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ARAŞTIRMA / RESEARCH

Effect of baricity of low dose diluted bupivacaine with fentanyl on the duration and quality of spinal block in transurethral prostatectomy

Düşük doz seyreltilmiş bupivakain ile fentanil yoğunluğunun transüretral prostatektomi için uygulanan spinal blok süresi ve kalitesi üzerine etkisi

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Abstract

Purpose: In this prospective randomized controlled trial, we investigated whether density of low dose diluted bupivacaine with fentanyl effects the duration and quality of the spinal block for transurethral prostatectomy (TURP) in elderly patients.

Materials and Methods: Sixty patients requiring elective TURP were randomly allocated into two groups. Group H (n=30) received fentanyl 20 mcg+hyperbaric bupivacaine 0.5% (1.5 ml)+ saline 1.1 ml. Group I (n=30) received fentanyl 20 mcg+plain bupivacaine 0.5% (1.5 ml)+ saline 1.1 ml in total, bupivacaine 0.25% (3 ml) intrathecally. Onset, duration of the sensory block, the degree of motor block, perioperative anesthesia quality, side-effects, analgesic-free period were assessed.

Results: The median peak level of the sensory block was significantly higher in Group H than in Group I. The time to the first analgesic request was longer in Group H). There were no differences between the groups for degree of the motor block, quality of anaesthesia, or adverse effects.

Conclusion: Low-dose diluted hyperbaric bupivacaine with fentanyl provides adequate anaesthesia, postoperative analgesia without haemodynamic instability or prolonging the recovery time for TURP in elderly patients.

Key words: Intrathecal,density, bupivacaine, fentanyl

Öz

Amaç: Bu prospektif randomize kontrollü çalışmada, yaşlı hastalarda düşük doz, dilue bupivakain ile fentanilin yoğunluğunun transüretral prostatektomi (TURP) için uygulanan spinal blok süresini ve kalitesini etkileyip etkilemediğini araştırdık.

Gereç ve Yöntem: Transüretral prostat rezeksiyonunu planlanan 60 hasta randomize olarak iki gruba ayrıldı. Grup H (n=30): Fentanil 20 mcg + hiperbarik bupivakain % 0.5 (1.5 ml) + normal salin 1.1 ml . Group I (n=30): Fentanil 20 mcg + plain bupivacain % 0.5 (1.5 ml) + normal salin 1.1 ml. Toplam %0.25 bupivakain (3 ml) intratekal uygulandı. Duyusal bloğun başlama zamanı ve blok süresi, motor bloğun derecesi, perioperatif anestezi kalitesi, yan etkiler ve analjezik gerekmeyen süre değerlendirildi.

Bulgular: Pik duyusal blok seviyesi Grup H' de, Grup I' ye göre anlamlı derecede yüksekti. İlk analjezik gerekme zamanı Grup H' de daha uzun idi. Motor blok derecesi, anestezi kalitesi veya yan etkiler açısından gruplar arasında fark yoktu.

Sonuç: Düşük doz dilue hiperbarik bupivakain ve fentanil birlikteliği, yaşlı hastalarda TURP için hemodinamik instabiliteye sebep olmadan ve derlenme süresini uzatmadan yeterli anestezi ve postoperatif analjezi sağlar.

Anahtar kelimeler: intratekal, yoğunluk, bupivakain, fentanil

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INTRODUCTION

Transurethral resection of the prostate (TURP) remains the surgical gold standard for the treatment of benign prostatic hyperplasia. Spinal anesthesia is the most commonly used anesthetic technique for transurethral resection of the prostate[1]. Patients are usually elderly and have co-existing diseases involving several systems. Therefore, it is important to limit the block level to reduce adverse cardiopulmonary effects and to allow rapid recovery in such patients.

More than 20 factors have been postulated to alter spinal anaesthetic block height. Characteristics of the injected solution such as density, volume, dose, concentration, temperature, patient characteristics such as height, intra-abdominal pressure, spinal anatomy, lumbosacral cerebrospinal fluid volume, the patient's position that affect intrathecal spread of local anesthetics[2].

Low-dose diluted local anesthetic can limit the distrubition of spinal block and shorten recovery time from spinal anaesthesia, but may not provide an adequate level of sensory block[2,3]. Use of intrathecal adjuvants with local anaesthetics has become a very popular practise in recent years for the better post-operative analgesia as well as to improve the quality of spinal block to facilitate functional recovery of patients[2] . Its combination with opioids can increase the perioperative quality of spinal blocks, with fewer cardiovascular changes in elderly patients[4,5]. Several clinical trials inwhich used to low dose diluted bupivacaine with fentanyl have shown that this combination can provide sufficient anaesthesia with rapid recovery in patients undergoing ambulatory surgery or TURP[6-8]. These studies did not evaluate the actual densities of the local anesthetics used, and it is not clear whether the results reported therein are related to concentration differences or density differences. To the best of our knowledge, this is the first comparative study of intrathecal fentanyl combined with low-dose diluted bupivacaine which is different density spinal anaesthesia for TURP in elderly patients.

We hypothesized that dilution of bupivacaine and addition of fentanyl may change the density of low-dose bupivacaine and the associated clinical profile in elderly patients undergoing TURP.

MATERIALS AND METHODS

Sixty patients requiring elective transurethral resection of the prostate were enrolled in a prospective study at the Ankara Diskapi Training and Research Hospital between June2013 and October 2013. The study was approved by the Ankara Diskapi Training and Research Hospital Ethical Committee, Ankara, Turkey on 17 December 2012 (06/43), (Clinicaltrials registration NCT01861041). Patients with a history of back surgery, infection at injection sites, coagulopathy, hypersensitivity to local anesthetics or opioids, mental disturbance, or neurologic disease were excluded.

All patients signed an informed consent form before operation. Sample randomization was used to allocate patients into one of two groups by an independent observer using a computer-generated sequence of numbers and sealed envelopes.

Group H (n=30) received Hyperbaric bupivacaine 0.5% (7.5 mg) (1.5 ml) (Marcaine®Spinal heavy, 0.5%, 4 mL ampule, AstraZeneca) + Fentanyl (20 mcg) (0.4 ml)(FentanylCitrate® 50 mcg/ml, Abbott Laboratories, North Chicago, USA) + Normal saline (1.1ml) (Izotonik Sodium Klorur® Turktıpsan, Ankara, Turkey), all intrathecally. The final solution administered to Group H contained 0.25% bupivacaine (3 ml) and had a density of1.02151±0. 00004 mg/ml.
Group I (n=30) received Plain bupivacaine 0.5% (7.5 mg) (1.5 ml) (Marcaine® 0.5%, 20mL flacon, AstraZeneca) + Fentanyl (20 mcg) (0.4 ml)(Fentanyl Citrate® 50 mcg /ml,Abbott Laboratories, North Chicago, USA) + Normal saline (1.1) (Izotonik Sodium Klorur®Turktıpsan, Ankara, Turkey), all intrathecally. The final solution administered to Group I contained 0.25% bupivacaine and had a density of 1. 00865±0. 00004 mg/ml.

Spinal anesthetic solutions were prepared aseptically just before injection. Density measurements and calibration of the densitometer were performed using the method of *pycnometry* at room temperature with a pycnometer at the Hacettepe University Faculty of the Pharmacy Department in Ankara, Turkey. A total of 5 density measurements were performed for each solution and expressed as mean ± SD. Density was measured according to the method of *pycnometry*, in which *wl* (the mass of the

empty pycnometer), *w2* (the mass of the pycnometer when it is filled with the liquid), and *w3* (the mass of the pycnometer when it is filled with a liquid having known density - in this case, ethanol, with a density of 0.79 g/ ml) are measured.

The density of the test liquid is then calculated as: $d_{liquid} = [(w2 - w1)/(w3 - w1)] \times d_{ethanol}$

The following parameters were recorded: age, body mass index (BMI), American Society of Anesthesiologists physical status (ASA PS), duration of operation, volume of intraoperative irrigation, and ultrasound estimated prostate volume. Heart rate (HR) and peripheral oxygen saturation (SaO2) were monitored continuously; systolic, diastolic and mean arterial pressures (SAP, DAP and MAP, respectively) were measured non-invasively with 5 min intervals during the procedure. Baseline values were recorded. Patients were not premedicated.Before spinal anesthesia patients received 0. 9% sodium chloride solution for 20 minutes(total volume: 500 ml). The intravenous (i.v.) infusion was minimally maintained during the surgical procedure and the patients stayed in the post-anesthesia care unit (PACU) to avoid overloading associated with absorption of the irrigating solution.

This study was conducted in a randomized, double-blind, controlled fashion. One of the investigators prepared the drug solution before anaesthesia. The anaesthetic administrator and the patients were blinded to the type of drug solution and the patient groups.

Spinal anesthesia was performed at the L4-5 or L3-L4 intervertebral space with the patient in the sitting position using a midline approach and a 25gauge Quincke needle. After verifying free flow of clear cerebrospinal fluid (CSF), the prepared solution was injected into the intrathecal space over the course of 30 sec. Following intrathecal injection, all patients were placed in a supine position.

Sensory block was measured at the midclavicular line with a pinprick test (using a22 gauge hypodermic needle) with 2 min intervals until the maximum block was achieved,then every 10 min thereafter until the resolution of the block. Motor block was measured when the maximum dermatomal spread was achieved according to the Modified Bromage Scale (0: no motor block, 1: hip blocked, 2: hip and knee blocked, 3: hip, knee and ankle blocked).Block at the T10 dermatome was the accepted readiness for surgery. Time of subarachnoid injection, time to T10-level sensory block, time to reach the maximum level of sensory block and this time motor block level were recorded. The quality of anesthesia was assessed as excellent (no discomfort or pain), good (mild pain or discomfort, no need for additional analgesic),fair (pain that required analgesic), or poor (severe pain that required analgesic) duringthe operation. Pain was measured on a 100-mm linear scale, the visual analogue scale (VAS,0: no pain, 100 mm: worst pain). Intra-operatively, patients who experienced pain, defined as having a VAS > 30 mm, were managed with 1 mcg/kg fentanyl i.v. as rescue analgesic. If the patient experienced mild discomfort and did not need additional analgesic, sedation was provided using 0.03 mg/kg midazolam bolus i.v. Additional analgesia and sedation requirements were recorded.

Hypotension (defined as a ≤30% decrease in the systolic blood pressure incomparison with baseline values or a systolic blood pressure of less than 80 mm Hg) was treated with 250 ml crystalloid boluses or 5 mg i.v. ephedrine. Patients having a heart rate of ≤50 beats/ min were treated with 0.5 mg of intravenous atropine and were classified a bradycardia requirement treatment.

At the end of the surgery, patients were transferred to PACU. A blinded observer assessed each patient's PACU discharge eligibility using Aldrete PACU discharge criteria. Patients were allowed to leave the PACU after achieving an Aldrete score of ≥9 and a spinal block level that has regressed below T10. The duration of the stay in the PACU,was recorded, and patients were transferred to the surgical ward after leaving the PACU. Patients with VAS >30 mm for analgesia received 1 g acetaminophene i.v. Time to first analgesic request was alsorecorded.

Statistical analysis

A sample size calculation was performed based on previous study [8],including the standard deviation of the time to the first request for analgesics. To detect a 30 min difference in the duration of the first request for analgesics (two-sided a of 5% and b of 10%), 23subjects were required per group. We decided to include 30 patients per group to allow for possible dropouts. SPSS 11.5 for Windows (SPSS Inc., Chicago, IL) was used for statistical analyses.

Patients' characteristics, age, weight, height, BMI, ASA PS, duration of operation, irrigation volume, preoperative prostate volume, time to peak block level, timeto two segment regression, and time to the first analgesic requirement were compared between groups using Student's t-test.

Results are shown as median (min-max) or mean(±standard deviation). The t-test was used for comparison of normally distributed data.The Mann-Whitney U test and log-rank test were used for nonparametric values. Categorical data (analgesics and side effects) were compared using Fisher's Exact Test. For analyses, $p<0.05$ was considered statistically significant.

RESULTS

The study was conducted on 60 male patients. Thirty-nine of 60 patients (65%) had one or more diseases such as hypertension, coronary disease, arrhythmia, chronic obstructive pulmonary disease, diabetes mellitus, parkinsonism.

Table1. Patient characteristics

	Group I (n=30)	Group H (n=30)	P*
Age (year)	65 (50- 86)	65 (53 - 86)	0,65
Weight (kg)	78. 2±9. 4	78.7 ±8. 7	0.83
Height (cm)	169. 4 ±5.7	171. 4±6. 9	0.22
Body mass index	26.8 ±2.5	26.3 ± 3.5	0.66
Duration of surgery	63.5 ± 31.3	69.9 ±24. 2	0.17
Irrigation volume	10.3±4.1	9.1± 2.3	0.11
Prostate volume (g)	58.3±24.8	51.3±15.9	0.44
Duration of PACU	34.1±27	26 ±14	0.14

Values are expressed as median (range) or mean ± SD *Significant difference at $p<0.05$

There was no difference between the groups regarding patient characteristics (Table1). The overall quality of spinal anesthesia was similar in both groups. All operations were finished using the planned anesthesia method; there was no conversion to general anesthesia. No significant differences were found in SAP or DAP and HR between the groups.The duration of surgery and discharge time from the PACU was similar in both groups (Table 1).

The densities of the local anesthetic solutions were 1. 02151±0. 00004 mg/ml in group H and 1. 00862±0. 00004 mg/ml in group I. The peak sensory block level [median (range)] was significantly higher in GroupH [T10 (L5–T8)] than in Group I [T12 (L5–T6)] (P=0.03). Time to T10 blockade (readiness for surgery) was similar between the groups (p=0.08).

Table 2. Characteristics of spinal blocks

	Group I (n=30)	Group H (n=30)	p*
Time to T10(min)	12.4±8. 1	8.7±4. 3	0.08
Time to peak block(min)	18.6±8. 8	11.3±4. 8	0.001
Time to two segment reg	68.4±22.6	90.6±31. 5	0.005
Maximum motor block	2(1-3)	2(0-3)	0.09
Peak sensory block	T12 (L5-T6)	T10 (L5-T8)	0.03
Time to motor block resolution	154±105. 2	182±60. 3	0.22

Values are median (range) or mean ± SD. *Significant difference at $p<0.05$

Table 3. Supplemental analgesic use and side-effects

	Group I (n=30)	Group H (n=30)	P*
Supplemental analgesics intraoperative	4 (%13)	0	0.113
Time to first analgesic request (h)	278.2 ± 62.6	421.8±247	0.03
Bradycardia	0	1 (%3.3)	0.492
Hypotension	0	2 (%6.7)	0.238
Nausea/Vomiting	5 (%16.1)	1 (%3.3)	0.195
Pruritus	2 (%6.7)	0	0.238

Values are mean ± SD or number of patients (%).*Significant difference at $P<0.05$

Time to reach maximum block was shorter in Group H than in Group I (p=0.001), but no significant difference occured level of motor blockade at the time of maximum blockade (p=0.09). Time to two-segment regression was significantly shorter in Group I compared to Group H (p=0.0005), but no significant differences occurred in the time to motor block resolution (p=0.22) (Table 2). During the postoperative period, the time to the first analgesics request was longer in Group H. Patients in the hyperbaric group had longer pain-free periods (p=0.03). There were no

differences in the adverse effects between the two groups (Table 3).

DISCUSSION

Our study showed that in comparison with adding fentanyl to a diluted low-dose plain bupivacaine, using hyperbaric bupivacaine confers the advantage of prolonging the duration of analgesia without increasing the duration of motor block or prolonging recovery time in elderly patients, despite the same mass of local anesthetic used.

Because of the prostate gland is mainly supplied by sensory branches from the pelvic plexus, a sacral block may provide sufficient analgesia for TURP, but to prevent the pain abdominal discomfort from the bladder distention with irrigation fluid the block must extend to sensory dermatome T12–L1.

Low-dose diluted local anesthetics shorten recovery time from spinal anesthesia and limit the distribution of the block[3]. The addition of fentanyl to low-dose bupivacaine has been increased the perioperative quality of spinal blocks with fewer cardiovascular changes in elderly patients. This combination can have a synergistic enhancement of somatic analgesia, without any associated effects on the level of local-induced sympathetic or motor block[7,8].

In our study the increased block level in Group H compared with Group I may be related to the density of drug solution. More than 20 factors have been postulated to alter spinal anaesthetic block height. Characteristics of the injected solution such as density, volume, dose, concentration, temperature, patient characteristics such as height, intra-abdominal pressure, spinal anatomy, lumbosacral cerebrospinal fluid volume, the patient's position that affect intrathecal spread of local anesthetics[2,9]. The density of compounds is believed to be a major determinant in controlling the extent of neural block[10].Fentanyl is a hypobaric (0.9933 mg/ml) agent and will render a resulting mixture even more hypobaric when added to a local anesthetic. We added 20 mcg fentanyl to the local anesthetics in order to increase the quality of the spinal block[8,10-12]. In our study, the solution density in Group H was 1. 02151 mg/ml, and 1. 00862 mg/ml in Group I. We measured the densities of our solutions at room temperature (23°C), but at body temperature (37°C), solution densities decrease. This decrease is significant with plain bupivacaine[13].For every increase in temperature by 1°C between 23°C and 37 °C the density of local anesthetic solution falls by 0.0003 mg/ml. Because a density difference may influence the movement of local anesthetic in a spinal canal model, the increased block level in Group H compared with Group I in our study may be related to the density of drug solution. The other possible cause may be the posture of the patients[9,14]. When using a hyperbaric solution, keeping the patients supine after injection will cause the local anesthetic to roll down the lumbar curvature into the mid-thoracic region, resulting in an average maximum sensory block level between T3 and T4. The positional change may have affected the block level in our study might as well.

The onset time of the sensory block depends on the time for the local anesthetic to move in the cerebrospinal fluid to reach spinal cord segment and the concentration of the local anesthetic to produce sensory block. Since the density of compounds is believed to be a major determinant in controlling the extent of neural block [10]. The shorter time to reach peak sensory block level in H compared with the group I may be related to the density of drug solution.

On the other hand, the peak block level was variable in each group (Table2). Positional change may extend the sensory block after subarachnoid administration of a plain bupivacaine solution that is slightly hypobaric at body temperature [14]. A greater spread of the block, due to density, resulted in a more expeditious elimination of the local anesthetic secondary to its increased exposure to the meninges and blood vessels. In our study the peak block level in Group I extended T6 and two-segment regression occurred significantly earlier than that of the Group H. Moreover, although this result is not statistically significant, 4 patients in Group I required supplemental analgesics during surgery, which can affect the quality of spinal anesthesia.

In our study, the time to the first analgesic request was longer in Group H (Table 3). Hyperbaricity of intrathecally administered local anesthetic prolongs the duration of analgesia according to at least two separate studies by Kooger et al. and Teoh et al[15,16]. Our study also proved that in Group H, a limited dermatomal spread resulted in a prolonged spinal analgesia as well as prolonged postoperative analgesia.

The incidence of adverse effects was very low in this study (Table 3). The low incidence of nausea and vomiting in our patients supports results obtained by other investigators in elderly patients [17]. Although pruritus has previously been reported as the most common adverse effect of intrathecal fentanyl, the patients in our study did not experience it, consistent with a previously reported finding that pruritus may not be a problem in elderly patients[18,19]. One limitation of this study is that we do not know the actual density of anesthetic in the CSF because we measured the densities at room temperature and baricity can change with body temperature.

In conclusion, low-dose diluted hyperbaric bupivacaine (7.5 mg) with fentanyl(20 mcg) provides adequate anaesthesia and postoperative analgesia without haemodynamic instability, increasing the intensity of motor block or prolonging the recovery time for TURP in elderly patients.

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