of all hormones evaluated, particularly catecholamine and ACTH production. This is probably related to the major tissue trauma. Whenever possible, laparoscopy should be performed for the treatment of pelvic benign disease as it causes a lower stress response and possibly a shorter recovery time.

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