Wound Infiltration with Bupivacaine and Intramuscular Diclofenac Reduces Postoperative Tramadol Consumption in Patients Undergoing Radical Retropubic Prostatectomy: A Prospective, Double-blind, Placebo-controlled, Randomized Study

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OBJECTIVES To assess the impact of wound infiltration with bupivacaine and i.m. diclofenac administration on patient-controlled analgesia (PCA) tramadol consumptions and postoperative pain in patients who underwent radical retropubic prostatectomy (RRP) under general anesthesia. Previous studies have found only limited or no benefits of local anesthetics for postoperative opioid consumption and pain relief after RRP.

METHODS In this prospective, double-blind, placebo-controlled, randomized trial, 96 men who underwent RRP were randomized into 2 groups. Each group (n = 48) received either wound infiltration with 0.5% bupivacaine during surgical closure and i.m. 75 mg diclofenac (group BD) or wound infiltration with saline during surgical closure and i.m. saline (group P). PCA with i.v. tramadol was used for postoperative analgesia. PCA tramadol consumptions and pain scores were collected at 1, 2, 6, 12, and 24 hours postoperatively.

RESULTS The mean cumulative tramadol consumption was significantly lower in group BD (184.43 ± 38.58 mg) compared with group P (269.52 ± 52.46) at 24 hours ($P < .001$). The pain scores were significantly lower in group BD compared with group P ($P < .05$). The number of patients who required rescue antiemetic and analgesic was lower in group BD than in group P, revealing a significant difference ($P < .05$). Patients' satisfaction scores were significantly higher in group BD than in group P ($P < .001$).

CONCLUSIONS This prospective, double-blind, placebo-controlled, randomized study demonstrated that wound infiltration with bupivacaine during surgical closure combined with i.m. diclofenac administration might decrease in 24 hours with PCA tramadol consumption in patients who underwent RRP under general anesthesia. UROLOGY 78: 1281–1286, 2011. © 2011 Elsevier Inc.

Prostate cancer is one of the most frequently diagnosed cancers in the male population, which were predicted to have resulted in >32,050 deaths and 217,730 new cancer diagnoses in the United States in 2010.[1] Currently, radical prostatectomy is the standard treatment for patients with early-stage prostate cancer.[2]

A considerable number of patients experienced moderate to severe pain after radical prostatectomy, and administration of opioid analgesics are one of the most common methods for postoperative pain management. However, opioid analgesics have side effects, such as postoperative nausea and vomiting (PONV), sedation, ileus, ventilatory depression, pruritus, and cognitive dysfunction. Clinicians would aim reduction in opioid requirement and alleviate pain after radical prostatectomy. There is now good evidence that patients benefit from the use of multimodal, or balanced, analgesia after surgery.[3,4] Nonsteroidal antiinflammatory drugs (NSAIDs), local anesthetics, other nonopioid analgesics, and opioids are used in combination to improve pain relief. In contrast to using individual agents, current recommendations for pain management after surgery would approve

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the minimization of opioids and prefer the use of multimodal opioid-sparing therapy.[3,4]

Recent studies have been contradictory, and most of them emphasize the procedure-specific techniques for postoperative pain relief.[4] To our knowledge, the effects of wound infiltration with local anesthetics and NSAIDs on opioid consumptions after radical retropubic prostatectomy (RRP) have not been reported in a well-designed prospective study. In this prospective, double-blind, placebo-controlled, randomized study, we hypothesized that wound infiltration with bupivacaine during surgical closure combined with i.m. diclofenac administration in patients who underwent RRP under general anesthesia might decrease with patient-controlled analgesia (PCA) tramadol consumptions.

MATERIAL AND METHODS

After institutional review board approval and written informed consent, 96 men who underwent elective RRP under general anesthesia were included in this prospective, double-blind, placebo-controlled, randomized trial. Patients who were 18 years or older and American Society of Anesthesiologists (ASA) physical status ≤3 were included in the study. Patients who had allergy to any of the study medications, inability to use the PCA device, history of chronic pain conditions or chronic opioid medication, history of significant liver or kidney diseases, history of gastroduodenal ulcer, or bleeding disorders were excluded from the study. All patients were taught to use the PCA pump (Pain Management Provider, Abbott Laboratories, North Chicago, IL) and the verbal rating scale (VRS) for pain assessment before operation.

The hospital pharmacy prepared 2 medication sets as bupivacaine and diclofenac (BD) and placebo (P), using computer–generated randomized numbers, and therefore the patients were randomized into 2 groups (group BD and group P). The contents of set BD were 20 mL of 0.5% bupivacaine (Marcaine 0.5% AstraZeneca Plc, London, UK; half-life range 120-240 min) in the syringe and 3 mL 75 mg diclofenac (Dikloron, Deva, Istanbul, Turkey; half-life range 100-180 min) in the syringe. In set P, 20 mL saline was in the syringe and 3 mL saline was in the syringe. Group BD patients (n = 48) received set BD, whereas group P (n = 48) received set P. The patients and study teams were unaware of the group allocation.

Each patient underwent the same anesthesia and surgical technique. The patients received premedication with midazolam i.v. (0.15 mg kg^{-1}). Anesthesia was induced with thiopental sodium (5 mg kg^{-1}) and maintained with sevoflurane (2-2.5%) in a mixture of 65% nitrous oxide in oxygen. Neuromuscular relaxation was induced and maintained by i.v. boluses of vecuronium bromide. The patients were intubated and ventilated mechanically to maintain the end-tidal carbon dioxide between 4.7 and 6 kPa. Heart rate, invasive arterial blood pressure, central venous pressure, and S_pO_2 were recorded at 5-min intervals throughout the surgical procedure.

In group BD, the wound was infiltrated with 20 mL of 0.5% bupivacaine during surgical closure, and 3 mL 75 mg diclofenac i.m. was performed. In group P, the wound was infiltrated with 20 mL of saline during surgical closure and 3 mL saline i.m. was performed. Metoclopramide 10 mg was administered for PONV prophylaxis. For postoperative analgesia, PCA with i.v. tramadol (initial dose 1 mg kg^{-1}, bolus dose 0.2 mg kg^{-1}, 10-min lockout) was used, starting on arrival to the postanesthesia care unit (PACU). The evaluation of pain and tramadol consumption was begun at that point. In the 2 groups, i.v. fentanyl 1 μg kg^{-1} was used for analgesic rescue (VRS ≥4), and i.v. metoclopramide 10 mg was given as an antiemetic drug, when required. The patients discharged to home with flurbiprofen 100 mg tablet, 2-3 times a day, as needed for their pain.

Data were collected by an anesthesiologist blinded to the patients' randomization at 1 min after recovery and at 1, 2, 6, 12, and 24 hours postoperatively. The primary outcome measure was PCA tramadol consumption. The secondary endpoints included the evaluation of pain at rest (11-point VRS, 0 = no pain, 10 = worst possible pain); sedation scores (modified Ramsay score 1 = anxious, restless or both; 2 = cooperative, oriented, and tranquil; 3 = responding to commands; 4 = brisk response to stimulus; 5 = sluggish response to stimulus; 6 = no response to stimulus)[5]; fentanyl requirement; and metoclopramide requirement. At 24 hours, satisfaction with postoperative pain management was evaluated (11-point VRS, 0 = not satisfied, 10 = extremely satisfied).

Statistics

Statistical analyses were done using SPSS software, version 11.5 (SPSS, Inc., Chicago, IL). Assuming a difference of 20% total tramadol consumption between the groups, we calculated that 48 patients in each group would be required with 80% power and .05 significance level. Normality assumption was checked by the Shapiro-Wilk test, and independent sample *t*-test was used to test statistically significant difference between age, weight, anesthesia and surgical time, and total tramadol consumption of the 2 groups. Differences between groups according to ASA, blood loss, and patient satisfaction were evaluated by the Mann-Whitney *U* test. Chi-square test was used to evaluate categorical values. Although repeated analysis of variance was used to assess measures between and within subjects' differences for PCA tramadol values, the Friedman test was used to detect differences of repeated measures for VRS values. A P value $<.05$ was considered statistically significant.

RESULTS

All 96 men enrolled in this study completed the protocol. No significant differences were observed in the mean age, weight, ASA status, duration of surgery, duration of anesthesia, and estimated blood loss between the 2 groups ($P > .05$) (Table 1). PCA tramadol consumption, pain scores, and other postoperative data are summarized in Table 2. The mean cumulative tramadol consumption was significantly lower in group BD compared with group P at 24 hours ($P < .001$). The primary outcome, cumulative PCA tramadol consumption at 24 hours, was 184.43 mg in the BD group compared with 269.52 mg in the P group (difference −85.09, 95% CI −103.75 to −66.43, $P < .001$). Compared with that in group P, tramadol consumption at each time point was significantly lower in group BD ($P < .001$) (Fig. 1).

The pain scores were significantly lower in group BD compared with group P ($P < .05$). The number of patients who required rescue antiemetic and analgesic was lower in group BD than in group P, revealing a significant

Table 1. Patient characteristics and operative parameters

	Group BD (n = 48)	Group P (n = 48)	*P*
Age (y)	61.81 ± 5.55	62.96 ± 5.22	NS
Weight (kg)	79.90 ± 11.77	81.90 ± 12.97	NS
ASA status	2 (2-2)	2 (2-2)	NS
Duration of surgery (min)	159.27 ± 23.43	173.75 ± 19.09	NS
Duration of anesthesia (min)	184.67 ± 23.70	201.12 ± 20.42	NS
Estimated blood loss (mL)	1050 (950-1175)	1050 (980-1300)	NS
Preoperative hemoglobin (g/dL)	14.6 ± 1.4	14.5 ± 1.6	NS
Postoperative hemoglobin (g/dL)	12.1 ± 1.3	11.9 ± 1.2	NS
Preoperative hematocrit (%)	44.1 ± 4.2	43.9 ± 4.4	NS
Postoperative hematocrit (%)	38.1 ± 2.8	37.9 ± 2.4	NS
Preoperative creatinine (mg/dL)	0.88 ± 0.11	0.89 ± 0.09	NS
Postoperative creatinine (mg/dL)	0.89 ± 0.17	0.91 ± 0.12	NS

Data are median (interquartile range) or mean ± SD.
NS = not significant.

Table 2. Postoperative parameters

	Group BD (n = 48)	Group P (n = 48)	*P*
Tramadol consumption in PACU (mg)	0.29 ± 2.02	11.92 ± 7.65	<.001
Pain score in PACU	2 (1-2)	4 (3-4)	<.05
Tramadol consumption at 1 h (mg)	45.5 ± 17.39	90.05 ± 20.11	<.001
Pain score at 1 h	2 (2-2)	3 (2-3)	<.05
Tramadol consumption at 2 h (mg)	81.05 ± 27.16	156.65 ± 34.43	<.001
Pain score at 2 h	2 (2-2)	3 (2-3)	<.05
Tramadol consumption at 6 h (mg)	145.60 ± 33.85	212.20 ± 45.41	<.001
Pain score at 6 h	2 (2-2)	3 (3-4)	<.05
Tramadol consumption at 12 h (mg)	171.83 ± 36.55	250.80 ± 50.03	<.001
Pain score at 12 h	2 (2-2)	3 (2-3)	<.05
Tramadol consumption at 24 h (mg)	184.43 ± 38.58	269.52 ± 52.46	<.001
Pain score at 24 h	1 (1-2)	2 (1-2)	<.05
Need for rescue antiemetic	11 (22.9)	33 (68.8)	<.05
Need for rescue analgesic	13 (27.1)	36 (75)	<.05
Satisfaction score	9 (6-10)	8 (5-9)	<.001
Length of stay (h)	63 ± 6.2	65 ± 6.8	>.05

Data are median (interquartile range), mean ± SD, or number (%).

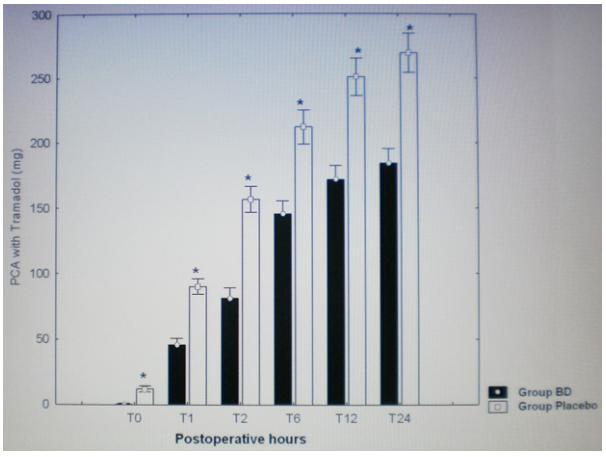

Figure 1. PCA tramadol consumption. Group BD = bupivacaine and diclofenac; group P = placebo. *P <.001 between the groups.

difference (P <.05). Patients' satisfaction scores were significantly higher in group BD than in group P (P <.001). The sedation scores were similar in both groups. There was no complication related to wound infiltration. The hospital length of stay was not different among groups. No patients had signs of renal impairment or bleeding and postoperative ileus during the study.

COMMENT

The results of our study demonstrated that wound infiltration with bupivacaine during surgical closure combined with i.m. diclofenac administration reduces PCA tramadol consumption in patients who underwent RRP under general anesthesia. Our data also show that this multimodal approach resulted in improvement in pain scores, increased patient satisfaction, and diminished need for rescue analgesics or antiemetics.

Postoperative pain after RRP can be moderate to severe and the consumption of opioid analgesic drugs may be excessive. Because opioids have side effects, current recommendations for pain management after surgery would prefer the use of multimodal opioid-sparing therapy.[3,4] More recently, several studies have focused on the combination of different analgesics, including NSAIDs and local anesthetics.[4] It has been demonstrated that those regimens improved postoperative pain relief with minimal side effects.[4] By contrast, the surveys in the US and Europe have confirmed that the quality of postoper-

ative pain management remains suboptimal.[6,7] In the current study, we have used bupivacaine for wound infiltration during surgical closure. The evidence suggests that the use of local anesthesia for wound infiltration is simple and cost-effective and provides good analgesia for various surgical approaches.[8,9]

There have been some conflicting results with regard to the effects of local anesthetics on postoperative pain and opioid requirement after RRP. Ben-David and colleagues reported that multimodal analgesia, including paravertebral blocks using ropivacaine before RRP in combination with wound infiltration using bupivacaine during surgical closure reduced pain score and opioid requirement.[10] By contrast, the study was retrospective and did not have prospective data. In another randomized, double-blind study performed by Wu et al, the analgesic efficacy of subfascial continuous infusion of 0.5% bupivacaine was investigated in patients undergoing RRP.[11] They found that their technique did not provide a reduction in opioid requirements or an improvement in pain scores, postoperatively. This may be explained by the fact that subfascial placement of the catheter may not be the optimal location for patients who underwent RRP, and drainage of local anesthetic infusate via pelvic drain may be a reason for failure of the procedure.

In a prospective study, Tauzin-Fin et al found that coadministration of magnesium sulfate with ropivacaine for postoperative infiltration analgesia after RRP decreased the requirement for tramadol.[12] By contrast, they reported that pain scores obtained from the groups were similar. In a recent prospective study, Habib and others evaluated the analgesic efficacy of lidocaine patches on postoperative pain after RRP.[13] They found that topical application of a lidocaine patch reduces pain scores. However, their results showed no significant reduction in opioid requirement. Although the conflicting results stated above may be clarified in part by differences in design and drugs, we found that wound infiltration with bupivacaine during surgical closure combined with diclofenac administration after RRP produces a significant reduction in both postoperative pain and PCA tramadol consumption.

In the current study, i.m. diclofenac was performed after RRP. Parenteral preparations of NSAIDs have been widely used in the acute postoperative pain.[4] The benefit of reducing opioid consumption is thought to be related to improved recovery from surgery and anesthesia, and several studies have demonstrated the opioid-sparing effect of diclofenac administration.[14] Despite the obvious benefits of using NSAIDs, potential side effects of NSAIDs, including gastrointestinal mucosal damage and renal tubular and platelet dysfunction, may limit their use. However, exclusion criteria in the current study included the patients with history of significant liver or kidney diseases, history of gastroduodenal ulcer, or bleeding disorders.

There were some limitations in the current study. This study was not designed to assess the effects of bupivicaine or diclofenac alone. However, we performed only a method of wound infiltration with bupivacaine, and we did not compare the different techniques, including continuous infusion in combination with intermittent injection, or their combination. Our successful results may encourage other investigators to compare those techniques in the future. The current study demonstrated the short-term outcomes and we did not examine the long-term influence of our multimodal approach after RRP. Unfortunately, most clinical studies have used only multimodal analgesia for evaluating short-term results after surgery. However, a recent systematic review emphasized the failure of major benefits with regard to clinically meaningful endpoints, such as resumption of dietary intake and normal physical activities.[15] Further studies are required to evaluate the long-term effect of our multimodal approach after RRP. We did not measure dose vs response relationship for either drug. However, the doses of the drugs used in the current study correspond to those in previous studies.[14]

CONCLUSIONS

The results of the current study showed that wound infiltration with bupivacaine during surgical closure combined with i.m. diclofenac administration might be used as an effective and safe approach in patients undergoing RRP. Owing to a simple, exciting method with potential for clinical improvement in pain related outcomes, the peripheral approach may offer the greatest promise for advancing acute pain management in the future.[4,16] Although previous studies have reported only limited or no benefits of local anesthetics for postoperative opioid consumption and pain relief after RRP, the results of the current study emphasize that our multimodal approach may be effective in decreasing both PCA tramadol consumption and postoperative pain in patients who underwent RRP under general anesthesia.

Open, laparoscopic, and RRP that are performed in high-volume centers are safe options for treatment of patients with localized prostate cancer, presenting similar overall complication rates.[17,18] Although open RRP is fast becoming an uncommon procedure at least in the United States, wound infiltration with bupivacaine during surgical closure combined with i.m. diclofenac administration might be useful in centers where open RRP is more common.

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EDITORIAL COMMENT

The current study evaluates the potential benefit of wound infiltration with local anesthetic (bupivacaine) and intramuscular analgesia in the form of a nonsteroidal antiinflammatory drug (NSAID, diclofenac) on postoperative narcotic requirements within the first 24 hours after radical retropubic prostatectomy (RRP). Patients were randomized to the combination of bupivacaine and diclofenac vs a placebo saline injection. This well-designed study demonstrated that the combination did decrease postoperative narcotic requirements in the first 24 hours after surgery.

Surgical advances are often driven by the desire to reduce pain and minimize morbidity for the patient. Despite the increase in the number of minimally invasive surgeries performed worldwide, surgeons must continue to be knowledgeable about postoperative pain management and its impact on patient recovery. On the surface, the type, complexity, and length of a particular surgical procedure should impact the amount of pain experienced by an individual. In reality, patient perception and expectations, prior experience, tolerance to discomfort, and associated medical conditions likely play as large a role in postoperative pain as the incision we make to perform the operation.[1]

A cursory review of this study of patients undergoing RRP in the day and age of robotic surgery could lead to a conclusion that this study is not relevant to most urologists' management of localized prostate cancer. That would be a mistake because this study confirms what previous studies have shown for both laparoscopic and open surgical procedures: that the use of local anesthetic and NSAIDs can reduce the use of narcotics and their unwanted side effects.[2,3] However, careful review of the results demonstrate that although there is a statistically significant difference in pain scores between the 2 study groups, the clinical difference is likely not that great.

Although postoperative pain management is critical in preventing complications, such as pneumonia and thromboembolic events, a more critical issue for society and patients is how quickly they can resume normal activity, which this study fails to address. As suggested above, patient perception can greatly influence pain and recovery. When we first initiated a robotic assisted prostatectomy program, our initial data demonstrated earlier resumption of normal activity for the robotic-assisted compared with the open surgical cases. However, further investigation revealed that the 2 patient groups were given different education and instruction for postoperative activity, and when we provided the same preoperative counseling to patients, the original gap in recovery disappeared.[4]

Studies that either evaluate new pain regimens or compare newer procedures with conventional approaches should evaluate both immediate and short-term impact of the variable in question. In addition, patient level factors and processes of care should be evaluated to fully understand the potential benefit of a new pain regimen or surgical approach. Validated instruments exist to understand the impact of these factors on the recovery of patients after surgery.[5] Although this study clearly shows a benefit to the use of a multitargeted pain regimen, future studies need to examine longer-term benefits of new interventions.

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