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A COMPARATIVE , DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF INTRAPERITONEAL ADMINISTRATION OF BUPIVACAINE AND LIDOCAINE FOR PAIN CONTROL AFTER DIAGNOSTIC LAPAROSCOPY

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ABSTRACT

The purpose of this study was to compare the effect of intraperitoneal bupivacaine and lidocaine administration on pain reduction after diagnostic laparoscopy. In this randomized, double blind, placebo controlled study, diagnostic laparoscopy was done for one-hundred and ninety-six infertile women with unexplained infertility. Patients were randomized to 4 groups (A, B,C, and D). At the end of the procedure, 30 mL of 0.125% bupivacaine, 30 mL of 5% lidocaine and 30 mL of normal saline was instilled in the pelvic cavity and 15 mL of the same solution over the diaphragmatic vault in group A, B and C, respectively. Group D received no intraperitoneal substance. The verbal pain scale questionnaire was used for assessment of postoperative pain.

In conclusion, when instilled intraperitoneally after diagnostic laparoscopy, bupivacaine significantly decreases postoperative pain for a long period. It also reduces the rate of analgesic needed, increases the rate at which patients were discharged 2 hours after surgery, and decreases hospital stay. It is highly effective compared to lidocaine and placebo.

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Keywords: Infertility, laparoscopy, pain, bupivacaine, lidocaine.

INTRODUCTION

The use of gynecologic endoscopic procedures, particularly laparoscopy, has increased dramatically in recent years. Although routinely performed in the outpatient setting, laparoscopy is associated with considerable discomfort, with most women requiring postoperative analgesia for abdominal, back, and/or shoulder pain. The reported incidence of postoperative pain following diagnostic laparoscopy varies from 35% to 65%.[1] Reducing postoperative pain to a level at which narcotic analgesics are no longer required is an important step toward performing outpatient laparoscopic procedures.[2] This pain, presumed referred and secondary to peritoneal stretching and diaphragmatic irritation, contributes to patient morbidity by increasing analgesic requirement postoperatively. The need for postoperative analgesia after outpatient surgery has been identified as the most important factor in postponing the resumption of normal daily

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activity.[3] Opioid drugs have a poor side effect profile; a reduction in their use should contribute significantly to patient care. The benefits of intraperitoneal instillation with various local anesthetics in reducing the intensity of postoperative pain after various laparoscopic procedures have been demonstrated previously.[2,13] But none have designed a study to incorporate a comparative, double blind, and randomized evaluation of two local anesthetic agents, placebo and no intervention for the reduction of pain after diagnostic laparoscopy. We designed this placebo-controlled study to test the effect of intraperitoneal instillation of bupivacaine and lidocaine on pain reduction after diagnostic laparoscopy.

MATERIAL AND METHODS

One-hundred and ninety-six infertile women aged between 19 and 31 years undergoing diagnostic laparoscopy were enrolled in this study at the Department of Obstetrics and Gynecology and Anesthesiology, Shiraz University of Medical Sciences. The University Ethics Review Committee for Human Research approved the study. Informed consent was obtained from each individual. Indication for laparoscopy was unexplained infertility. All laparascopies were performed between 0800h and 1300 h, under general anesthesia. Before surgery, each patient underwent a complete clinical history and physical examination to exclude the presence of metabolic or cardiorespiratory disorders. We excluded patients who had systemic disease, psychological problems, morbid obesity, previous pelvic operations and those who had allergy to protocol medications.

Patients were prospectively randomized to one of four groups (A,B,C,D) using standard random number table. So the surgeon, anesthetist and recovery personnel were blinded to the substance instilled. All patients underwent a standardized general anesthetic induction and maintenance. Patients were premedicated with Morphine 0.1mg/kg and Diazepam 0.1m/kg intravenously (IV). Anesthesia was induced with IV sodium thiopental 5mg/kg.

Muscle relaxation was achieved with succinylcholine chloride 1.5mg/kg. Anesthesia was maintained with halothane 1-1.5% and atracurium along with inhalation nitrous oxide and oxygen in a 50/50mix. Halothane was gradually discontinued. The muscle relaxant was reversed with neostigmine methylsulfate 50μg/kg (not exceeding 5mg) and atropine sulphate 15μg/kg. Patients were extubated in the operating room as clinically indicated. Under general anesthesia the patients were prepared and draped in lithotomy position with carbon dioxide insufflation. The sites of trocar insertion (umbilical and suprapubic area) were infiltrated with 2-4 mL of 2% lidocaine solution before incision. Diagnostic laparoscopy was carried out in the usual manner with two trocar sites and intraabdominal presure was maintained below 12 mmHg. In group A, at the end of the procedure, 30 mL of 0.125% bupivacaine was instilled to the pelvic cavity and 15mL of the same solution was instilled in each dome of diaphragm using an irrigator advanced through the ancillary port sites under direct vision. The same procedure was performed for group B and C with the same volume of 5% lidocaine and normal saline respectively. We did not give any intraperitoneal substance for group D. At the end of the procedure, the abdomen was deflated and the sites of trocar insertion were sutured. All patients were prescribed postoperative analgesia with 15 mg pethidine intravenously if needed. Recovery personnel gave analgesics again when requested by the patient.

In the recovery room, the patients and personnel were blinded to the intraperitoneal substance used. The verbal pain scale questionnaire,[14,15] ranging from 0 to 4 was used for patients' self-assessment of postoperative pain: 0= No pain, 1= Mild (pain on movement), 2= Moderate (pain on deep inspiration or coughing), 3= severe (pain at rest but no need for analgesics, 4= Very severe (severe pain at rest that needs analgesia). Patients remained in the recovery room until they were alert, and were then dicharged from the outpatient surgery unit. Patients' condition were assessed by recovery personnel and confirmed by an anesthesiologist.

Table I: Demographic and operative data of patients undergoing diagnostic laparoscopy.

Variable	Group A	Broup B	Group C	Group D
No. of patients	33	35	31	35
Age	24.483.3	24.883.1	24.83.4	252.8
Weight	64.397.1	63.55.5	62.96.6	63.26.7
Height	159.24.0	159.84.3	159.14.9	157.94.1
Gravidity	0.40.7	0.340.6	0.450.7	0.450.8
Parity	0.210.4	0.230.4	0.30.5	0.260.5
Operative time	23.44.9	23.14.8	23.75.7	22.25.6

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The patient was discharged if she was alert, had stable vital signs, and was ambulatory with minimal assistance. Furthermore patients had to tolerate oral fluids and have voided spontaneously. Time to discharge was measured from extubation until discharge from the outpatient surgery unit. Pain scores were assessed at 2 and 24 hours postoperatively.

Statistical analysis

Statistical analysis was accomplished using χ^2 test for proportional data and analysis of variance for parametric data. Verbal pain scale scores were compared using Kruskal Wallis test. Post-op comparisons were performed using the Tukey-HSD test. In all cases, $p<0.05$ was considered significant.

RESULTS

All patients who were found to have a condition that required operative laparoscopy, laparotomy or more than two punctures for laparoscopy and those patients who had any problem with general anesthesia were excluded from the study. One-hundred and thirty-four of one-hundred and ninety-six women were enrolled in the study from September 1996 to March 2002. Ten patients were excluded because of deviation from the standard general anesthesia, 2 from group A, 4 from group B, one from group C and 3 from group D. Twenty-two patients were excluded because operative laparoscopy was required for endometriosis or adhesions, 6 from group A, 5 from group B, 7 from group C and 4 from group D. The four treatment groups did not differ significantly in age, weight, height, parity, indication and operating time (Table I). Overall, group A contained 33 patients, group B contained 35 patients, group C contained 31 patients and group D contained 35 patients.

Pain scores at 2 and 24 hours postoperatively were significantly lower in group A as compared with group B (p= 0.038 for two hours and 0.014 for 24 hours postoperation) and group C (p= 0.0001 for two and 24 hours postoperation). As shown in Table II, pain scores in group B is also significantly lower than group C (p= 0.0001) and D (p= 0.524 for two and 24 hours postoperation respectively). The need for additional analgesic (pethidine) was significantly lower in group A (21.2%), compared with group B (31.4%) (p= 0.001), group C (61%, p= 0.001) and group D (62%, p= 0.001) (Table III).

The rate at which patients were discharged 2 hours after operation (NOPD) was significantly higher in group A (68.6%) compared with group B (63.8%), C (42%), and D (28.5%) (p= 0.001) (Table III). The mean±SD postoperative hospital stay was significantly shorter in the bupivacaine group (123±52 minutes) compared with group B (126±50),C (160±72) and D (177±72) (p= 0.001).

DISCUSSION

It is likely that the post-operative pain associated with diagnostic laparoscopy is secondary to peritoneal stretching, diaphragmatic irritation and to a lesser extent, abdominal puncture. The receptors involved seem to have been susceptible to blockade with a relatively low dose of local an-

Table II: Pain score in the four groups, 2 and 24 hours after operation.

Variable	G(A)	G(B)	P.V.	G(C)	P.V.	G(D)	P.V.
2 H	1.09±0.2	1.34±0.5	0.03*	3.16±0.7	0.0001*	3.28±0.6	0.0001*
24 H	0.15±0.2	0.15±0.2	0.01*	1.77±0.7	0.0001*	1.77±0.8	0.0001*

* p- value= Compared with group A

*: Significant

H= Hours postoperation.

G= Group

P.V.= p- value

Table III: Clinical outcome of the four groups.

Variable	Group A	Group B	Group C	Group D
Hospital stay*	126.6±52	123.6±50	160.8±72	177±72
NOPD(%)	68.6	63.5	42	28.5
NFA(%)*	21.2	31.4	61	62

* p- value= 0.001

NOPD=Number of patients discharged after 2 hours

NFA=Need for analgesia

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esthetics. Whereas the incidence in the lidocaine and control group is comparable with those reported in the literature, the incidence of pain in the bupivacaine group is significantly lower. In addition, the need for postoperative analgesics and time to discharge was reduced in the bupivacaine group. Although comparisons of pain scores between various studies are likely to be misleading, trials conducted previously[6,11] have not reported similar success with intraperitoneal local anesthetics in reducing the intensity of postoperative pain.

We anesthetized abdominal puncture sites in all patients to eliminate any bias that might be generated from puncture site pain. So as recommended by many authors,[16,17,18,19,20,21] all patients received local infiltration of 2-4 mL of 2% lidocaine at the surgical site before skin incision. Lee et al.[12] in their randomized, double blind study on patients who underwent laparoscopic cholecystectomy showed that intraperitoneal lidocaine instillation could not reduce postoperative pain. Saleh and coworkers[21] in their randomized study on 150 women undergoing laparoscopy for various gynecologic indications found that local administration of bupivacaine before incision and intraperitoneally was effective in reducing pain immediately after operative laparoscopy, but the effect was not seen beyond 30 minutes. This may be due to the fact that their patients had undergone operative laparoscopy and the pain could originate from the sites that were manipulated, cut and/or cauterized during the surgical procedure. Cunniffe et al.[1] showed that intraperitoneal irrigation with bupivacaine effectively reduced post-laparoscopy pain in comparison with placebo. He believed that the increased efficacy of intraperitoneal bupivacaine in his study might be because the solution was applied to both hemidiaphragms. We irrigated both hemidiaphragms with bupivacaine, lidocaine and placebo, however the efficacy of bupivacaine was significantly higher. Pasqualucci et al.[22] emphasise that the timing of administration of local anesthetics is fundamental to preempt postoperative pain. They believed that visual analogue pain scores and the consumption of analgesics were significantly lower in patients receiving intraperitoneal bupivacaine immediately after the creation of pneumoperitoneum than at the end of surgery. In our subjects, the possibility of a similar outcome upon instillation of bupivacaine solution at the beginning of surgery was not assessed. However our comparative, double blind study showed that intraperitoneal instillation of bupivacaine effectively reduces post-operative pain even if it was used at the end of the procedure.

Although we did not measure the plasma concentration of bupivacaine used, no associated complications during laparoscopy have been reported in other studies,[23,24] and peak plasma concentrations of this drug remained well below suggested limits to avoid cerebral toxicity.[25] Discharge time that was reduced significantly in group one may be the result of patients having fewer postoperative symptoms, sense of well-being, and less sedation. We concluded that intraperitoneal instillation of bupivacaine to both hemidiaphragms and pelvis at the end of diagnostic laparoscopy significantly reduces postoperative pain, hospital stay, and need for analgesics and is superior to lidocaine. We recommend that this protocol regimen be considered for women undergoing diagnostic laparoscopy.

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