Surg Endosc (2001) 15: 463–466
DOI: 10.1007/s004640000348

Surgical Endoscopy
Ultrasound and
Interventional Techniques

Prospective evaluation of the systemic immune response following abdominal, vaginal, and laparoscopically assisted vaginal hysterectomy

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Received: 10 March 2000/Accepted in final form: 9 August 2000/Online publication: 13 March 2001

Abstract

Background: Alterations in serum levels of cytokine interleukin-6 (IL-6) and acute-phase protein C-reactive protein (CRP) correlate directly with extent of tissue damage and inflammatory reaction. We therefore prospectively compared the postoperative levels of IL-6 and CRP following abdominal (AH), vaginal (VH), and laparoscopically assisted vaginal hysterectomy (LAVH).

Methods: A total of 29 patients were included in the study (10 VH, 10 LAVH, 9 AH). Nine blood samples were taken from each patient at various time points before, during, and after surgery. CRP and IL-6 were measured under standardized conditions using ELISA and turbidometry.

Results: Preoperative levels of IL-6 and CRP were low in all three patient groups. There was a significant increase in the IL-6 level in patients undergoing AH at the time of peritoneal closure that reached a maximum 2 h postoperatively and remained significantly elevated for 12 h postoperatively when compared to the IL-6 levels of patients undergoing VH or LAVH ($p < 0.05$). The levels of the IL-6 time courses differed significantly among the three operative procedures ($p = 0.013$). In contrast, the levels of the CRP time courses did not differ significantly ($p = 0.066$); however, CRP expression was elevated 36 h postoperatively in patients undergoing AH, as compared with those undergoing VH.

Conclusion: Elevated IL-6 levels subsequent to AH may reflect significantly greater tissue damage in these patients than in patients who undergo VH or LAVH. LAVH should therefore be considered in cases that cannot be managed by the vaginal route alone.

Key words: Laparoscopically assisted vaginal hysterectomy — Hysterectomy — Surgical stress — Cytokine — IL-6

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Operative procedures cause metabolic and inflammatory changes that correlate with the extent of tissue damage [2, 3]. Their subjective impact on the human organism can be judged by assessing the intensity and duration of postoperative pain and time taken until activity returns to normal. One objective method of judging the extent of the trauma is the measurement of markers of the acute-phase reaction [20]. IL-6, IL-1, and tumour necrosis factor α are the major mediators of the acute-phase reaction. IL-6 primarily regulates the hepatic component of the acute-phase response and produces acute-phase proteins such as CRP, fibrinogen, α-1-antitrypsin, and haptoglobin [2, 5]. IL-6 is a 20–30 KD protein comprising 212 amino acids [5]. IL-6 is secreted by monocytes, T and B lymphocytes, keratinocytes, endothelial cells, and fibroblasts. It interacts with different growth factors and precursor cells of hematopoesis [20]. The expression of IL-6 is a sensitive and early marker of tissue damage and correlates with the extent of surgical trauma [2, 15, 20]. Numerous trials have demonstrated the impact of minimally invasive surgery vs traditional open surgery on the acute-phase reaction. Laparoscopic cholecystectomy, for example, leads to a significantly lower IL-6 expression than an open procedure [1, 12, 18, 20]. A linear correlation between IL-6 and CRP levels has been demonstrated [12].

Hysterectomy is one of the most common procedures worldwide. In the United States alone, ~600,000 hysterectomies are performed annually [4]. Since the first documented procedure in 1989, laparoscopically assisted vaginal hysterectomy (LAVH) [16] has become a popular alternative to abdominal hysterectomy (AH) (in cases apparently difficult to manage via the vaginal route alone). This study was initiated to compare AH, vaginal hysterectomy (VH), and LAVH in terms of their impact on the acute-phase reaction. Mean outcome variables were serum levels of IL-6 and CRP.

Patients and methods

Between 1998 and 1999, 29 patients were included in the study (9 AH, 10 VH, 10 LAVH). All patients signed a written informed consent form. The study was approved by the local ethics committee.

Table 1. Patient characteristics

Treatment	*n*	Age (yr)	Height (cm)	Weight (kg)	Uterus size (cm)	Operating time (min)	Hb difference (mg/dl)
VH	10	50 ± 8.6	166 ± 8	68 ± 10	11 × 7.8 × 6.2	86 ± 37	1.3 ± 0.9
LAVH	10	50 ± 9.7	165 ± 6	75 ± 9	12.5 × 8.5 × 5.1	109 ± 20	1.7 ± 1
AH	9	56 ± 13	169 ± 8	74 ± 10	12 × 10 × 6	111 ± 29	1.9 ± 0.8

VH, vaginal hysterectomy; LAVH, laparoscopically assisted vaginal hysterectomy; AH, abdominal hysterectomy
All data given as mean ± SD
Uterine size according to the pathologist's report (length × width × depth in cm)
Mean blood loss given as drop in hemoglobin level measured preoperatively and on the 1st postoperative day

Blood samples of 8 ml were taken from each patient. The first sample was taken on the day of admission, the second during initiation of anesthesia, the third after opening the peritoneum or placement of the trocar, the fourth 30 min afterward. Blood samples five through nine were taken on peritoneal closure and 2, 12, 24, and 36 h postoperatively.

Twenty-five women presented with uterine fibroids, while four had relapsing bleeding anomalies. Treatment was determined by the performing consultant. At our hospital, the vaginal approach is most favored for simple hysterectomies. LAVH is favored for nulliparous patients, immobile uterus, previous pelvic surgery, or suspected adhesions. The abdominal route was chosen on the insistence of the patient or according to the preference of the performing surgeon. Patient selection therefore followed subjective criteria.

LAVH was performed according to the LAVH II previously described by Reich et al. [16]. AH and VH proceeded in the standard fashion described by Hirsch et al. [6]. A standardized anesthesia protocol was followed throughout all procedures, including a 0.1–0.2 mg alfentanile bolus, 0.07 mg/kg vecuronium bromide, and 2 mg/kg propofol for anesthesia, and 0.6–1.0 vol% isoflurane to maintain anesthesia. Postoperative pain management was based exclusively on intramuscular injections of piritramide and documented on a time scale.

IL-6 was measured in the university's Institute of Immunology using an ELISA assay (Bender MedSystems, Boehringer, Ingelheim, Germany). The assay detects IL-6 concentrations as low as 1.4 pg/ml and has an intraassay and interassay variation coefficient of 3.4% and 5.2%, respectively. CRP levels were measured by means of turbidometry (Boehringer). Measurements were blinded without the investigator knowing the surgical procedure.

Postoperative pain duration and need for analgesics (in αg piritramide) were documented on a standardized chart. Additional outcome variables were operative time and estimated blood loss as determined by preoperative and postoperative hemoglobin concentration.

Statistical analysis was performed using an analysis of variance (ANOVA) with repeated measurements. Extreme outliers were identified by a Q-Q plot and excluded from the analysis. Post-hoc tests were done with a *t*-test (Bonferroni correction). Results were considered significant with $p < 0.05$.

In order to indicate the effect of variables such as operating time, an analysis of variance with repeated measurements and one covariable was performed.

Results

The patient's mean age, height, weight, and postoperative size of the uterus (length × width × depth in cm) according to the pathology report are given in Table 1. The patient group undergoing VH had the shortest mean operating time (86 min), followed by LAVH (109 min) and finally AH (111 min). Due to these differences, we investigated the operative time as a possible covariable of the IL-6 and CRP expression. We demonstrated that these differences in operative times are not significant and do not interfere with the time courses. The fall in the hemoglobin concentration did not differ significantly among the three groups.

Figure 1 shows the IL-6 concentrations at the different time points in the three patient groups.

The ANOVA testing of within-subjects effects showed significant differences in the expression of Il-6 with respect to the time course and the parallelism within each group. Testing of between-subjects effects showed significant differences in the height of the expression of Il-6 between the three groups ($p < 0.013$).

The preoperative levels of IL-6 were comparably low. There was a significant increase in the IL-6 level in patients undergoing AH at the time of peritoneal closure. In all three groups, this increase reached a maximum 2 h postoperatively. In the group undergoing AH, it was significantly higher than the IL-6 levels of patients undergoing VH or LAVH (113.4 pg/ml vs 42.4 pg/ml and 46.5 pg/ml). The IL-6 level in the AH group remained significantly elevated for 12 h postoperatively. The concentration then fell and was comparable in all three groups 24 h after surgery. The post-hoc tests yielded significant differences at the time of opening of the peritoneum and 2 and 12 h after surgery among the patient groups.

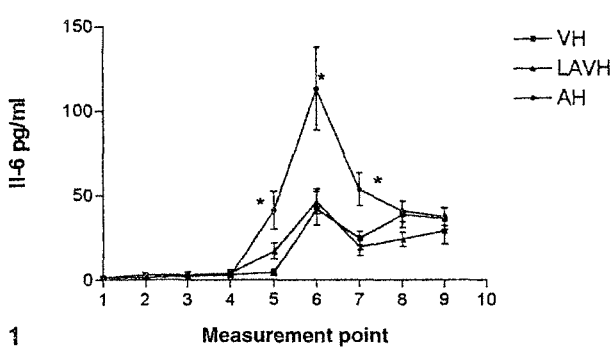
Figure 2 shows the CRP concentrations at the various time points in the three patient groups. Preoperative and intraoperative levels of CRP were comparably low. At 12 h after surgery, there was a linear rise of the CRP concentration that reached a peak after 36 hs. The post-hoc tests yielded significant differences between AH and VH 36 hs after surgery. However, the levels of the time courses did not differ significantly ($p = 0.06$).

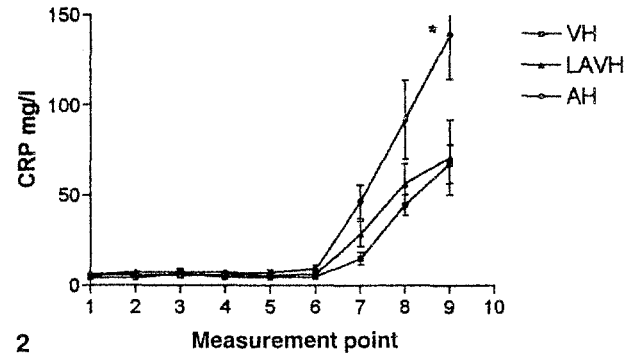
Pain duration after AH was 0.8 to 1.5 days longer than that following VH and LAVH (Fig. 3). Analgesic requirements were higher in the AH group (Fig. 3). However, these differences were not statistically significant.

Discussion

There are three different routes for hysterectomy: AH, VH, and LAVH. Numerous studies have compared the subjective parameters of surgical trauma, such as pain duration and intensity, postoperative analgesic requirements, and time taken to return to normal activity [10, 11, 14, 17]. According to these subjective criteria, the surgical trauma provoked by AH is significantly greater than that experienced with VH or LAVH.

This is the first prospective study to compare the surgical trauma of the three different techniques in terms of an





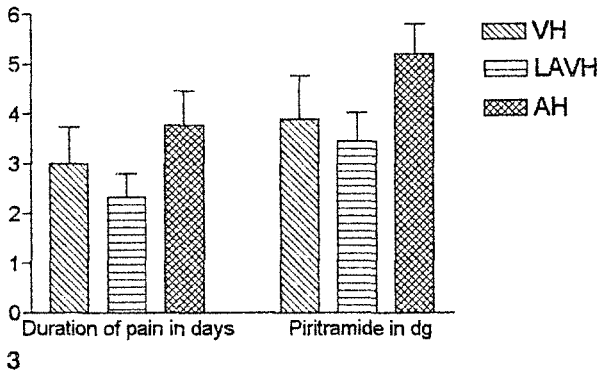


Fig. 1. Pre-, intra-, and postoperative IL-6 concentrations in 10 cases of vaginal hysterectomy (VH, $n = 10$), laparoscopically assisted vaginal hysterectomy (LAVH, $n = 10$), and abdominal hysterectomy (AH, $n = 9$). Measurement points: 1 = admission, 2 = during anesthesia, 3 = opening of the peritoneum, 4 = 30 min after opening of the peritoneum, 5 = closure of the peritoneum, 6 = 2 h after surgery, 7 = 12 h after surgery, 8 = 24 h after surgery, 9 = 36 h after surgery. All data are given as mean ± SEM. Levels of the time courses between the patient groups are different ($p = 0.013$). *AH vs VH and LAVH $p < 0.05$.

Fig. 2. Pre-, intra-, and postoperative CRP concentrations in 10 cases of vaginal hysterectomy (VH, $n = 10$), laparoscopically assisted vaginal hysterectomy (LAVH, $n = 10$), and abdominal hysterectomy (AH, $n = 9$). Measurement points: 1 = admission, 2 = during anesthesia, 3 = opening of the peritoneum, 4 = 30 min after opening of the peritoneum, 5 = closure of the peritoneum, 6 = 2 h after surgery, 7 = 12 h after surgery, 8 = 24 h after surgery, 9 = 36 h after surgery. All data are given as mean ± SEM. Levels of the time courses between the patient groups are different ($p = 0.013$). *AH vs VH and LAVH $p < 0.05$.

Fig. 3. Duration of pain (in days) and need for analgesics (in dg piritramide) after vaginal hysterectomy (VH, $n = 10$), laparoscopically assisted vaginal hysterectomy (LAVH, $n = 10$), and abdominal hysterectomy (AH, $n = 9$). Measurement points: 1 = admission, 2 = during anesthesia, 3 = opening of the peritoneum, 4 = 30 min after opening of the peritoneum, 5 = closure of the peritoneum, 6 = 2 h after surgery, 7 = 12 h after surgery, 8 = 24 h after surgery, 9 = 36 h after surgery. All data are given as mean ± SEM. *AH vs VH $p < 0.05$.

objective parameter such as the acute-phase reaction. Labib et al. [8] have compared AH to LAVH, demonstrating that 24 and 36 hs after AH the IL-6 concentration was significantly higher than it was after LAVH. There was a linear correlation between IL-6 and CRP levels.

In our study, levels of IL-6 and CRP were significantly higher following AH than after VH and LAVH. There was no difference in the acute-phase reaction provoked by VH or LAVH. IL-6 rose 12 h prior to the increase in CRP. The levels of the CRP time courses did not differ significantly among the patient groups; however, a pair-wise comparison showed an elevated CRP expression 36 h postoperatively in patients undergoing AH, as compared with VH.

Minimization of a possible selection bias is an important issue in observer studies. Table 1 shows that there were no significant differences among the three patient groups. Even the operation time had no impact on IL-6 and CRP expression. However, operation time, surgeon, indication, and choice of operative procedure can be important covariables. The last three factors cannot be eliminated completely. This aspect is reflected in the differing rates of vaginal approaches reported in publications concerning hysterectomies, which range from 81% [7] to 12% [19]. Experts in the vaginal approach argue that it is not necessary to apply additional laparoscopic techniques in this setting. Therefore, the indications for laparoscopically assisted vaginal hysterectomies vary significantly in the literature [9, 10, 13].

Even if objective criteria for the choice of the operative procedure existed, a certain selection bias could not be excluded completely. A single surgeon would have to perform all of the operations, and even then the surgeon's experience with the various operative approaches might differ.

Labib et al. [8] measured IL-6 and CRP levels only twice, at 24 and 36 hs after surgery. Closer monitoring of the serum parameters allowed us to document the progress of the acute-phase reaction. In contrast to our findings, Labib et al. [8] did not find any elevation in the IL-6 level after LAVH. However, our results correlate with the findings in numerous trials of laparoscopic vs open cholecystectomy showing a significantly greater increase of the IL-6 and CRP levels when open surgery was performed—a finding that is consistent with the greater tissue trauma following laparotomy [1, 12, 15, 20]. Our results regarding postoperative pain and analgesic requirements following the three

different surgical procedures are comparable to previously published data [6, 10, 11, 14, 17]; however, the number of patients in our series is too small to achieve significant results.

Our study shows that VH should be the first choice when standard hysterectomy is performed. In benign diseases of the uterus that are apparently difficult to manage via the vaginal route alone, LAVH should replace traditional open hysterectomy.

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