Inflammatory responses after laparoscopic uterine myomectomy compared to open surgery in current clinical practice

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ABSTRACT

Objective: To determine the differences in inflammatory response and clinical outcome of current clinical practice in women undergoing laparoscopic myomectomy (LM) and abdominal myomectomy (AM) for symptomatic fibroid.

Methods: A total of 36 women entered the study between October 2004 to June 2005 at the Department of Gynecology and Obstetrics and the Endoscopy Training Center at the Baby Friendly Hospital in Kladno, Czech Republic, based upon an ultrasonographic assessment size of dominant fibroid (DM) before surgery. All women were allocated to one of 2 groups: group 1 (n=17), DM <6 cm and treated with LM, and group 2 (n=19) DM ≥6 cm, treated with open myomectomy. Surgical characteristics, hospital stay and complications were analyzed. Blood samples for assay of the acute phase reactants and markers of tissue trauma [C-reactive protein (CRP), interleukin-6 (IL-6), serum amyloid A (SAA), white blood cell count (WBC) and creatine kinase (CK)] were taken preoperatively and on the first and third postoperative day.

Results: The difference between the groups in the mean size of DM was statistically significant (4.8 cm in group 1 versus 6.9 cm in group 2, $p<0.05$). Statistically, significant differences were found between the compared groups in intra-operative blood loss ($p<0.05$) and length of hospital stay ($p<0.001$). No complication was reported after LM. There were significantly higher levels of CRP, IL-6, SAA, WBC and CK in both groups after surgery. Increased levels of IL-6, WBC and CK were greatest on the first postoperative day in both groups, and increased levels of CRP and SAA on the third postoperative day in the open group. The serum CRP, IL-6, SAA, WBC, CK and the fall in hemoglobin were statistically different between the 2 groups.

Conclusions: Compared with open myomectomy, LM was associated with a less intensive inflammatory response and a more favorable clinical outcome.

Saudi Med J 2006; Vol. 27 (11): 1693-1697

The effects of laparoscopic techniques on immunological responses have been increasingly studied since the introduction of minimally invasive surgical techniques. Clinical and experimental experience demonstrates that perioperative stress is lower during laparoscopic surgery than during laparotomy (LPT). A sensitive method for stress evaluation implies measuring of stress factors, which are important in the acute phase reaction. Acute phase reactants are heterogeneous group of proteins that mediate the acute phase responses.[1] Their function is to induce a non-specific host defense and limit

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Received 3rd January 2005. Accepted for publication in final form 9th March 2005.

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the local immune response. In the present study, we analyzed the C-reactive protein (CRP), interleukin-6 (IL-6), serum amyloid A (SAA) and white blood cells count (WBC).

Over the past decade laparoscopic myomectomy became integral to gynecologic surgical practice with advantages over an abdominal myomectomy of less postoperative pain and shorter recovery.[2,3]

Thus, we report a prospective, controlled, and non-randomized trial to determine the degree of inflammatory response to laparoscopic and open myomectomy in current clinical practice, evaluated by measuring the levels of acute phase reactants. Our second aim was to elucidate and compare early postoperative changes of serum proteins, CRP, IL-6 and SAA.

Methods. The prospective, controlled and non-randomized study was carried out at the Department of Gynecology and Obstetrics and the Endoscopy Training Center at the Baby Friendly Hospital in Kladno in the Czech Republic. During the period October 2004 to June 2005, consecutively selected patients requiring myomectomy for symptomatic fibroids were invited to participate in the trial. The diagnosis was confirmed by ultrasound or MRI. Symptomatic cases were defined as patients who had one of the following complaints: dysmenorrhea, menorrhagia, pelvic pain, pelvic pressure and urinary frequency. Only 36 patients who had a dominant fibroid between 4-10 cm in diameter were included in the study. The patients who had submucosal fibroids were excluded. The patients were allocated into 2 groups according to the size of dominant fibroid; group 1, fibroid <6 cm and treated with laparoscopic myomectomy (LM) and group 2, fibroid ≥6 cm treated with myomectomy by minilaparotomy (ML), laparoscopically assisted minilaparotomy (LA-ML) and LPT. Laparotomy was indicated in cases where fibroids larger than 8 cm, numerous or deep fibroids requiring extensive morcellation and suturing. Only patients who underwent surgery during the morning and who had shown no signs of endocrine, cardiovascular, hepatic, renal or any form of disease were enrolled in the laparoscopic (group 1, n=19) and open myomectomy (group 2, n=17) study groups.

The duration of the surgical procedure was calculated from the skin incision to the last skin suture. All operative procedures were performed by one surgeon. The intra-operative blood loss was measured as blood volume accumulated in the aspirator or surgical sponges and LPT packs were weighed dry before surgery and wet immediately after use. We used the measurement mode of blood loss, which was described in more detail by Ginsburg et al.[4] The postoperative blood loss was approximated from the postoperative fluid collection using Redon´s catheter. Febrile morbidity was defined as a body temperature of a least 38°C on 2 consecutive measurements at least 6 hours apart, excluding the first 24 hours after surgery.

The parameters monitored were as follows: duration of surgery (skin incision to skin suture), blood loss, fall in hemoglobin, perioperative complications, length of hospital stay, recovery, inflammation and tissue trauma markers [CRP, IL-6, SAS, WBC and creatine kinase (CK)].

A written informed consent was obtained and the procedure was explained to each woman. The study was approved by the Regional Research Ethics Committee of the Kladno Hospital and supported by the Grant Fund of Ministry of Health (NR 7982).

Biochemical investigations. Three blood samples were collected from the brachial vein, at 0600H on the day of surgery and at 24 hours and 72 hours later. All of the operations began at the same time, 0800H, in an attempt to standardize any effects arising from circadian biorhythms. The interval between the end of surgery and the first post-surgical sample collections varied from 18 hours to 20 hours.

The overall activity of CK (EC 2.7.3.2) was assessed using the International Federation of Clinical Chemistry kinetic method in the ultraviolet range (Pliva Lachema, Czech Republic) on the Aeroset analyser (Abbott,USA). The upper limit for females was 2.4 μkat l^{-1}. The CRP (in mg 1-1) was measured by turbidometric immunoassay at 37°C (Orion Diagnostic, Finland) on the Aeroset analyzer (Abbot,USA). The concentrations of IL-6 (in μg^{-1}) in serum was determined using the IL-6 ELISA test (Immunotech/Beckman Coulter) on the MiniSwift analyzer (Tecan, USA). Serum amyloid A (in mg/l) was measured with N Latex SAA diagnostic kit on the ProSpec analyser (Dade Behring, USA).

Operating procedure. **Laparoscopic myomectomy**. Laparoscopy was carried out with the patient under general anesthesia, with introduction of a 10-mm laparoscope through the umbilicus and 10-mm trocar suprapubically. Two or 3 5-mm ports were placed in the lower quadrant beside the lateral edge of the direct muscle. The 5-mm left higher suprapubic port is often changed to 10-mm for introducing the needle holder or the morcellator at the end of the procedure. An incision was made through the uterine wall and the pseudocapsule of the fibroid. Traction was applied to the fibroid along with harmonic scalpel dissection. After complete fibroid removal using the Steiner electric morcellator (Storz, Tuttlingen, Germany), the edges of the uterine defect were approximated using ultrasonically activated shears (LCS-K 5 or LCS-C, UltraCision; Ethicon EndoSurgery, Johnson & Johnson, Cincinnati, USA) coagulating the superficial myometrium without suturing. If the defect was deep or large (over 2 cm), the uterine incision, including myometrium and serosa, was closed with one to 3 of layers of interrupted absorbable sutures of 1-0 or 2-0 polyglactin (Vicryl, Ethicon, Edinburg).

Open procedure. Laparotomy was performed with a 10 cm supra-pubic incision. After examination of the uterus and adnexa, myomectomy using harmonic scalpel or cold knife was performed. The uterine defect was closed in a single to triple layer with interrupted sutures of Vicryl. No pharmacological agent or vascular occlusion technique was not used before uterine incision. Minilaparotomy was carried out with 4-5 incision, 2-3 cm above the pubic symphysis. A uterine manipulator was used to elevate the uterus toward the supra-pubic incision. The parietal peritoneum was then incised just above the fibroid during the traction, which was performed on the corkscrew, while the fibroid along with the uterus was forced out the minilaparotomic incision. Myomectomy and uterus reconstruction was performed directly outside the peritoneum, as in the LPT procedure. Laparoscopically-assisted myomectomy was performed in a manner which was first described by Nezhat et al,[5] where fibroid enucleation was carried out laparoscopically or through a 5 cm Pfannenstiel minilaparotomy. Which then the uterus could be exteriorized for palpation and multi-layered open suturing. They used 2/0 and 4/0 polydioxanone and avoided suturing the serosa.

Statistical analysis. Values are expressed as mean standard deviation or as a number or percentage. Statistical analysis was carried out using the Mann-Whitney U test in the case of unpaired results. Differences within groups were analyzed by means of the paired Wilcoxon test for 2 related samples. Statistical significance was defined as $p<0.05$.

Results. For the analysis of the tissue trauma and inflammatory changes, 36 uncomplicated myomectomies from both groups were included, which involved 17 patients in the laparoscopic group and 19 from the open surgery group. The demographic characteristics of the 2 groups were similar (**Table 1**). The difference between the groups in the mean size of dominant fibroid was statistically significant (4.8 cm in group 1 versus 6.9 cm in group 2, $p<0.05$); this difference was primarily influenced by patient selection according to the design of the trial, which was aimed to study the inflammatory response in

Table 1 - Patient characteristics and fibroids.

Variable	Group 1 (N=19)	Group 2 (N=17)	*P*-value
Age (years)	36.0 ± 4.0	37.1 ± 6.2	NS
Weight (kg)	63.4 ± 4.6	67.1 ± 4.4	NS
Previous pelvic surgery	3 (15.7)	2 (11.7)	NS
No. of fibroids per patient	2.8 ± 1.5	2.4 ± 1.5	NS
Size of dominant fibroid (largest diameter, cm)	4.8 ± 1.8	6.9 ± 0.7	<0.05

Values are expressed as n (percentage) and mean ± SD; NS - not significant

Table 2 - Results of surgery and recovery.

Variable	Group 1	Group 2	*P*-value
Operating time	63.3 ± 32.8	76.7 ± 18.9	NS
Intra-operative blood loss (ml)	76.1 ± 62.1	160.6 ± 127.2	<0.05
EPBL (ml)	85.4 ± 68.2	104.0 ± 98.3	NS
Decline in hemoglobin level (g dl^{-1})			
First day after surgery	0.4 ± 0.3	1.3 ± 0.6	<0.05
Third day after surgery	0.7 ± 0.5	2.1 ± 0.9	<0.01
Weight of specimen (g)	118.0 ± 56.7	190.7 ± 94.8	NS
Hospital stay (day)	2.7 ± 0.3	4.2 ± 1.1	<0.001
Complications			
Wound infection	0	1	NS
Febrile morbidity	0	1	NS

Values are expressed as N and mean SD, NS - not significant
EPBL - estimated postoperative blood loss

Table 3 - The values of the inflammatory and tissue trauma variables assessed before and after myomectomy in each group.

Variable	Post operative day	Group 1	Group 2	*P*-value
CRP (mg/L)	0	-	-	
	1	14.8 ± 11.7	31.8 ± 18.9	<0.05
	3	19.5 ± 20.6	54.4 ± 20.7	<0.01
IL-6 (ng/L)	0	11.3 ± 5.1	11.4 ± 4.9	NS
	1	22.9 ± 12.8	67.0 ± 51.5	<0.05
	3	13.9 ± 4.4	20.2 ± 11.3	NS
SAA (mg/L)	0	2.4 ± 1.2	2.5 ± 1.4	NS
	1	54.0 ± 44.4	151.4 ± 121.5	<0.05
	3	31.1 ± 36.3	281.2 ± 419.6	<0.001
WBC (10^9/L)	0	6.2 ± 1.6	6.3 ± 1.4	NS
	1	10.8 ± 3.7	10.3 ± 2.8	NS
	3	7.1 ± 2.2	7.2 ± 2.9	NS
CK (μkat/L)	0	1.4 ± 0.3	1.7 ± 0.6	NS
	1	3.4 ± 1.9	7.1 ± 14.1	<0.05
	3	2.0 ± 0.8	22.6 ± 5.5	<0.05

CRP - C-reactive protein, IL-6 - interleukin-6, SAA - serum amyloid A, WBC - white blood cell count, CK - creatine kinase current clinical practice. On the other hand, the difference between the studied groups in the mean weight of the removed specimen was statistically insignificant (118 g, group 1 versus 190.7 g group 2, not significant). This difference could be influenced by a higher number (2.8) of fibroids per patient in group 1 in comparison to number (2.4) of fibroids per patient in group 2.

Statistically significant differences were found between the compared groups in intra-operative blood loss ($p<0.05$) and length of hospital stay ($p<0.001$) (**Table 2**). Also, the difference was significant in hemoglobin decline on the first ($p<0.05$) and third postoperative day ($p<0.01$). No significant difference occurred in estimated postoperative blood loss.

The preoperative levels of the markers studied were low in the comparison groups, and the circulating concentrations of CRP, IL-6, SAA, WBC and CK increased significantly after surgery in both groups (**Table 3**). The increased levels of IL-6, WBC and CK were greatest on the first postoperative day, in both groups, and those CRP and SAA on the third postoperative day in the open group. The serum CRP, IL-6, SAA, WBC, CK and the fall in hemoglobin were statistically different between the 2 groups. No complication was reported after laparoscopic myomectomy. One patient after myomectomy via LPT developed postoperative fever (<39°C) on the second day. Maximal increase was found for SAA. The level of SAA achieved was 474 mg/l on the first day and 1410 mg/l on the third day after surgery. She was treated successfully using antibiotics.

Discussion. Laparoscopic myomectomy is increasingly being selected as a method of treating uterine leiomyomata. It may avoid hysterectomy and can preserve or restore fertility. Although the procedure is not inherently more difficult than open ones, it is more time consuming. However, the advantages of laparoscopic myomectomy may outweigh those of open techniques, such as less abdominal wall trauma, shorter hospital stay potentially corresponding to a decrease in hospital costs, and more rapid return to normal activity.[2] The time of surgery, blood loss, perioperative morbidity, damage to tissue, subsequent pain, duration of hospital stay and hospitalization cost have been used as criteria in the standard methods of comparing laparoscopic and open procedures.[2,3,6,7] However, some authors do not consider that assessment of surgical method using the above mentioned criteria as sufficiently objective.[8] Measurement of perioperative stress by means of metabolic, hormonal and inflammatory response markers is also more objective. Surgical trauma, tissue injury, infection and inflammation are followed by release of cytokines from monocytes, macrophages, fibroblasts and endothelial cells of damaged tissue. The major cytokine is IL-6. Receptors for IL-6 are found in cells with various functions, and when activated by this cytokine, they release secondary substances that mediate inflammation and tissue remodeling. The IL-6 induces specific hepatic proteins, the most important of which are CRP and SAA.[9] The CRP is the most extensively studied acute-phase response protein with regard to trauma and surgery. The CRP levels usually rise approximately 4-12 hours after operation and peak at 24 –72 hours, thereafter remaining raised for approximately 2 weeks.[9-11] The expression of IL-6 is believed to be directly proportional to the extent of surgical trauma.[10-12] The SAA is a second pentraxin and a positive acute phase-reactant, which increases during inflammation but somewhat faster than CRP.[13] However, as a whole measurements of SAA are still confined to research laboratories.[10]

In the present study, statistically significant differences were found between the 2 groups in the clinical parameters of blood loss, duration of surgery, hemoglobin decline and hospital stay. In contrast to most of the reported studies comparing laparoscopic myomectomy and open myomectomy, our operating time for laparoscopic myomectomy was shorter than that for the open procedure.[2,6] This difference was primarily influenced by patient selection according to size of a dominant fibroid. The presence of a dominant fibroid over 6 cm in size had been taken as an indication for an abdominal approach. This limitation of the present study could influence also other clinical surgical parameters and the markers levels of 2 studied groups of patients with symptomatic fibroids. On the other hand the design of present study was to reflect the situation in current clinical practice.

Our study results show that myomectomy, whether performed by laparoscopy or by the open procedure is associated with significant stress response, with increases in the measured biochemical markers. Statistically significant differences were found in the concentrations of inflammatory and tissue trauma markers following uncomplicated myomectomies. The IL-6, WBC, CK and SAA concentrations were highest on the first postoperative day in laparoscopic myomectomy group. The CRP, CK and SAA concentrations levels were highest on the third day after surgery in patients from the open myomectomy group. In this study, CRP was increased after a proper time lag (24 hours) and peaked 72 hours after the operation in both types of surgery (**Table 3**). Maximum increase was found for SAA concentrations in the woman with febrile morbidity after abdominal myomectomy. On the basis of the mentioned matter, we suggest that SAA seems to be a valuable marker of early postoperative inflammatory complications. Only few data regarding the role of SAA were found in the contemporary literature. Lycopoulou et al[14] reported that circulating SAA levels have a better discriminatory value than WBC or CRP in the assessment of acute appendicitis in children. Thus, this test appears to be of higher value than the current standards of care in the diagnosis of this condition. Controversial outcomes for SAA and CRP were found in Balduini et al[15] study regarding the diagnosis of acute graft rejection in heart transplant recipients. On the other hand, Fornara et al[16] concluded that when comparing patients who underwent conventional open prostatectomy, patients with laparoscopically radical prostatectomy had identical to slightly higher serum levels of the acute-phase parameters (CRP, SAA, IL-6 and IL-10), as evidence of an equal or a discretely manifested systemic response to the surgical trauma. The assumed less invasiveness of laparoscopic radical prostatectomy is not objectively supported by the data from this study.

A biological variability SAA is indubitable, very interesting matter, which is presented as a relatively high-risk variance of 70% and the inter-individual variability exceeds the intra-individual activity more than twice.[17] Based on potential growth of SAA concentrations in connection with the surgical stress, the biological variability does not become a substantial problem. The SAA is therefore an indicator with high dynamics of acute phase response.[10]

In conclusion, our study demonstrated that laparoscopic myomectomy was associated with a lesser inflammatory response compared with myomectomy carried out by an open approach. Acute phase reactants and CK have been shown to correlate with the severity of tissue trauma, blood loss and duration of the procedure. Surgical stress and possible inflammatory risk after myomectomy are best predicted by CRP and SAA. Maximal increase was found for SAA concentrations. Serum amyloid A seems a suitable marker of early postoperative complications in gynecologic surgery.

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