Local Anesthetic Administration Into Uterine Ligaments or Pelvic Cavity to Attenuate Surgical Stress Response During Abdominal Hysterectomy

Abdominal Histerektomi Sırasında Cerrahi Stres Yanıtını Azaltmak İçin Uterin Ligament veya Pelvik Kavite İçine Lokal Anestezik Uygulaması

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Geliş Tarihi/*Received:* 14.09.2009
Kabul Tarihi/*Accepted:* 06.04.2010

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ABSTRACT Objective: Surgically induced neural reflex responses and endocrine metabolic catabolic responses should be alleviated by effective pain-relieving techniques and neural block. The aim of this study was to compare the effects of two different local anesthesia techniques on the stress response during abdominal hysterectomy. **Material and Methods:** In this prospective, randomized study, 60 patients admitted for benign uterine diseases were divided into three groups; general anesthesia alone (Group CO-group control); general anesthesia plus 3 mL bupivacaine (0.5%) which was injected into the round and uterosacral ligaments (Group IN-group infiltration) bilaterally, and general anesthesia plus pelvic cavity irrigation with 40 mL bupivacaine (0.125%) (group IR-group irrigation). The heart rate, mean arterial pressure, plasma glucose and cortisol levels were recorded perioperatively. Recovery time was recorded and Numerical Rating Scale for pain was obtained 15 minutes after extubation. **Results:** Heart rate was the highest in Group CO compared to the other groups following the uterine removal and at the postoperative 15th minute ($P< 0.05$). The plasma cortisol level was the lowest in Group IN following the uterine removal and the highest in Group CO at the postoperative 15th minute ($P< 0.05$). Values of Numerical Rating Scale for pain were similar among the groups ($P> 0.05$). **Conclusions:** In addition to general anesthesia, local anesthetic administration into the uterine ligaments or the pelvic cavity may be more effective in attenuating the surgical stress response especially in whom this stress response would be deleterious.

Key Words: Hydrocortisone; blood glucose; round ligament; bupivacaine

ÖZET Amaç: Cerrahinin neden olduğu nöral refleks tepkiler ve endokrin metabolik katabolik cevaplar etkili ağrı-teknikleri ve sinirsel blokaj ile azaltılmalıdır. Bu çalışmada abdominal histerektomi sırasında stres yanıtına iki farklı lokal anestezi tekniğinin etkilerinin karşılaştırılması amaçlanmıştır. **Gereç ve Yöntemler:** Bu prospektif, randomize çalışmada, iyi huylu uterin hastalığı nedeniyle başvuran 60 hasta üç gruba ayrıldı; tek başına genel anestezi grubu (Grup CO-kontrol grup); genel anesteziye ek olarak bilateral round ve uterosakral ligament içine 3 ml bupivakain (%0.5) enjekte edilen grup (Grup IN-infiltrasyon grubu) ve genel anesteziye ek olarak 40 ml bupivakain (%0.125) ile pelvik kavite irrigasyon grubu (grup IR- irrigasyon grubu). Kalp hızı, ortalama arter basıncı, plazma glukoz ve kortizol düzeyleri perioperatif olarak kaydedildi. İyileşme süresi ve ekstübasyondan 15 dakika sonraki Sayısal Ağrı Değerlendirme Ölçeği de kaydedildi. **Bulgular:** Kalp hızları uterusun çıkarılmasını takiben ve postoperatif 15. dakikada Grup CO'da diğer gruplara göre en yüksek idi ($p< 0.05$). Plazma kortizol düzeyleri uterusun çıkarılmasını takiben IN Grubunda en düşüktü ve Grup CO'da postoperatif 15. dakikada en yüksekti ($p< 0.05$). Sayısal Ağrı Değerlendirme Ölçeği puanları gruplar arasında benzer bulundu ($P> 0.05$). **Sonuç:** Genel anesteziye ek olarak uterin ligamentler veya pelvik kaviteye lokal anestezik uygulaması özellikle stres tepkinin zararlı olacağı hastalarda cerrahi stres yanıtını azaltmada etkili olabilir.

Anahtar Kelimeler: Hidrokortizon; kan şekeri; halka ligaman; bupivakain

doi:10.5336/medsci.2009-15407

Turkiye Klinikleri J Med Sci 2011;31(2):438-42

Surgical injury is followed by profound changes in endocrine metabolic function and various host defense mechanisms leading to catabolism, immunosuppression, ileus, impaired pulmonary function and hypoxemia. As a result of endocrine and metabolic stress response in surgery, the plasma concentrations of cortisol, antidiuretic hormone, b-endorphin, lactate, catecholamine, glucose, other hormones and metabolites increase. Minimal physiological response would be beneficial. Particularly after a major trauma or operation such as a hysterectomy,[1] the response may lead to negative outcomes. Hypertension, tachycardia, increase in myocardial load, tissue hypoxia and acidosis resulting from vasoconstriction are some of these negative results. These negative physiologic changes are implicated in the pathogenesis of postoperative morbidity.[2] Surgically induced neural reflex responses and endocrine catabolic responses should be alleviated by effective pain-relieving techniques and neural block.[3] Inhalational anesthesia alone is generally insufficient in preventing these responses.[4] It has been claimed that the combination of general and local anesthesia methods could prevent these responses more effectively with minimal adverse effects. For example, general and epidural anesthesia have been combined successfully in thoracic surgery.[5] Additional local anesthetic administration has been reported during several plastic surgery operations e.g. liposuction under general anesthesia.[6] However, there is no known report about the effect of local anesthetic infiltration into the uterine ligaments during abdominal hysterectomy under general anesthesia.

It is known that the Lee-Frankenhauser sensory nerve plexuses and parasympathetic ganglia in the uterosacral ligaments carry pain from the uterus, cervix and other pelvic structures. Additionally, the round ligament contains branches of ilioinguinal and genitofemoral nerves. Consequently, in this novel study we aimed to investigate the effect prophylactic local anesthesia administration into the uterine ligaments for the prevention of metabolic and endocrine responses, decreased recovery times and decreased early postoperative pain following abdominal hysterectomy under general anesthesia.

We used bupivacaine as the local anesthetic. Bupivacaine is a member of the amide family. Its metabolism is relatively slow in comparison with other amide anesthetics. This delayed degradation accounts for the long duration of action of bupivacaine, which is 3 to 9 hours.[7]

MATERIAL AND METHODS

After obtaining their informed consents, sixty ASA physical status I-II patients admitted for benign uterine diseases were enrolled and in the study randomized. Randomization was performed by assigning patients into groups consecutively. The patients and investigators who assessed the plasma glucose, cortisol and pain levels were blinded to the groups; however, staff who applied interventions were not blinded to the groups. The patients with a history of allergy to local anesthetics, moderate or severe pain before the operation, endocrine or metabolic disorders, or therapy with analgesic drugs before the operation were excluded from the study. The study protocol and consent form were approved by the Ethics Committee of Ondokuz Mayis University. This study was performed under the principles of Declaration of Helsinki.

Patients were premedicated with diazepam 10 mg and famotidine 40 mg per orally. Non-invasive blood pressure monitoring, peripheral oxygen saturation and electrocardiography were applied to the patients. Prior to the induction of anesthesia, venous blood samples were obtained for measurements of glucose and cortisol as the control values. Anesthesia was induced using fentanyl 1 μg kg^{-1} and propofol 2.5 mg kg^{-1} followed by muscle relaxation with cis-atracurium 0.2 mg kg^{-1}. Endotracheal intubation was performed. Anesthesia was maintained with desflurane 3-6%, N_2O 60% in oxygen and fentanyl 1 μg kg^{-1} IV with 30 minutes intervals. Mean desflurane concentrations were calculated for each group. Patients were randomly assigned into one of the three groups at the beginning of the surgery. In the control group (Group CO), hysterectomy was performed under general anesthesia. In the infiltration group (Group IN), three ml of 0.5% bupivacaine (1.5 ml per ligament, 30 mg totally) was injected into each of the round

and sacrouterine ligaments after entering the peritoneal cavity. In the Irrigation Group (IR), 40 ml of 0.125% bupivacaine (50 mg) was used to irrigate the pelvic cavity. Operations were started 10 minutes after the procedure. Blood samples for glucose and cortisol measurements were obtained five minutes after uterine removal. Inhalation anesthetics were interrupted at the end of the skin closure. The time between induction of anesthesia and interruption of anesthetics was recorded as anesthesia duration. During the surgical closure of the peritoneum, meperidine 0.5 mg kg^{-1} IV was administered to the patients for early postoperative analgesia. Extubation was performed when the patients were able to follow verbal commands. The time between interruption of anesthetics and extubation was recorded as "recovery time". MAP, heart rate (HR) and peripheral oxygen saturation (SpO_2) were noted before the anesthesia induction (pre-induction), at the 5th minute after the uterine excision and at the 15th minute after the extubation. Blood samples for glucose and cortisol measurements were also obtained at the 15th minute after extubation. Postoperative pain was assessed with verbal numerical scale (NS) (0: no pain, 100: most severe pain) at the 15th minute after extubation.

Power analyses for estimation of case number: To show a plasma glucose level difference between two groups,[8] 107±16 mg dL^{-1} and 126±17 mg dL^{-1}, 12 patients in each group would be necessary using a type I error of 5% and a type II error of 20%. On the base of this calculation, we admitted 20 cases for each group. So, our study power was more than 80%.

The statistical analysis was performed using a commercially available software program (SPSS version 13.0, SPSS, Chicago, Illinois, USA). The normality of the data distribution was tested with Shapiro-Wilk test. Because the distributions of repeated measurement were normal; by using preoperative (pre-induction) data co-variant, co-variance analyses (ANCOVA) was used to compare second (at the 5th minute after the uterine excision) and third (15th minute after extubation) measurements. Post-hoc Tukey test was used for binary comparison.

One measurement data were compared between the groups by using ANOVA and Post-hoc Tukey if they were distributed normally. Because only NS values were not distributed normally, they were compared with Kruskal-Wallis tests variance analyses and then Mann-Whitney-U test. Data were presented as mean ± standard error of mean (SEM) and median (min;max). Significant levels were calculated for $P< 0.05$.

RESULTS

Case number, ages and body weights of the patients, anesthesia duration, recovery times, mean desflurane concentrations and values of NS were similar among the groups (Table 1).

Preoperative HRs were all similar among the groups, but HRs were the highest in Group CO when compared to Group IN and Group IR after the uterine excision and at the postoperative 15th minute ($P= 0.005$, $P= 0.007$; $P= 0.007$, $P= 0.009$, respectively) (Table 2).

MAPs were similar among the groups at all measurement times (Table 3).

Plasma glucose levels of Group CO were higher than levels of Group IR at the postoperative 15th minute ($P= 0.045$). All other values were similar between groups (Table 4).

Preoperative plasma cortisol levels were similar among the groups. Plasma cortisol levels of Group IN were lower than Group IR and Group CO

TABLE 1: Number of cases, age and body weight of the patients, desflurane consumption, operation time and recovery time were similar among the groups (mean ± SEM) ($P> 0.05$). NS values were also similar among the groups (median (min;max)) ($P> 0.05$).

	Group IN	Group IR	Group CO
n	20	20	20
Age (year)	45.45 ± 1.46	47.35 ± 1.65	44.70 ± 1.47
Body weight (kg)	67.35 ± 1.66	69.75 ± 2.54	68.55 ± 2.03
Anesthesia duration(min)	99.50 ± 4.84	100.30 ± 4.40	100.90 ± 6.10
Recovery time (min)	8.70 ± 0.45	8.30 ± 0.39	9.00 ± 0.69
Desflurane (%)	4.26 ± 0.07	4.43 ± 0.07	4.35 ± 0.07
NS	30.50 ± 30(10;60)	24.75 ± 20(10;60)	35.25 ± 35(10;60)

Group IN: Infiltration Group; Group IR: Irrigation Group; Group CO: Control Group; NS: Numerical Rating Scale for pain.

TABLE 2: Mean heart rate of control group was higher than the local anesthetic groups during the operation and early postoperative period (P< 0.05).

Heart Rate (beats/min)	Pre	ue	ext
Group IN	88.90 ± 2.09	70.55 ± 1.15*	75.15 ± 1.37**
Group IR	86.85 ± 3.15	73.65 ± 2.31&	74.70 ± 3.01&&
Group CO	91.60 ± 2.62	80.90 ± 2.17	87.40 ± 3.12

Group IN: Infiltration Group; Group IR: Irrigation Group; Group CO: Control Group; pre: preoperative; ue: 5 minutes after uterine excision; ext: 15 minutes after endotracheal extubation.

*: compared to Group CO, P= 0.005; &: compared to Group CO, P= 0.007;

**: compared to Group CO, P= 0.007; &&: compared to Group CO, P= 0.009.

TABLE 3: Mean arterial pressures were similar among the groups (P>0.05).

Mean Arterial Pressure (mmHg)	Pre	ue	ext
Group IN	99.50 ± 2.49	95.55 ± 2.71	97.55 ± 2.57
Group IR	102.65 ± 3.39	98.45 ± 2.83	97.75 ± 2.76
Group CO	95.90 ± 2.87	98.00 ± 3.22	97.85 ± 3.01

Group IN: Infiltration Group; Group IR: Irrigation Group; Group CO: Control Group; pre: preoperative; ue: 5 minutes after uterine excision; ext: 15 minutes after endotracheal extubation.

TABLE 4: Mean plasma glucose level of control group was higher than irrigation group at 15 minutes after endotracheal extubation (P< 0.05).

Plasma Glucose (mg/dL)	Pre	ue	ext
Group IN	90.80 ± 1.06	110.35 ± 1.89	117.75 ± 2.01
Group IR	93.45 ± 4.66	110.85 ± 3.39	115.40 ± 2.87*
Group CO	92.10 ± 2.88	112.55 ± 4.60	125.90 ± 4.79

Group IN: Infiltration Group; Group IR: Irrigation Group; Group CO: Control Group; pre: preoperative; ue: 5 minutes after uterine excision; ext: 15 minutes after endotracheal extubation.

*: compared to Group CO, P= 0.015.

after the uterine excision (P= 0.045; P= 0.016, respectively) and higher in Group CO than Group IN and Group IR at the postoperative 15th minute (P< 0.001; P= 0.001, respectively) (Table 5).

DISCUSSION

Hafizoğlu et al.[9] showed that better postoperative analgesia was achieved with local anesthetic wound infusion above fascia when compared to subfascial local anesthetic infusion after abdominal hysterectomy. In addition, it has been shown that prolonged sympathetic blockade associated with epidural analgesia might contribute to better preservation of glucose homeostasis in the perioperative period of abdominal hysterectomies.[10] It is not clear whether the metabolic and endocrine responses can be suppressed with the addition of a simple and easy local anesthetic administration to conventional inhalational anesthesia technique in hysterectomies. It is also known that sacrouterine nerve ablation can relieve chronic pelvic pain.[11,12] Most of the pain sensations of the uterine and pelvic structures are transmitted by the nerves in the sacrouterine and round ligaments. However, it is unclear whether the surgical stress response can be attenuated by infiltrating the uterine ligaments prior to uterine resection in abdominal hysterectomies.

Eriksson-Mjoberg et al.[13] reported that preoperative subcutaneous local anesthetic infiltration (bupivacaine 75 mg) did not prevent the increase of cortisol and interleukin-6 as a response to hysterectomy which is inconsistent with the results of our study. Of note, however, there is a significant difference between the methods of these two studies; in the Eriksson-Mjoberg study, local anesthetic solution was infiltrated into subcutaneous tissues, whereas, in our study, nerves which supply the uterus were blocked by the administration of local anesthetic into the peritoneal pelvic cavity (bupivacaine 50 mg) or into the uterine ligaments (bupivacaine 30 mg). Although we used a lower dose of local anesthetic, we targeted main nerves transferring uterine pain directly. In the present study, early postoperative glucose levels were lower in the local anesthetic groups when compared to inhalational anesthesia group. In addition, plasma cortisol levels were significantly higher in the control group compared to the study groups at the postoperative 15th minute.

TABLE 5: Mean plasma cortisol level of control group was higher than local anesthetic groups (P< 0.05).

Plasma Cortisol (µg/dL)	Pre	ue	ext
Group IN	15.95 ± 0.97	26.45 ± 0.82*,&	31.60 ± 1.47**
Group IR	14.00 ± 0.89	29.20 ± 0.82	31.35 ± 1.19&&
Group CO	14.75 ± 0.93	30.10 ± 1.54	39.80 ± 2.11

Group IN: Infiltration Group; Group IR: Irrigation Group; Group CO: Control Group; pre: preoperative; ue: 5 minutes after uterine excision; ext: 15 minutes after endotracheal extubation.

*: compared to Group IR, P= 0.045; &: compared to Group CO, P= 0.016; **: compared to Group CO, P< 0.001; &&: compared to Group CO, P= 0.001.

Heart rates were significantly lower in study groups compared to the control group. This has clinically significant implications, especially in patients in whom tachycardia would be detrimental. The effects of intraperitoneal local anesthetic infiltration in hysterectomies have been reported, however the changes in the heart rate and blood pressure values have not been determined.[14,15]

Pain scores (NS) were the highest in the control group, but the different was not statistically significant. We administered meperidine to all patients for postoperative analgesia. This might account for similar pain scores amone groups. Pain scores did not always correlate with heart rate and plasma cortisol level; different factors such as excess inflammation and stress response, anxiety and the use of analgesics, affect these parameters at different degrees. In studies which include more cases, pain scores can be found statistically different from control group.

Local anesthetic infiltrations did not lead to delay in recovery times from anesthesia, and the mean desflurane concentrations were equal in the groups. It has been reported that patients receiving combined epidural and general anesthesia required 21% less isoflurane than those receiving general anesthesia alone to maintain similar intraoperative spectral edge frequency, and this dose reduction resulted in faster emergence times in patients with nerve block.[16] However, our results were different, presumably because the nerve block was effective in a more limited area, blocked some part of pain transmission, and had shorter duration compared to epidural block.

In conclusion, the results of the present study show that irrigation of pelvic cavity with local anesthetic solution or local anesthetic infiltration into the uterine ligaments in addition to general anesthesia may be effective to control endocrine and hemodynamic disturbances during abdominal hysterectomy.

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