International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2018.528.533

Research Article
Effects of Regional and General Anesthesia on Survival in Head and Neck Cancer

Long Wang, YeLiKen YeErDaoLaiTi, Gang Yang and Jianhua Du

Department of Anesthesiology, The Second Affiliated Hospital Of Xinjiang Medical University, 830063 Urumqi, China

Abstract

Background and Objective: Surgical stress is a causative factor reducing natural killer cells (NK) cell activity and promoting cancer cell proliferation. Authors have assessed 5-years survival rates after general anesthesia and regional anesthesia in patients with head and neck cancer. **Materials and Methods:** The total sample comprised 180 patients who received surgery for head and neck cancer. Between June, 2010 and July, 2015, about 90 patients were treated under general anesthesia and 90 histopathologically proven cases were treated under regional anesthesia. **Results:** The average age of patients was greater in the general anesthesia group than in the regional group. The effective time of general anesthesia was about 30 min longer than that of regional anesthesia. The prevalence of recurrence of cancer during the 5 years following surgery was 1 ± 0.7 with general anesthesia and 0.4 ± 0.3 with regional anesthesia, however, this difference was not significant. Chi-square tests clearly demonstrated that the rate of achieving 5-years survival after surgery, was greater with regional anesthesia than with general anesthesia. This was confirmed by partial correlation analyses, which also indicated that regional anesthesia was associated with a longer recurrence-free period. **Conclusion:** To the best of our knowledge, this is the first study of its kind. Five-year survival was more often attained and cancer recurrence was lower, in patients who received surgery under regional anesthesia compared to general anesthesia.

Key words: Regional anesthesia, general anesthesia, head and neck cancer, overall survival, recurrence rate

Received: August 19, 2017 Accepted: December 12, 2017 Published: April 15, 2018

Citation: Long Wang, YeLiKen YeErDaoLaiTi, Gang Yang and Jianhua Du, 2018. Effects of regional and general anesthesia on survival in head and neck cancer. Int. J. Pharmacol., 14: 528-533.

Corresponding Author: Long Wang, Department of Anesthesiology, The Second Affiliated Hospital Of Xinjiang Medical University, NO.38, North East road, 830063 Urumqi, China Tel/Fax: 0086-0991-4605040

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Head and neck cancers occur at approximately 30 anatomical sites or regions, with the majority involving the upper aerodigestive tract (UAT), which includes the buccal mucosa, upper and lower lips, vestibule, lateral and ventral part of the tongue, the upper portion of the respiratory system (pharynx) and the larynx[1,2]. These cancers are most common among smokers, particularly those who also drink large amounts of alcohol. Head and neck cancer is considered the 6th most common cancer, responsible for 6% of all neoplasms. About 650,000 new cases of head and neck cancer are diagnosed each year, with a mortality of 350,000/year[2]. The surgical management of head and neck cancer has evolved rapidly in recent decades with continued improvements in anesthesia, antibiotics, blood-transfusion techniques, blood-banking and techniques for reconstruction. Radical resection has given way to approaches seeking both a cure and preservation of function. In cases where there is nodal metastasis, conservation techniques help preserve non-lymphatic structures. In cases without nodal metastasis, elective neck dissection is considered the treatment of choice[2].

In the field of anesthesia, surgeons and anesthesiologists are primarily concerned with safe procedures that deliver successful anesthetic results. The choice of anesthesia depends on adequate sedation for the surgical procedure, perioperative pain control, respiratory and hemodynamic stability and prevention of nausea and vomiting[3].

The rapidly increasing rates of head and neck cancer have increased the responsibilities of anesthesiologists, not only during perioperative procedures but also in the management of chronic pain in cancer patients. Surgical stress, along with neuroendocrine and inflammatory responses, aggravates the attenuation of cell-mediated immunity and favors tumor metastasis[4].

Some studies have suggested that regional anesthesia (in contrast to general anesthesia) may decrease stress caused by surgery, thus reducing recurrence[4]. Of particular interest is the influence regional anesthesia may have on the long-term morbidity and mortality of patients undergoing surgical intervention for cancer treatment. A recent review[5] concluded that intravenous and inhalation anesthetics have the potential to reduce immune responses and inhibit the activity of natural killer (NK) cells. They also identified surgical stress as a causative factor reducing NK cell activity and promoting cancer cell proliferation as do opioids. Regional anesthesia was identified as a preferential approach for maintaining immune function, with the benefits of decreasing cancer recurrence and metastasis (Fig. 1)[5]. Other studies have shown that the administration of halothane, isoflurane and nitrous oxide

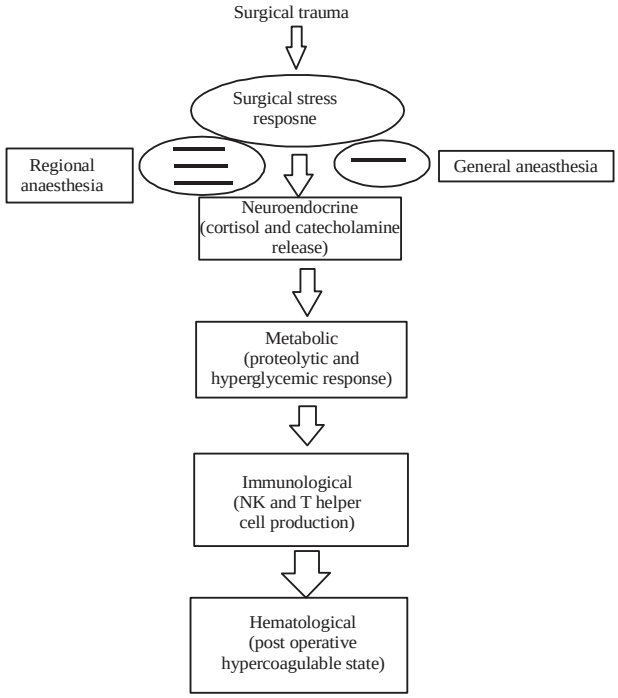

Fig. 1: Comparison of regional anesthesia and general anesthesia in response to surgical stress

increases metastasis in mice, volatile anesthetic agents can affect the metastatic rate via several mechanisms[6].

In contrast, propofol has been reported to reduce NK cell activity and inflammatory cytokine levels, leading to a decrease in metastasis[6] and to inhibit the synthesis and activation of hypoxia-inducible factors. However, Melamed *et al.*[7] compared the effects of propofol, ketamine, thiopental and halothane on the activity of NK cells and tumor metastasis in rats and concluded that all of the anesthetics except propofol reduced NK cell activity but also increased tumor progression. The maximum effect on tumor progression was seen with ketamine, which increased it up to 2.5-fold[7]. Thus, contradictory conclusions have been reached regarding the choice of anesthesia. With this in mind, authors analyzed the effects of regional versus general anesthesia on 5-years survival and cancer recurrence in head and neck cancer patients. To the best of our knowledge, this is the first study to examine such outcome differences in this patient population.

MATERIALS AND METHODS

This study was performed in a single research center and was a retrospective cohort study. Protocol approval was obtained from the Ethics and Research Board committee of the Second Affiliated Hospital of Xinjiang Medical University, China, filed as XMU/2012/8-80. Head and neck surgeries were performed by the same surgeon working with the same anesthesia team. From a total of 245 patients, 180 were included in the study. In all, 90 patients diagnosed with head and neck cancer received general anesthesia and cancer surgery between June, 2010 and July, 2015. Another 90 histopathologically proven cases received surgery under regional anesthesia. Exclusion criteria were lack of continuous follow-up for 5 years after surgery (Table 1).

Etomidate or propofol was used to administer general anesthesia, with rocuronium administered as a neuromuscular blocker. Isoflurane and sevoflurane were used to maintain the effects of general anesthesia. Intravenous ketorolac (30 mg) was administered to control pain after surgery. Lignocaine and bupivacaine were administered for epidural and spinal anesthesia, respectively. Postoperative pain in regional anesthesia patients was not managed with the analgesics used for general anesthesia patients. Outcome, mortality and 5-years survival rates were evaluated based on χ^2 tests. Rates of recurrence were compared using the Kruskal-Wallis test. Regression coefficients with the hazard ratio (HR) and 95% confidence interval were used to calculate risk for recurrence at the cancer site.

Table 1: TNM staging and histological findings

TNM stage*	Regional anesthesia	General anesthesia	Total
Tis*	10	10	20
TisN1*	12	30	42
T1N0 M0*	14	18	32
T1N1 M0*	18	10	28
T2N0 M0*	16	10	26
T2N1 M0*	20	12	32
Total	90	90	254

*T: Tumor size, N: Nodal involvement, M: Metastasis, Tis: carcinoma *in situ*, T1, T2, T3, T4: Size and/or extension of the primary tumor. Nx: Lymph nodes cannot be assessed, N0: No regional lymph nodes metastasis, N1: Regional lymph node metastasis present, at some sites, tumour spread to closest or small number of regional lymph nodes, N2: Tumour spread to an extent between N1 and N3 (N2 is not used at all sites). M0: No distant metastasis, M1: Metastasis to distant organs (beyond regional lymph nodes)

Statistical analysis: All data were analyzed using SPSS software (Version 20.0 for Windows, Armonk, NY). Differences between continuous variables were analyzed using t-tests and differences between categorical variables were analyzed using χ^2 tests. The $p<0.05$ or $p<0.01$ were considered statistically significant.

RESULTS

Demographic and treatment details of the study population are shown in Table 2. No significant differences between treatment groups were noted in any parameters other than patient age and duration of anesthesia. Patients who had undergone general anesthesia had a mean age of 68±7 years. The mean age of those who received regional anesthesia was 61.2±8.8 years. The effective time of general anesthesia was about 30 min longer than that of regional anesthesia, this difference in the effect duration is considered the most common reason for considering general anesthesia. No patients in any group received a blood transfusion during surgery.

The prevalence of cancer recurrence during the 5 years of follow-up was 1±0.7 in patients who had received general anesthesia and 0.4±0.3 in those who had received regional anesthesia, a nonsignificant difference.

The 5-years survival rate was 97% (87 of 90 patients) in the regional anesthesia group and 83% (75 out of 90 patients) in the general anesthesia group, lower in the latter but not with statistical significance (Table 3). Logistic regression analyses indicated that age was the largest risk factor reducing the 5-years survival rate. Multi variate correlation analyses confirmed these results and also indicated that the rate of recurrence was also significantly correlated with age. Pearson's analysis showed that younger patients had a significantly longer time of recurrence-free survival. Diabetes

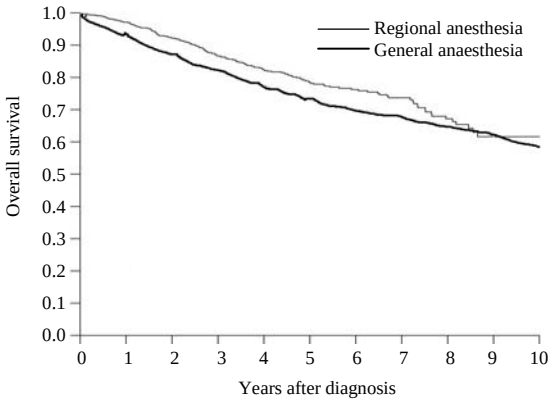

Fig. 2: Kaplan meier analysis for the evaluation and for the comparison between the 5 years survival rate between both the anesthetics

Table 2: Demographic data of the subjects

	General anesthesia (n = 90 (±SD)	Regional analgesia (n = 90)	p-value
Age (year)	67.5±9.0	62.4±10.8 0.029	0.09
Sex (M/F)	51/39	60/30	0.70
Weight (kg)	62.0±9.2	62.0±9.0	0.822
Height (cm) 163.1±7.3	151.2±7.1	161.1±6.9	0.30
Diabetes mellitus	8	15	0.20
Hypertension	21	31	0.40
Anesthesia time (minutes)	82.3±11.2	52.1±9.2	0.001
Hospital stay (days)	10.9±6.2	7.1±4.2	0.101
Smoking history (pack year)	11.7±9.1	15.7±8.1	0.111

Table 3: Comparison of 5-years survival according to anesthesia type

	General	Regional	Total	p- value
Survival	87	75	90	
Dead	3	15	90	
Total	90	90	180	0.3

Table 4: Partial correlation analysis with 5-years survival

Partial correlation with survival	Control variables	Coefficient	p-value
Age (year)	All other variables	-0.180	0.001
Sex (M/F)		0.061	0.890
Weight (kg)		0.790	0.890
Height (cm) 163.1±7.3		1.870	1.230
Anesthesia type (regional/general)		-0.166	0.041
Recurrence (number during 5-years)		0.230	0.310
Recurrence free time (months)		0.220	0.006
Diabetes mellitus		-0.771	0.890
Hypertension		-0.050	0.556
Anesthesia time (min)		1.110	1.200
Hospital stay (days)		-0.071	0.411
Smoking history (pack year)		-0.0132	0.097

mellitus was negatively correlated with survival, anesthesia time was positively correlated with cancer recurrence and hospital stay and longer anesthesia time was correlated with shorter recurrence-free time.

Next, to remove the influence of correlated variables, it is performed partial correlation analyses to identify the variables primarily influencing 5-years survival. After controlling for all influencing variables, regional anesthesia was associated with higher rates of survival, compared to general anesthesia. Patient age (but no other variables) was also statistically significantly associated with 5-years survival (p>0.01) (Table 4).

Finally, Kaplan-Meier log rank analyses comparing survival between patient groups indicated that overall survival was higher in patients who received regional anesthesia. The 1-year and 5-years survival rates were 4.1 and 6.5% higher in patients under regional vs. general anesthesia for all sites of cancer, respectively (Fig. 2).

These 2 years contributed to advancement of knowledge as the patients in the group of regional analgesia is living the higher quality of life when comparison was done with the patients under the general anatehesia.

DISCUSSION

Head and neck cancer generally arises from the squamous components of the oral cavity as well as from regions of the pharynx. Head and neck cancers have traditionally been considered difficult to cure beyond very early-stage disease. However, recent advances in the use of chemotherapy plus radiation and hyper-fractionated radio therapy have led to longer survival times in clinical trials.

To address the central aims in the management of tumors, the prevention of recurrence and the avoidance of cancer progression and metastasis, surgery is generally combined with chemotherapy and radiotherapy[8]. Advances in diagnosis as well as in management have increased survival rates from 70% in 1970 to 84% in 2010[8]. If patients with metastasis are excluded (as in the present study), the 5-years survival rates approach 97%[8].

Surgical resection plays a very important role in the management of cancer but metastasis can occur via the blood or lymphatic circulation[9,10]. Choices made at the time of surgery can also affect rates of recurrence and mortality. Surgical stress and anesthesia decrease immune responses, including cell-mediated immunity[9,10]. Anesthetics may affect immune responses by having direct effects on macrophages, neutrophils, natural killer cells and T cells[10,11]. Opioid anesthetics also decrease cell-mediated as well as humoral immunity, which further increases vascularity and promotes conditions for cancer cells to proliferate[12].

There is much evidence supporting an association between general anesthesia and both cancer recurrence and lower survival. Cummings *et al.*[13] conducted a large study of 42,151 patients and found that significantly more patients who had received a colectomy under epidural anesthesia achieved 5-years survival compared to those who had been administered general anesthesia[13]. Similar results were presented by De Oliveira *et al.*[14], who also found that epidural anesthesia increased recurrence-free time. Lin *et al.*[15], reported that epidural anesthesia during surgery and postoperative epidural analgesia decreased the mortality rate of patients with serous ovarian adenocarcinomas.

Our results indicate that regional anesthesia is associated with less recurrence and a better chance of survival compared to general anesthesia. However, many studies contradict our results. Lacassie *et al.*[16] concluded that epidural anesthesia had no effect on 5-years survival or on the rate of cancer recurrence. Roiss *et al.*[17] also determined, in a large study of 4773 subjects, that cancer survival rate was not affected by spinal anesthesia. Wuethrich *et al.*[18] found that when general anesthesia was combined with regional anesthesia, it did not affect overall survival rate or rate of recurrence in cases of prostate cancer, even after a long-term follow up of 14 years. As these studies involved different types of cancers, general anesthesia may have a differential impact on tumor types, perhaps in part because of varying molecular sensitivity towards volatile agents.

Enlund *et al.*[4], Jang *et al.*[19] also concluded that epidural anesthesia can improve the 5-years survival rate after cancer surgery. Many previous studies have involved subjects with end-stage terminal cancers. Because the variables affecting survival are very complex in such patients, authors focused on patients with early cancers, this probably accounts for the strong influence of age on prognosis that authors observed.

CONCLUSION

The 5-years survival rate was greater and cancer recurrence rates were lower in patients who received regional rather than general anesthesia during surgery. While chi-square and logistic regression tests found these effects to be nonsignificant, anesthesia may have effects on overall cancer survival, any factor that can affect survival on the order of 5% or more must be investigated. Authors suggest that there is no need to select a particular anesthesia method to achieve a better prognosis for patients with non-metastatic head and neck cancers.

SIGNIFICANCE STATEMENT

This study discovers that the anesthesia showed effects on the overall cancer survival. Author's partial correlation clearly demarcates that the 5-years survival rate was more and cancer recurrence rate was less in the patients who underwent regional anesthesia when compared with the patients who underwent surgery under the general anesthesia. This study will help the researchers to uncover the critical areas of impact of general and regional anesthesia on cancer survival.

REFERENCES

1. Torre, L.A., F. Bray, R.L. Siegel, J. Ferlay, J. Lortet-Tieulent and A. Jemal, 2015. Global cancer statistics, 2012. CA: Cancer J. Clin., 65: 87-108.

2. Collins, R., A. Flynn, A. Melville, R. Richardson and A. Eastwood, 2005. Effective health care: Management of head and neck cancers. Qual. Safety Health Care, 14: 144-148.
3. Zambouri, A., 2007. Preoperative evaluation and preparation for anesthesia and surgery. Hippokratia, 11: 13-21.
4. Enlund, M., A. Berglund, K. Andreasson, C. Cicek, A. Enlund and L. Bergkvist, 2014. The choice of anaesthetic-sevoflurane or propofol-and outcome from cancer surgery: A retrospective analysis. Upsala J. Med. Sci., 119: 251-261.
5. Snyder, G.L. and S. Greenberg, 2010. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br. J. Anaesthesia, 105: 106-115.
6. Wigmore, T.J., K. Mohammed and S. Jhanji, 2016. Long-term survival for patients undergoing volatile versus IV anesthesia for cancer surgerya retrospective analysis. Anesthesiol.: J. Am. Soc. Anesthesiol., 124: 69-79.
7. Melamed, R., S. Bar-Yosef, G. Shakhar, K. Shakhar and S. Ben-Eliyahu, 2003. Suppression of natural killer cell activity and promotion of tumor metastasis by ketamine, thiopental and halothane but not by propofol: Mediating mechanisms and prophylactic measures. Anesthesia Analgesia, 97: 1331-1339.
8. Gudaityte, J., D. Dvylys and I. Simeliunaite, 2017. Anaesthetic challenges in cancer patients: Current therapies and pain management. Acta Med. Lituanica, 24: 121-127.
9. Denis, M.G., C. Lipart, J. LeBorgne, P.A. LeHur and J.P. Galmiche, 1997. Detection of disseminated tumor cells in peripheral blood of colorectal cancer patients. Int. J. Cancer, 74: 540-544.
10. Page, G.G., 2005. Surgery-induced immunosuppression and postoperative pain management. AACN Adv. Crit. Care, 16: 302-309.
11. Loop, T., D. Dovi-Akue, M. Frick, M. Roesslein and L. Egger *et al*., 2005. Volatile anesthetics induce caspase-dependent, mitochondria-mediated apoptosis in human T lymphocytes *in vitro*. J. Am. Soc. Anesthesiol., 102: 1147-1157.
12. Vallejo, R., O. de Leon-Casasola and R. Benyamin, 2004. Opioid therapy and immunosuppression: A review. Am. J. Therapeut., 11: 354-365.
13. Cummings, K.C., F. Xu, L.C. Cummings and G.S. Cooper, 2012. A comparison of epidural analgesia and traditional pain management effects on survival and cancer recurrence after colectomy: A population-based study. J. Am. Soc. Anesthesiol., 116: 797-806.
14. De Oliveira, Jr. G.S., S. Ahmad, J.C. Schink, D.K. Singh, P.C. Fitzgerald and R.J. McCarthy, 2011. Intraoperative neuraxial anesthesia but not postoperative neuraxial analgesia is associated with increased relapse-free survival in ovarian cancer patients after primary cytoreductive surgery. Regional Anesthesia Pain Med., 36: 271-277.
15. Lin, L., C. Liu, H. Tan, H. Ouyang, Y. Zhang and W. Zeng, 2011. Anaesthetic technique may affect prognosis for ovarian serous adenocarcinoma: A retrospective analysis. Br. J. Anaesthesia, 106: 814-822.
16. Lacassie, H.J., J. Cartagena, J. Branes, M. Assel and G.C. Echevarria, 2013. The relationship between neuraxial anesthesia and advanced ovarian cancer-related outcomes in the Chilean population. Anesthesia Analgesia, 117: 653-660.
17. Roiss, M., J. Schiffmann, P. Tennstedt, T. Kessler and I. Blanc *et al*., 2014. Oncological long-term outcome of 4772 patients with prostate cancer undergoing radical prostatectomy: Does the anaesthetic technique matter? Eur. J. Surg. Oncol., 40: 1686-1692.
18. Wuethrich, P.Y., G.N. Thalmann, U.E. Studer and F.C. Burkhard, 2013. Epidural analgesia during open radical prostatectomy does not improve long-term cancer-related outcome: A retrospective study in patients with advanced prostate cancer. Plos One, Vol. 8. 10.1371/journal.pone.0072873.
19. Jang, D., C.S. Lim, Y.S. Shin, Y.K. Ko, S.I. Park, S.H. Song and B.J. Kim, 2016. A comparison of regional and general anesthesia effects on 5 year survival and cancer recurrence after transurethralresection of the bladder tumor: Aretrospective analysis. BMC Anesthesiol., Vol. 16.