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Original article

Effect of multimodal analgesia with paravertebral blocks on biochemical recurrence in men undergoing open radical prostatectomy

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Abstract

Background: Recent studies suggest that anesthetic technique during radical prostatectomy for prostate cancer may affect recurrence or progression. This association has previously been investigated in series that employ epidural analgesia. The objective of this study is to determine the association between the use of a multimodal analgesic approach incorporating paravertebral blocks and risk of biochemical recurrence following open radical prostatectomy.

Patients and methods: Using a prospective database of 3,029 men undergoing open radical prostatectomy by a single surgeon, we identified 2,909 men who received no neoadjuvant androgen deprivation and had at least 1 year of follow up. We retrospectively compared patients who received general analgesia with opioid analgesia (1999–2003, $n = 662$) to those who received general analgesia with multimodal analgesia incorporating paravertebral blocks (2003–2014, $n = 2,247$). The primary outcome was time to biochemical recurrence. Biochemical recurrence-free interval was assessed using the Kaplan-Meier technique and compared using a multivariate Cox-proportional hazards regression model.

Results: In total, 395 patients (14%) experienced biochemical recurrence following radical prostatectomy, including 265 (12%) who received multimodal analgesia and 130 (20%) who did not (adjusted $P = 0.27$). After adjusting for age, race, body mass index, preoperative prostate specific antigen, grade, stage, perineural invasion, margin status, percent of tumor in the gland, and diameter of the dominant nodule, there was no difference in recurrence-free interval between groups (HR = 0.92, 95% CI: 0.73–1.17).

Conclusion: Use of a multimodal analgesic approach incorporating paravertebral blocks is not associated with a reduced risk of biochemical recurrence following radical prostatectomy.

Keywords: Open prostatectomy; Regional analgesia; Cancer surgery; Biochemical recurrence; Prostate cancer; Anesthesia

1. Introduction

As many as 35% of men treated for localized prostate cancer will recur after radical prostatectomy [1]. Oncologic factors such as prostate specific antigen (PSA), cancer stage classification, Gleason score, and margin status have been shown to be important in determining risk [2]. Recurrence results in the added cost and morbidity of additional treatments and also affects disease-specific survival [2]. To mitigate this, researchers have investigated the potential role of perioperative anesthetic drug selection in modifying cancer-specific outcomes after radical prostatectomy, as well as for other cancers [3–10].

Results from such studies are mixed. Some suggest that opiates and [3,5,10] volatile inhaled anesthetics may be associated with prostate cancer recurrence or progression, potentially through immune modulation [3,5,10]. Others found that epidural analgesia during major cancer surgery may serve a protective role in cancer recurrence, mediated

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through lower utilization of potentially detrimental anesthetic agents [3,5]. Finally, some investigations showed no relationship between anesthetic technique and cancer recurrence [9,11]. This discrepancy may be due small sample sizes, differing biology between solid tumor types, variable analgesia protocols, and systemic differences between patients meeting eligibility criteria for regional techniques.

Thus, there is ongoing debate regarding whether perioperative anesthetics are a potential modifiable risk factor for cancer recurrence. In prostate cancer, this has been studied for epidural analgesia in small cohorts [3,5,10]. Yet, to our knowledge this phenomenon has not been studied in the setting of paravertebral blocks. For these reasons we use a large, single-institutional cohort to investigate whether there is an association between receipt of multimodal analgesia incorporating a preoperative paravertebral block during open radical prostatectomy and prostate cancer outcomes.

2. Materials and methods

2.1. Study population

Between November 1999 and July 2014, 3,029 men underwent radical prostatectomy at the University of Pittsburgh Medical Center by a single surgeon (J.B.N.) and were followed in a prospectively populated, longitudinally maintained database. Patients with long-term opiate dependence, preoperative receipt of neoadjuvant hormone therapy, or less than 1 year of follow up were excluded from analysis.

2.2. Outcomes

Outcomes were selected a priori with biochemical recurrence, defined as a PSA of 0.2 ng/dl postprostatectomy, as the primary outcome. Secondary outcomes included overall and prostate cancer-specific survival.

2.3. Exposures

The primary exposure of interest was analgesia/anesthetic modality. Both modalities included general anesthesia (described later). One group additionally had paravertebral blocks with multimodal analgesia, and the other group had postoperative opiates. Multimodal analgesia consisted of a T10–12 paravertebral infusion of 5 ml of 0.5% ropivicaine before induction, as previously described [12,13]. These patients also received 2 celecoxib 200 mg tablets 45 to 120 minutes before surgery and ketamine 10 mg iv (1 ml) following induction of analgesia. Following surgery, celecoxib 200 mg was administered twice a day for 7 days.

The anesthetic induction regimen for both groups is standardized at our institution. After preoxygenation, general analgesia was induced with propofol 2 mg/kg, succinylcholine 1 mg/kg, and fentanyl 2 μg/kg, and the underwent endotracheal intubation. Paralysis was maintained with rocuronium titrated by twitch monitor to maintain fewer than 2 twitches on a train-of-four. Isoflurane (0.5%–1.5% end-tidal) and fentanyl were used to maintain general analgesia. Postoperatively the standard analgesia group of patients was managed with morphine patient-controlled analgesia. Henceforth the 2 exposure groups are referred to as multimodal and standard analgesia.

2.4. Statistical analysis

Demographic, clinical, and pathologic characteristics of the cohort were compared among the 2 analgesia groups using *t*-test for normally distributed and Wilcoxon test for nonnormally distributed continuous variables, and Pearson chi-square or Fisher exact test for categorical variables, as appropriate

The outcomes progression-free survival and overall survival, were analyzed using techniques for survival data. The Kaplan-Meier method was used to estimate survival probabilities for each of the 2 groups and compared using 2-sided log-rank test. Unadjusted and adjusted association between demographic, clinical, and pathological variables and progression-free survival was investigated using Cox proportional hazards regression. The results are reported as hazard ratios and 95% CI.

Competing risks analysis was used to examine associations with prostate cancer-specific mortality, treating deaths from other causes as a competing event. Cumulative incidence was calculated nonparametrically for each of the exposure groups. Univariable analysis used Gray's test [14] and a Fine and Gray proportional subdistribution hazards model [15] for categorical and continuous variables, respectively. The Fine and Gray proportional subdistribution hazards model is a Cox-type model for competing risks regression. Instead of the marginal hazards function, it models the hazards of the subdistribution, or cumulative incidence function. Unadjusted subdistribution hazards ratios (SHR) for the exposure groups were calculated using the proportional subdistribution hazards model. Adjusted analysis was not pursued due to the small number of prostate cancer-specific deaths.

Statistical analyses were performed using SAS (version 9.4); and R (version 3.2.0) [16]. All tests were 2-sided and statistical significance was defined as $P < 0.05$. The University of Pittsburgh institutional review board approved the study protocol.

3. Results

After exclusions, 2,906 men were eligible for analysis. Of these, 662 had standard analgesia between 1999 and 2003 with median follow up of 135 months (interquartile