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# The Efficacy of Intrathecal Morphine with Bupivacaine for Postoperative Analgesia After TUR-B

# İntratekal Bupivakain İle Morfinin TUR-M Sonrası Postoperatif Analjeziye Etkisi

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**Öz**

**Amaç:** Bu randomize çalışmada transüretral mesane rezeksiyonu (TUR-M) sonrası analjezi için bupivakain ile iki farklı intratekal (IT) morfin dozu değerlendirildi.

**Gereç ve Yöntem:** Yetmiş beş hasta rastgele üç gruba ayrıldı. IT morfin (100 ug) ile 12,5 mg %0,5 bupivakain (1. Grup), IT morfin (200 ug) ile 12,5 mg %0,5 bupivakain (2. Grup) ve morfinsiz IT 12,5 mg %0,5 bupivakain (3. Grup) alanlar olarak. Postoperatif ağrı 24 saat boyunca VAS ile değerlendirildi ve ağrı şiddeti orta derecede olan her hastaya intravenöz parasetamol ve Dexketoprophen trometamol verildi.

**Bulgular:** Grup I ve II'de VAS skorları 1 saat, 2 saat, 4 saat, 6 saat, 12 saatte Grup III'e göre anlamlı olarak düşüktü ($p<0.05$). Analjezi talebi Grup III'te diğer iki gruba göre anlamlı derecede yüksekti ($p< 0.05$). Grup II'de postoperatif bulantı, diğer iki gruba göre daha fazla rapor edildi ($p<0.05$).

**Sonuç:** IT %12,5 mg %0,5 bupivakain ile morfin (100 ug ve 200 ug), yanlız IT %12,5 mg %0,5 bupivakain'e kıyasla postoperatif ağrı skorlarında anlamlı bir azalma sağladı. TUR-M sonrasında postoperatif ağrı kontrolünde IT 100 ug morfin, IT 200 ug morfinden önemli ölçüde karşılaştırılabilir daha düşük yan etkiler sağladı.

**Anahtar Kelimeler:** Spinal anestezi, morfin, postoperative ağrı, transüretral mesane rezeksiyonu.

**Abstract**

**Objective:** In this randomized study, we evaluated two different doses of intrathecal (IT) morphine with bupivacaine for analgesia after transurethral resection of bladder (TUR-B).

**Material and Method:** Seventy-five patients were randomly divided into three groups. They were allocated to receive IT morphine (100 µg) with 12.5 mg 0.5% bupivacaine (Group 1), IT morphine (200 µg) with 12.5 mg 0.5% bupivacaine (Group 2), and IT 12.5 mg 0.5% bupivacaine without morphine (Group 3). Postoperative pain was evaluated by VAS during 24 h and each patient was given intravenous paracetamol and Dexketoprophen trometamol if pain severity was moderate.

**Results:** VAS scores were significantly lower in Groups I and II than Group III at 1h, 2h, 4h, 6h, 12h ($p< 0.05$) (Figure 1). The request for analgesia was significantly higher in Group III than the other two groups ($p< 0.05$). More patients reported postoperative nausea in Group II than the other two groups ($p< 0.05$) (Figure 2).

**Conclusion:** IT morphine (100 µg and 200 µg) with 12.5 mg 0.5% provided a significant reduction in postoperative pain scores compared to IT 12.5 mg 0.5% bupivacaine alone. IT morphine 100 µg provided comparable postoperative pain control with significantly lower side effects than IT morphine 200 µg after TUR-B.

**Keywords:** Spinal anesthesia, morphine, postoperative analgesia, transurethral resection of bladder

## 1. Introduction

Transurethral resection of bladder (TUR-B) is a procedure that aims to find tumor's diagnosis and treatment. [1]. TUR-B is a treatment method, which is applicable for superficially invasive transitional cell tumors and radical cystectomy in high-risk patients with deeply non-invasive tumors [1]. Spinal or epidural anesthesia, which achieves sensory block at T10 level, provides excellent anesthesia and appropriate operating conditions in TURP procedures. Regional anesthesia, when compared to general anesthesia, reduces the incidence of postoperative venous thrombosis. In addition, it is preferred as the anesthetic technique since it does not mask signs and symptoms of major complications of bladder perforation [2, 3]. Therefore, it is recommended that spinal anesthesia is the technique of choice for in patients under going transurethral resection (TUR) [4].

Opioid analgesia is known to be one of the most effective pain management techniques [5]. The direct administration of morphine into the spinal cord provides spinal anesthesia. Therefore, intrathecal morphine provides long-term pain relief in the postoperative period [5, 6]. The addition of morphine to local anesthetics intratechally during spinal anesthesia has provided effective postoperative analgesia after a number of surgical procedures [7, 8]. However, opioids cause side effects such as postoperative nausea, vomiting, sedation, respiratory depression and pruritus. Therefore, the risks and benefits of intrathecal morphine as well as dose responses have been investigated for different surgical procedures [6].

Cunningham et al [9] reported that excellent surgical anesthesia and postoperative analgesia was achieved with the addition of intrathecal morphine 1 mg to local anesthetics. However, morphine 1 mg caused a considerable increase in the incidence of side effects. Succeeding investigators studied lower doses of intrathecal morphine in patients undergoing TURP and reported that effective analgesia could be achieved with doses below 200 µg without causing severe respiratory depression [3, 10, 11].

Patients report postoperative pain and distress after TURB especially due to the presence of urinary catheter. Addition of intrathecal morphine to local anesthetics for spinal anesthesia has not been studied in patients undergoing TURB. This prospective randomized controlled study aims to compare the effects of 100 µg and 200 µg intrathecal morphine added to local anesthetic bupivacaine during spinal anesthesia in patients undergoing TURB and the side effect profiles of the two doses of morphine.

## 2. Materials and Methods

This study was conducted as a prospective randomized trial at the department of Urology. After Faculty ethic committee approval (04-02-2011. No:10-12./43), the patients were informed about the details of the study during pre-anesthetic evaluation and each patient was asked to read the informed consent form.

A total of 75 ASA I-III patients aged between 30-85 years who were scheduled to undergo TURB with spinal anesthesia were enrolled in this study. Patients who had allergic reactions to paracetamol, morphine, non-steroidal anti-inflammatory drugs (NSAIDs), those who had sleep-apnea syndrome, liver failure, gastrointestinal hemorrhage, hemorrhagic diathesis, coagulopathy, Crohn's or ulcerative colitis and neuropathy or patients receiving anticoagulant therapy and those who routinely receive analgesics and who had received analgesics in the last 24 hours were excluded from the study.

Vascular access was performed via an 18 G catheter in all patients and noninvasive blood pressure, electrocardiography (ECG), and SpO2 were used for standard monitoring. Patients were divided into three groups based on a computer-generated randomization scheme and they were not informed of which group they were assigned to. Patients received no premedication. Spinal anesthesia was performed through L3-L4 intervertebral space using a 26 G Quincke needle with the patients in the sitting position. Patients in Group I (n= 25) were injected with 100 µg intrathecal morphine (0.5 ml) + 12,5 mg of 0.5% bupivacaine heavy (2,5 ml). Patients in Group II (n= 25) were injected with 200 µg intrathecal morphine (0.5 ml) + 12,5 mg of 0,5% bupivacaine heavy (2,5 ml). Patients in Group III (n=25) were injected saline (0.5 ml) + 12,5 mg of 0,5% bupivacaine heavy (0.5 ml). With the patients in the lithotomy position, oxygen was delivered at a flow rate of 5 L/min via a transparent facemask. After motor and sensory block was achieved, surgical procedure was allowed. In the intraoperative period, arterial blood pressure (ABP), heart rate (HR) and SpO2 were recorded at 5-minute intervals. A decrease in ABP by 20% compared to baseline values was regarded as hypotension. In such a situation, the requirement for vasopressor was recorded and ephedrine 5 mg was administered. In the postoperative recovery room, pain scores (VAS= Visual Analogous Scale; 0= no pain and 10= extreme pain), vital findings (heart rate, blood pressure, respiratory rate (RR), SpO2) and side effects (nausea, vomiting, pruritus, respiratory depression) were recorded every 15 minutes in the first one hour and afterwards at 2, 4, 6, 8, 12, 18 and 24 hours for each patient. Respiratory depression was defined as RR less than 12 breaths/minute. Nausea, vomiting, pruritus were recorded as absent or present. During the postoperative follow up, paracetamol infusion 1 g/100 ml was administered for at least 20 minutes to patients with VAS scores of > 3. Dexketoprofen trometamol 50 mg was administered by slow infusion (at least 20 minutes) to patients in whom pain control was not achieved and

patients' need for additional analgesics was recorded. At the end of the study, patient satisfaction was recorded as very good, good, moderate, poor.

*2.1 Statistical Analysis*

Statistical data were analyzed using SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented as mean ± standard deviation. Student t test was used for the comparison of parametric data between the groups and Mann Whitney U test was used for the comparison of nonparametric data between the groups. The comparison of qualitative data was performed using the Chi-square test. A p value of $< 0.05$ was considered statistically significant with 95% confidence intervals.

## 3. Results

The groups were similar in demographic data and duration of surgery (Table 1). Intraoperative HR and ABP were similar in both groups. Adequate surgical anesthesia was achieved in all patients and none required intraoperative additional analgesia. During the surgery, 2 cases in Group I and II, 1 case in Group III required ephedrine and no significant differences were noted between the groups in the need of ephedrine. No patients had respiratory depression in the perioperative and postoperative period.

**Table 1.** Demographic data and duration of surgery in three groups (mean ± SD)

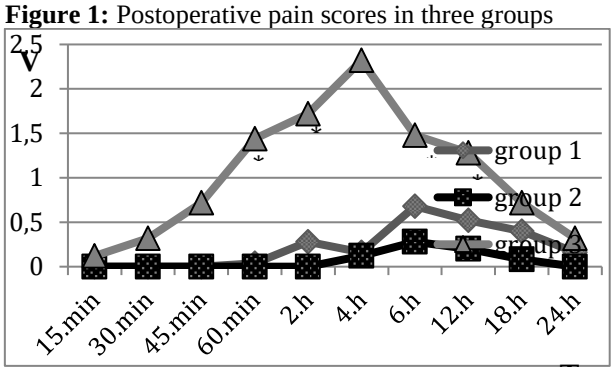
| | Group I (n=25) | Group II (n=25) | Group III (n=25) | P |
|---|---|---|---|---|
| **Age** (year) | 68±11 | 65±9 | 64±10 | 0.413 |
| **Weight** (kg) | 77±13 | 78±13 | 75±12 | 0.686 |
| **Length** (cm) | 171±7 | 173±6 | 171±4 | 0.141 |
| **Duration of surgery** (min) | 36±8 | 36±11 | 36±9 | 0.976 |

cm: santimetre, kg: kilogram, min: minimum

VAS scores were significantly lower in Groups I and II than Group III at 1, 2, 4, 6, 12 hours postoperatively (Figure 1). With regard to the need for additional analgesia; 1 patient in Group I and 0 patient in Group II, and 11 patients in Group III required the administration of additional analgesic paracetamol 1 g/100 ml due to high postoperative pain scores (VAS > 3). The need for rescue analgesia was significantly higher in Group III compared to the other groups ($p<0.05$). Three patients in Group III were given Dexketoprofen trometamol 50 mg because pain control was not achieved with parasetamol infusion.

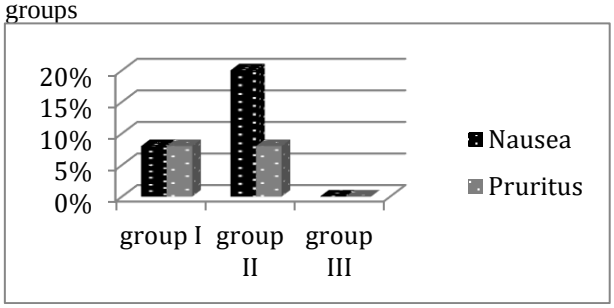
Time to the first request for analgesia was 2 hours in one patient in Group 1. The distribution of patients for the time for the first request for analgesia in Group III was as follows: 4 patients in 1 hour, 4 patients at 2 hours, 3 patients at 4 hours.

**Figure 1:** Postoperative pain scores in three groups




With regard to the postoperative nausea; no patients in Group III had nausea, 2 patients (8%) in Group I and 5 patients (20%) in Group II had nausea in the postoperative period. No patients needed treatment for nausea. The incidence of nausea was significantly higher in Group II compared to the other groups ($p<0.05$). (Figure 2).

**Figure 2:** The incidence nausea and pruritis in three groups



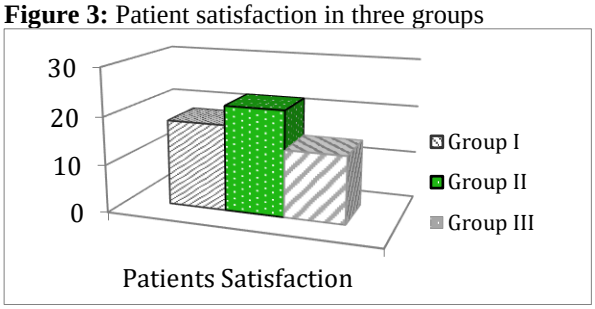

With regard to the pruritus; no patients in Group III had pruritus. In Group I and II 2 patients (8%) had pruritus. No patients required treatment for pruritus. There were not statistically significant differences between the groups in pruritus (Figure 2).

The distribution of the cases with regard to patient satisfaction is presented in Figure 3. Patient satisfaction was similarly high in both groups (Group I %72, Group II %88, Group III %56).

## 4. Discussion

In this study, we found that postoperative pain scores and analgesic requirement were significantly reduced in patients undergoing TURB with spinal anesthesia who received 100 and 200 µg intrathecal morphine versus those who did not receive intrathecal morphine. Since the incidence of nausea was significantly higher in patients receiving 200 µg intrathecal morphine, we concluded that the use of 100 µg intrathecal morphine is effective and appears to be preferable in patients undergoing TURB with spinal anesthesia. Excellent surgical anesthesia and postoperative analgesia with the addition of intrathecal morphine 1 mg to local anesthetics was first reported by Cunningham et al in 1983 in patients undergoing transurethral prostatectomy [9].

**Figure 3:** Patient satisfaction in three groups




However, the incidence of unfavorable side effects such as respiratory depression, nausea, vomiting and pruritus was found to be high because of the use of high dose morphine (1 mg) in that study. After several studies demonstrating that effective postoperative analgesia without respiratory depression could be achieved with lower doses, Kirson et al [3] in 1989 compared the administration of 100 µg versus 200 µg intrathecal morphine to evaluate the effectiveness and duration of postoperative analgesia together with the incidence of side effects after transurethral resection of the prostate. In the study by Kirson et al [3], spinal anesthesia was achieved with lidocaine 75 mg and, in case of need for additional analgesia, paracetamol 650 mg was used for mild pain, paracetamol plus codeine phosphate 60 mg or oxycodone 10 mg were use for moderate pain and parenteral morphine sulphate was used for severe pain. The authors reported that patients receiving 100 µg and 200 µg morphine intratechally required fewer additional analgesia compared to the control group. None of the patients had respiratory depression and the incidence of nausea and vomiting was found to be 10% in the control group, 20% in the group receiving intrathecal morphine 100 µg and 60% in the group receiving intratechal morphine 200 µg which was significantly higher compared to those in the other groups. The incidence of pruritus was reported to be 20% in the group receiving intrathecal morphine 100 µg. Additionally, nausea and vomiting due to intrathecal morphine 200 µg was treated with a bolus of naloxone 0.1 mg, however, no data were provided concerning the severity of nausea and vomiting and the number of patients requiring treatment for nausea and vomiting. The authors reported that both doses were effective in reducing postoperative pain, however, intrathecal morphine 100 µg was not associated with nausea and vomiting, thus being more advantageous [3].
In another study by Sakai et al [10], the efficacy of intrathecal morphine doses of 50 µg and 100 µg in patients undergoing transurethral resection of the prostate with spinal anesthesia using tetracaine 10 mg and the side effect profiles were compared. The authors, in contrast to the study of Kirson et al [3], used visual analogue scale to evaluate pruritus and nausea. However, pain and side effects were only treated when requested by patients and pain was treated with diclofenac suppository 25 mg. Metoclopramide 10 mg iv was used for nausea, and naloxone 0.1 mg iv for pruritus. In the study by Sakai et al [10], there were no statistically significant differences between the use of 50 µg and 100 µg doses of intrathecal morphine in pain control and additional analgesia. The incidence of nausea was found to be 23% in the 50 µg intrathecal morphine group and 33% in the 100 µg intrathecal morphine group. The incidence of pruritus was found to be high in both groups, with 43% in the 50 µg intrathecal morphine group and 93% in the 100 µg intrathecal morphine group, thus requiring no treatment. The authors concluded that, because of the high incidence of pruritus due to 100 µg intrathecal morphine, the optimal dose of intrathecal morphine for postoperative analgesia was 50 µg in TURP procedures [10].

Addition of intrathecal morphine to local anesthetics for spinal anesthesia has not been studied in patients undergoing TURB. Therefore in this study we compared the administration of 100 µg and 200 µg doses of intrathecal morphine in patients undergoing TURB with spinal anesthesia. We found that we found that postoperative pain scores and analgesic requirement were significantly reduced in patients undergoing TURB with spinal anesthesia who received 100 and 200 µg intrathecal morphine versus those who did not receive intrathecal morphine. The time to the first request for analgesia was also recorded and all the patients in the control group necessitated analgesic therapy within the first 4 hours postoperatively. Considering the side effects of intrathecal morphine 100 µg caused less nausea compared to 200 µg (8% in Group I and 20% Group II). In the studies by Kirson et al [3] and Sakai et al [10] the incidence of nausea was reported as 20% for 50 µg intrathecal morphine and 33% for 100 µg intrathecal morphine. In our study, 8% of the patients in the groups I and II experienced mild pruritus. This incidence was lower than those reported as 43% and 93% for intrathecal morphine doses of 50 µg and 100 µg, respectively, by Sakai et al [3]. In our study, pruritus was not severe and no treatment was required. Therefore, intrathecal morphine 100 µg seems to be an appropriate and preferable dose.
Duman et al [11] compared 25 µg and 50 µg doses of intrathecal morphine on postoperative analgesic requirements in patients undergoing TURP with spinal anesthesia. However, the results of the study by Duman et al [11] revealed that 31-36% of patients experienced pain and the mean postoperative pain scores were still high at postoperative 12 hour.

At least T10 dermatome is required in TURP procedures. Lower doses of bupivacaine were used for spinal anesthesia in some studies [11, 12], in which, however, adequate level of sensory block could not be obtained. Spinal anesthesia is preferred to general anesthesia in TURM procedures since it allows early diagnosis of severe complications such as fluid overload and bladder perforation. In this study, we preferred to use bupivacaine 12.5 mg to eliminate the possibility of inadequate anesthesia with low dose local anesthetics and the necessity to shift to general anesthesia. No patient experienced inadequate anesthesia or required additional

analgesia with the selected doses of bupivacaine and morphine during the procedure.

The most feared side effect of the use of intrathecal morphine in postoperative analgesia is respiratory depression. Respiratory depression may occur up to 18-24 hours due to cephalad spread of morphine, a hydrophilic opioid, in the CSF [4]. Gustefsson et al [13] reported that the incidence of late respiratory depression was 0.36% in patients receiving intrathecal morphine at doses of between 0.2 mg and 0.8 mg and no patients receiving intrathecal morphine at doses below 0,3 mg had respiratory depression. The other studies demonstrate that the efficacy of intrathecal morphine is limited at doses over 300 µg due to its side effects [5]. In the studies evaluating the incidence and severity of side effects such as nausea and vomiting together with the quality of analgesia, the optimal dose has been defined as the one that minimizes nausea and pruritus without reducing analgesia. Previous studies on the use of intrathecal morphine in postoperative analgesia in patients undergoing TURP with spinal anesthesia have reported effective analgesia at doses of 200 µg or lower without respiratory depression [3, 9, 10]. These studies have reported different values for the incidence and severity of nausea and pruritus, which may have been caused by different evaluation criteria in study protocols.

In this study, we found that postoperative pain scores and analgesic requirement were significantly reduced in patients undergoing TURB with spinal anesthesia who received 100 and 200 µg intrathecal morphine versus those who did not receive intrathecal morphine. Since the incidence of nausea was significantly higher in patients receiving 200 µg intrathecal morphine, we concluded that the use of 100 µg intrathecal morphine is effective and appears to be preferable in patients undergoing TURB with spinal anesthesia.

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