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Anestezi Seçiminin Mesane Kanseri Nedeniyle Cerrahiye Giden Hastalarda Sağkalım Üzerine Etkisi: Retrospektif Değerlendirme

The Effect of Anesthesia Choice on Survival in Patients Undergoing Surgery for Bladder Cancer: A Retrospective Analysis

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Öz

AMAÇ: Rejyonel anestezinin mesane kanseri bulunan hastalarda sağkalım üzerindeki rolünü incelemiş olan çalışma sayısı sınırlıdır. Bu geriye dönük çalışma rejyonel ve genel anestezinin mesane kanseri nedeniyle cerrahi geçiren hastalarda sağkalım üzerine etkilerini karşılaştırmayı amaçlamıştır.

GEREÇ ve YÖNTEMLER: Mesane kanseri nedeniyle cerrahi geçiren toplam 181 hasta (ortalamayaş 62±11 yıl, % 82 erkek) bu geriye dönük çalışmaya dahil edilmişlerdir. Hastalara ilişkin tüm veriler hasta dosyalarından alınmıştır. Hastalar rejyonel anestezi (RA grubu, n=120) ve genel anestezi (GA grubu, n=61) olmak üzere iki gruba ayrılmışlardır.

BULGULAR: Rejyonel anestezi uygulanan hastalarda 3 yılllık sağkalım genel anestezi grubuna gore anlamlı olarak yüksekti (% 96.6'ya karşı % 86.8, p=0.012). Lojistik regresyon analizi postoperative enfeksiyon gelişiminin (OO: 0.221, % 95 GA: 0.065-0.754, p=0.016) ve rejyonel anestezi uygulamasının (OO: 4.275, % 95 GA: 1.230-14.852, p=0.020) 3 yıllık sağ kalım için anlamlı belirleyiciler olduklarını göstermiştir.

SONUÇ: Bu çalışmanın bulguları mesane kanseri nedeniyle cerrahiye giden hastalarda rejyonel anestezinin genel anesteziye gore daha iyi 3 yıllık sağkalım sağladığını göstermiştir. Postoperatif enfeksiyon gelişimi ve anestezi tekniği sağkalımın önemli belirleyicileri olarak tespit edilmişlerdir.

AnahtarKelimeler: Mesane kanseri, rejyonel anestezi, genel anestezi, sağkalım

Abstract

OBJECTIVE: Data investigating the role of regional anesthesia on survival in bladder cancer is lacking. This retrospective study aimed to compare the impact of regional anesthesia and general anesthesia on survival in patients who underwent surgery for bladder cancer.

MATERIALS and METHODS: A total of 181 patients (mean age 62±11 years, 82 % male) who underwent surgery for bladder cancer were enrolled in this retrospective study. All data were collected from patient case charts. Patients were divided into two study groups according to the type of anesthesia used: Regional anesthesia group (RA Group) (n=120) and general anesthesia group (GA Group) (n=61).

RESULTS: Three-years survival following surgery was significantly higher in patients receiving regional anesthesia compared to those receiving general anesthesia (96.6% vs. 86.8%, p=0.012). Logistic regression analyses showed that postoperative infection (OR: 0.221, 95 % CI: 0.065-0.754, p=0.016) and implementation of regional anesthesia (OR: 4.275, 95 % CI: 1.230-14.852, p=0.020) were predictive for 3-years survival.

CONCLUSION: Findings of the present study demonstrate that regional anesthesia provides better 3-year survival compared to general anesthesia in patients undergoing surgery for bladder cancer. Postoperative infections and anesthesia technique are the predictors of survival in these patients.

Keywords: Bladder cancer, regional anesthesia, general anesthesia, survival

INTRODUCTION

Bladder cancer has become a significant public health problem with the high worldwide incidence, environmental factors playing an important role in development, and increasing expenditures on diagnosis and treatment. Based on data from eight provinces with population-based cancer registry centers in our country, the incidence of bladder cancer was estimated to be 19.6 per 100000 in men and 2.5 in women (1). According to that study, it is the 3rd most common type of cancer in males and 13th in women, and its share in all cancers is 8.5%. Bladder cancer is four times more common in men than in women (2). The excessive use of cigarettes in males, which is one of the most important etiologic factors, is responsible for this distribution. Bladder cancer is seen at more

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advanced ages. Ninety percent of newly diagnosed patients are over 60 years of age. Bladder cancer-related deaths are one of the most common causes of cancer-related deaths (3).

Surgical stage of the tumor is unquestionably the major determining factor of recurrence, prognosis, and survival. Furthermore, grade, histological type, genetic structure, and additional pathologies may influence the cancer prognosis (4). Numerous studies states that anesthetic pain control systems alter the prognosis (5-7). Even though the mentioned outcomes are speculative, quite a few meta-analyses have verified this assumption. Regional anesthesia reduces surgery- stimulated stress and opioid use; therefore, many suppose that it decreases the probability of cancer recurrence due to less administration of these agents which are shown to inducedepression of both humoral and cellular immunity (8, 9).

We aimed to reveal whether mortality caused by bladder cancer varies between cases whose surgeries include general versus regional anesthesia. Consequently, this retrospective study was organized to explore which anesthetic method results in better survival in patients with bladder cancer.

MATERIALS and METHODS

Patient selection

All consecutive patients who underwent surgery for bladder cancer between January 2013 and February 2016 in our institute were enrolled in this retrospective study. All data were collected from patient case charts. Patients' gender, age, body mass index (BMI), presence of comorbid diseases, duration of anesthesia, amount of blood transfusion during surgery, duration of hospital stay, requirement for intensive care unit (ICU) stay, presence of postoperative infection, presence of postoperative bleeding, final pathological diagnosis, and presence of postoperative chemotherapy were recorded. We excluded reoperations and patients who did not have 3 years of follow up. We also excluded patients with benign lesions and those with biopsy specimen stages III and IV (Figure 1).

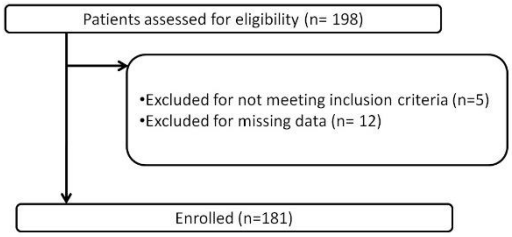

Figure 1: Flowchart demonstrating subject enrollment

Patients were divided into two study groups according to the type of anesthesia used: Regional anesthesia group (RA Group) (n=120) and general anesthesia group (GA Group) (n=61). Retrospective data were available only for 3 years follow-up, thus, the primary outcome of the study was 3-years survival. Postoperative bleeding and postoperative infections were the secondary outcomes.

Anesthesia and Analgesia

General anesthesia was induced using propofol or sodium thiopental, fentanyl, and midazolam and maintained with isoflurane with or without nitrous oxide. IV morphine, fentanyl, hydrocodone, or hydromorphone and occasionally with meperidine or sufentanil were utilized to manage perioperative analgesia. Spinal anesthesia was performed with a spinal needle inserted through the L3–L4 interspace. Following the return of 3ml clear cerebrospinal fluid, 0.5% levobupivacaine (15 mg) was injected over 20–30 s through 24 G Whitacre/Quincke spinal needle. When requires, additional doses of levobupivacaine were administered during surgery. For postoperative analgesia, patients received 4000 mg of paracetamol (in four separate doses of 1000 mg). If necessary, diclofenac 150 mg in three doses of 50 mg and morphine substitutes were also given.

All surgical procedures and subsequent management by medical oncology department was performed by the same teams for all patients.

Statistical Analyses

Data were analyzed using the IBM Statistical Package for Social Sciences v20 (SPSS Inc., Chicago, IL, USA). A normal distribution of the quantitative data was checked using Kolmogorov-Smirnov test. Parametric tests were applied to data of normal distribution and non-parametric tests were applied to data of questionably normal distribution. Independent-samples t-test and Mann-Whiney U-test were used to compare independent groups. The distribution of categorical variables in both groups was compared using Pearson chi-square test. Logistic regression was performed to find the risk factors for overall survival. Data are expressed as mean±SD or median (interquartile range), as appropriate. All differences associated with a chance probability of .05 or less were considered statistically significant.

RESULTS

A total of 181 patients (mean age 62±11 years, 82 % male) were enrolled in this retrospective analysis. Patient characteristics, postoperative complications and 3 years survival are shown in Table 1. No differences were observed between groups for gender, age, BMI, ASA Class, presence of comorbid diseases, tumor stage, duration of anesthesia, intensive care unit (ICU) requirement, iv. opioid requirement, and final pathological diagnosis. Operation time was 67.2±24.0 min for regional and 70.1±23.6 min for general anesthesia (p=0.565). Postoperative bleeding was similar in the two groups (4.1 % vs. 9.8 % p=0.131), whereas postoperative infections (22.9 % vs. 10.8 %, p=0.035) and length of hospital stay (3.6±1.9 days vs. 2.95±1.6 days, p=0.019) were significantly higher in patients undergoing general anesthesia compared to those undergoing regional anesthesia. Three-year survival following surgery was significantly higher in patients receiving regional anesthesia compared to those receiving general anesthesia (96.6% vs. 86.8%, p=0.012).

Logistic regression analyses showed that postoperative infection (OR: 0.221, 95 % CI: 0.065-0.754, p=0.016) and implementation of regional anesthesia (OR: 4.275, 95 % CI: 1.230-14.852, p=0.020) were predictive for 3-years survival (Table 2).

Table 1: Patient characteristics and survival

		Regional (n =120)	General (n =61)	*p* Value
Gender (male/female)		101/19	47/14	0.241¥
Age (yr) mean±SD		63.2±11.2	61.2±11.2	0.265§
BMI (kg/m2) mean±SD		23.6±4.8	23.9±4.1	0.407₸
ASA Class I		85 (71%)	47 (77%)	0.374¥
ASA Class II		34 (28%)	12 (20%)	0.206¥
ASA Class III		1 (1%)	2 (3%)	0.263
Comorbid diseases		6 (4.9 %)	6 (9.8%)	0.070¥
Diabetes		4 (3.3%)	3 (5%)	0.586¥
Hypertension		2 (2.5%)	3 (5%)	0.378¥
Tumor stage I		26(21.7%)	17 (28%)	0.309
Tumor stage II		68 56.7%)	36 (59%)	
Tumor stage III		26(21.7%)	8 (13%)	
Pathological diagnosis	**Urothelial carcinoma (n)**	116(96.7%)	60(98.6%)	0.664¥
	Adenocarcinoma (n)	4 (3.3 %)	1 (1.4%)	
Anesthesia time (minutes) mean±SD		67.2±24.0	70.1±23.6	0.565§
Hospital stay (days) mean±SD		2.95±1.6	3.6±1.9	0. 019₸
ICU requirement, n		6 (4.9 %)	5 (8.1%)	0.395¥
Postoperative infection		13 (10.8 %)	14(22.9%)	0.035¥
Postoperative bleeding, n		5 (4.1%)	7 (9.8 %)	0.109¥
Iv. morphine requirement, n		16 (13%)	11 (18%)	0.508¥
Posoperative chemotherapy, n		5 (4.1%)	6 (9.8%)	0.131¥
3 years survival, n		116(96.6%)	53(86.8%)	0.012¥

ICU: Intensive care unit; BMI: Body mass index

¥: Pearson correlation; §: Samples t test; ₸: Mann Whitney U test

Table 2: Logistic regression analysis for overall survival

	Odds ratio	95 % CI	*p* Value
Anesthesia type(regional/general)	4.275	1.230-14.852	0.020
Gender	0.389	0.048-3.125	0.375
Age (yr)	0.977	0.926-1.031	0.400
BMI (kg/m²)	1.651	0.961-2.114	0.757
Postoperative infection	0.221	0.065-0.754	0.016
Anesthesia time (minutes)	0.790	0. 462-1.116	0.872
Comorbid diseases	0.348	0.068-1.788	0.206
Operation **time (minutes)**	0.790	0. 462-1.116	0.991
Hospital stay (days)	1.040	0.731-1.479	0.826

BMI: Body mass index

DISCUSSION

In the present study, we aimed to determine whether mortality due to bladder cancer differs between patients whose surgeries involve general versus regional anesthesia. The present study showed that 3-year survival was significantly higher among patients receiving regional anesthesia compared to those receiving general anesthesia. In addition, the rate of the postoperative infections was higher in patients receiving general anesthesia than that of the participants undergoing regional anesthesia. The present study shows that 3-year survival is significantly higher among patients receiving regional anesthesia compared to those receiving general anesthesia and the presence of postoperative infections and implementation of regional anesthesia are predictive for 3-years survival in patients undergoing surgery for bladder cancer.

Surgery, doubtless, is the mainstay of treating patients with cancer and frequently eliminates a considerable amount of cancer cells. However, some individual cancer cells, often referred to as micrometastasis, might be left at the margins. In addition, previous data have demonstrated that surgery itself might promote metastasis in different ways. Management of tumor-releasing tumor cells into circulation, reduction of angiostatin and endostatin which are assumed as antiangiogenics, increased release of growth factors in response to injury and postoperative immunsupression are the major determinants of the role of surgery in promoting metastasis (10-12). Furthermore, hypotermia and blood transfusions performed to overcome the bleeding occurring during the surgery might also influence cancer recurrence (8).

Anesthetic technique has also been shown to impact the rate of the recurrence of the disease in many types of cancers. In a large study of 42,151 patients, Cummings et al. revealed that cases who had undergone epidural analgesia during cholectomy had longer 5-year survival (hazard ratio=0.91, p<0.001) (5). De Oliveira et al. revealed that ovarian cancer surgery managed with epidural anesthesia reduces the need for volatile agents and increases recurrence-free survival (6). Lin et al. stated that epidural anesthesia and postoperative analgesia reduce the mortality rate of ovarian carcinoma (7). Conversely, other studies state that regional anesthesia / analgesia has no effect on the prognosis of a patient with cancer. Lascassie et al. stated that there is no profit of epidural anesthesia during cancer surgery to overall recurrence-free time or survival-time in patients with advanced ovarian cancer (13). Roiss et al. stated that the survival of 4772 patients who had undergone radical prostatectomy were not influenced by regional anesthesia (14). Wuethrich et al. observed patients who had undergone retro-pubic radical prostatectomy over a median observation time of 14 years and stated that general anesthesia combined with epidural analgesia did not decrease cancer

progression risk in patients with prostate cancer (15). Recently, in a study of 531 patients undergoing surgery for bladder cancer, Jang et al. demonstrated that higher 5-year survival tended to be higher in patients receiving regional anesthesia compared to those receiving general anesthesia (16). Chipollini et al. revealed in a retrospective analysis of patients with clinically nonmetastatic urothelial carcinoma of the bladder who underwent surgery that epidural anesthesia was associated with worse recurrence and disease-free survival than the general anesthesia (17). However, tumor stages and the opioid use were higher in that study compared to our findings. The outcomes could therefore be influenced by these factors.

The role of immune system in promoting metastasis constitutes the basis for majority of the research investigating the impact of anesthetic technique on prognosis in cancer surgery the immune system performs a well-known role in the host protections versus progression of cancer. It is essential to maintain the act of natural killer cells, a subgroup of lymphocytes which instinctively identify and execute tumor cells (18, 19). Numerous perioperative issues might weaken immunologic protections. Particularly, surgical manipulation disseminates malignant cells into the bloodstream, surgical stress endorses metastatic development by immunosuppression throughout neuroendocrine conduits, and the application of opioids straightforwardly reduces natural killer cell (NK) action (10, 20).

General anesthesia is believed to inhibit proper immune function. Anesthetic agents might suppress cell-mediated immunity or alter the balance between pro-and anti-inflammatory cytokines. As shown previously, drugs used for general anesthesia such as such as thiopental or halogenated volatile agents might alter host immunity by inhibiting natural killer cell, dendritic cell, macrophage, and neutrophil function (21). Volatile anesthetics have also been shown to upregulate hypoxia-inducible factors which are influential on angiogenesis and cell migration (22). In addition, research in animal models has shown that the psotoperative pain itself and opioids used for pain management following general anesthesia might inhibit immune function and stimulate angiogenesis (23, 24).

Regional anesthesia reduces the stress related to surgery, postoperative pain and improve neuroendocrine function and cytokine-mediated stress response. In the study of Ahlers et al. Epidural anethesia was found in association with higher number of T-helper (Th)

cells, higher number of lymphocytes and preserved IFN-gamma concentrations (25). Regional anesthesia also increases circulating IL-4 levels and decreases IL-10 levels whereas administration of fentanyl in general anesthesia was associated with increased plasma concentrations of IL-10 indicating a predominant anti-inflammatory and immunosuppressive profile with general anesthesia (26, 27).

Our findings demonstrating the favorable impact of regional anesthesia in bladder cancer surgery are consistent with the results of the previous studies comparing regional and general anesthesia in various types of cancer. With this background in mind, we suppose that compared to general anesthesia, regional anesthesia provides less post-operative pain and stress and improves immune response, and therefore, is associated with favorable 3-year survival following surgery.

Limitations of our study are the retrospective design and lack of definite criteria for selection of patients; far fewer patients received general than regional anesthesia. However, we hope that this study will pioneer further studies on this topic. In addition, some details of history and factors that may influence the outcome may not be completely documented. Due to these restrictions, associations should be interpreted

with caution.

This is one of the leading studies to investigate the effect of anesthetic method on the prognosis of patients with non-metastatic bladder cancer. Our results demonstrate that regional anesthesia provides better 3-year survival compared to general anesthesia in patients undergoing surgery for bladder cancer. Postoperative infections and anesthesia technique are the predictors of survival in these patients.

Informed Consent: Written consent was obtained from the participants.

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