World Journal of Surgery and Surgical Research

Editorial
Published: 20 May, 2022

Anesthetic Agents and Immunomodulation in Colon Cancer

Yehuda Raveh[1], David Raveh[2] and Ramona Nicolau-Raducu[1]*

[1]*Department of Anesthesiology, University of Miami/Jackson Memorial Hospital, USA*

[2]*Departments of Physics and Mathematics, University of Miami, USA*

Editorial

The lifetime probability of suffering from cancer is 43% for men and 38% for women [1]. Surgical excision remains a cardinal element in the oncological care of most solid cancers; surgery is used to prevent, diagnose stage, palliate, and treat cancer [2]. Unfortunately, ample data suggest that the surgical procedure itself, along with a multitude of perioperative factors, generate a permissive, pro-neoplastic environment for cancer progression [2]. The excision or debulking of the primary neoplastic mass induces and promotes metastatic or residual disease by releasing satellite tumor foci from the inhibitory concomitant tumor resistance of the primary tumor [3]. Many different immune cells play an important role in both inhibiting and promoting metastatic disease, and the perioperative suppression of natural killer or cytotoxic T cells' antimetastatic capacities was shown to mediate postoperative cancer progression [4,5]. Additionally, several perioperative variables are believed to impact the oncological outcomes, such as surgical stress, anesthetic management, transfusion of red cells, hypothermia, and occurrence of postoperative complications [6]. General anesthetics and opioid analgesic agents are long believed to influence cancer recurrence by direct impact on the micro-environment and growth of the neoplasia [2,6]. Similarly, the use of opioids to control pain have been shown in animals and humans to activate stress responses, suppress cell mediated immunity, increase angiogenesis, and promote the progression of metastatic disease [6]. The volatile anesthetics sevoflurane and isoflurane are frequently used for maintenance of general anesthesia. *In-vitro* studies have implicated volatile anesthetics in promoting metastasis *via* direct survival-enhancing effects on cancer cells, as well as suppression of immune cell function and tumoircidal activities [7-9]. However, the molecular mechanisms for such effects are not completely understood, and differ between inhaled agents and cancer cell lines. Propofol is the most widely used agent for induction and maintenance of intravenous anesthesia. Some preclinical data suggest that propofol may possess antitumor effects on several cancer cell lines [10,11]. Propofol antineoplastic effects are plausibly mediated either *via* its regulatory role on ribonucleic acid pathways and signaling in cancer cells, or *via* enhancement of natural killer cell activity. Additionally, propofol's anti-inflammatory and anti-oxidative properties may subsequently mitigate or protect against perioperative immune suppression [8,9,11]. The results of clinical studies addressing the effects of specific anesthetic and analgesic agents remain inconclusive since they were retrospective in nature, lacked the statistic power to detect small effects, and suffered from inevitable methodological limitations [6]. Therefore, available clinical evidence is insufficient to support a preferred anesthetic agent or establish guidelines for oncological surgery.

The recent, prospective, double-blind trial by Chung-Sik et al. [12] randomized patients undergoing colorectal cancer surgery to maintenance of anesthesia with either the volatile agent sevoflurane or the intravenous agent propofol. The authors then compared immune cells' profiles before and after anesthesia in both groups. Expression profiles of circulating immune cells, e.g., natural killer, helper and cytotoxic T cells, neutrophils, lymphocytes, and monocytes, after propofol or sevoflurane anesthesia were comparable. The authors concluded that propofol is not superior to sevoflurane for colorectal cancer surgery.

We salute the authors on this detailed and important investigation. Their finding that the choice of general anesthetic for colorectal cancer surgery has minimal if any effect on early perioperative immune status illuminates an important and controversial topic. However, several limitations of the study are to be acknowledged. First, matching the pathological stage of the colon cancer in the two treatment groups is, of course, essential. The authors conclude that the two study groups had comparable pathological stages of colon cancer. However, a single significance test comparing the two groups for all five-stages combined yielded p=0.071 [12], thus indicating that the groups most likely differ in at least one of these stages (i.e., $p<0.05$). Such a difference may have skewed the results; therefore, a statistical sub-analysis for each pathological stage should have been planned

Correspondence:
Yehuda Raveh, Department of Anesthesiology, University of Miami/ Jackson Memorial Hospital, 1611 NW 12th Avenue, DTC 318, Miami, FL, 33136, USA, Tel: 305 585 6983; E-mail: yraveh@miami.edu

Received Date: *29 Apr 2022*
Accepted Date: *12 May 2022*
Published Date: *20 May 2022*

Citation:
Raveh Y, Raveh D, Ramona N-R. Anesthetic Agents and Immunomodulation in Colon Cancer. World J Surg Surgical Res. 2022; 5: 1385.

for such an eventuality, or at the least the authors should have implemented a set of unplanned post hoc comparisons [13]. Second, the authors state that propofol was reported to have a greater (i.e., desirable) antitumor effect than volatile anesthetics in oncological surgery, yet they hypothesized that propofol-based anesthesia would have fewer harmful effects on circulating immune cells than equipotent doses of volatile anesthetics. This apparent inconsistency remains unexplained. Lastly, a trade-off between type I and II error rates is inevitable [14]. The authors chose traditional type I and type II errors of 0.05 and 0.2, respectively. However, we are certain that in this clinical context failure to reject the null hypothesis (type II error) is as important as falsely rejecting it (type I error); therefore, the type I and II errors should have been equal when calculating the necessary sample size and statistical power [15].

The novel findings of Chung-Silk et al. [12] randomized, double-blind, and prospective trial-namely that the fraction of circulating natural killer cells and T lymphocytes was comparable between propofol and sevoflurane-based anesthesia in patients undergoing colorectal cancer surgery-are an important contribution to the topic. The immunomodulatory aftermaths of general anesthetics are well-described [16]. Immunosuppressive effects are ascribed to an increased apoptosis or a decrease in circulating immune cells [17]. Nevertheless, compelling evidence suggests simultaneous, opposing immuno-activation [16]. General anesthetics-induced immunosuppression and immuno-activation may be either detrimental or beneficial, subject to the clinical scenario [16,18]. Thus, the clinical significance of findings of studies implementing laboratory measures as a surrogate of immunocompetence could not be readily inferred. Additional clinical trials of longitudinal oncological outcomes are required to determine the safer general anesthetic for cancer surgery.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5-29.
2. Tohme S, Simmons RL, Tsung A. Surgery for cancer: A trigger for metastases. Cancer Res. 2017;77(7):1548-52.
3. Chiarella P, Bruzzo J, Meiss RP, Ruggiero RA. Concomitant tumor resistance. Cancer Lett. 2012;324(2):133-41.
4. Bartal I, Melamed R, Greenfeld K, Atzil S, Glasner A, Domankevich V, et al. Immune perturbations in patients along the perioperative period: Alterations in cell surface markers and leukocyte subtypes before and after surgery. Brain Behav Immun. 2010;24(3):376-86.
5. Shakhar G, Ben-Eliyahu S. Potential prophylactic measures against postoperative immunosuppression: Could they reduce recurrence rates in oncological patients? Ann Surg Oncol. 2003;10(8):972-92.
6. Horowitz M, Neeman E, Sharon E, Ben-Eliyahu S. Exploiting the critical perioperative period to improve long-term cancer outcomes. Nat Rev Clin Oncol. 2015;12(4):213-26.
7. Benzonana LL, Perry NJ, Watts HR, Yang B, Perry IA, Coombes C, et al. Isoflurane, a commonly used volatile anesthetic, enhances renal cancer growth and malignant potential *via* the hypoxia-inducible factor cellular signaling pathway *in vitro*. Anesthesiology. 2013;119(3):593-605.
8. Buckley A, McQuaid S, Johnson P, Buggy DJ. Effect of anaesthetic technique on the natural killer cell anti-tumour activity of serum from women undergoing breast cancer surgery: A pilot study. Br J Anaesth. 2014;113(1):i56-62.
9. Desmond F, McCormack J, Mulligan N, Stokes M, Buggy DJ. Effect of anaesthetic technique on immune cell infiltration in breast cancer: A follow-up pilot analysis of a prospective, randomised, investigator-masked study. Anticancer Res. 2015;35(3):1311-9.
10. Efremov SM, Kozireva VS, Moroz GB, Abubakirov MN, Shkoda OS, Shilova AN, et al. The immunosuppressive effects of volatile versus intravenous anesthesia combined with epidural analgesia on kidney cancer: A pilot randomized controlled trial. Korean J Anesthesiol. 2020;73(6):525-33.
11. Liu S, Gu X, Zhu L, Wu G, Zhou H, Song Y, et al. Effects of propofol and sevoflurane on perioperative immune response in patients undergoing laparoscopic radical hysterectomy for cervical cancer. Medicine (Baltimore). 2016;95(49):e5479.
12. Oh CS, Park HJ, Piao L, Sohn KM, Koh SE, Hwang DY, et al. Expression profiles of immune cells after propofol or sevoflurane anesthesia for colorectal cancer surgery: A prospective double-blind randomized trial. Anesthesiology. 2022;136(3):448-58.
13. Ruxton GD, Beauchamp G. Time for some a priori thinking about post hoc testing. Beh Eco. 2008;19(3):690-3.
14. Walley RJ, Grieve AP. Optimising the trade-off between type I and II error rates in the Bayesian context. Pharm Stat. 2021;20(4):710-20.
15. Banerjee A, Chitnis UB, Jadhav SL, Bhawalkar JS, Chaudhury S. Hypothesis testing, type I and type II errors. Ind Psychiatry J. 2009;18(2):127-31.
16. Zingoni A, Fionda C, Borrelli C, Cippitelli M, Santoni A, Soriani A. Natural killer cell response to chemotherapy-stressed cancer cells: Role in tumor immunosurveillance. Mini Review. Front Immunol. 2017;8:1194.
17. Miyata T, Kodama T, Honma R, Nezu Y, Harada Y, Yogo T, et al. Influence of general anesthesia with isoflurane following propofol-induction on natural killer cell cytotoxic activities of peripheral blood lymphocytes in dogs. J Vet Med Sci. 2013;75(7):917-21.
18. Janssen LME, Ramsay EE, Logsdon CD, Overwijk WW. The immune system in cancer metastasis: Friend or foe? J Immunother Cancer. 2017;5(1):79.