RESEARCH ARTICLE

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Effect of Anaesthesia Technique on anti-tumor Immunity through TGF-β levels in Adult Patients Undergoing Surgery for Oral Cancer

Tanmay Mathur, Sachidanand Jee Bharati, Lata Kumari, Shivani Kaushik, Brajesh Kumar Ratre, Sushma Bhatnagar, Seema Mishra, Nishkarsh Gupta, Rakesh Garg, Vinod Kumar, Maroof Ahmad Khan, Sunil Kumar, Rakesh Kumar Deepak*

Abstract

Background: There is a paucity of literature regarding the effect of anesthetic techniques on anti-tumor immunity, especially in Oral cavity Malignancies. We designed a study to evaluate the effect of 3 anesthetic techniques – Opioid, Lignocaine infusion and Dexmeditomedine infusion-based on anti-tumor immunity, using TGF-β, T-helper cell profile and inflammatory markers such as *IL-6* and IL-10. **Methods:** A pilot prospective randomized trial was conducted in 90 patients undergoing surgery for Oral cavity malignancy under general anesthesia in a tertiary specialty cancer hospital. Adult cancer patients of the American Society of Anaesthesiologists (ASA) physical status I-III fulfilling the inclusion criteria were randomized to either group A (Opioid general anesthesia), group B (lignocaine infusion-based general anesthesia), or group C (Dexmedetomidine infusion-based general anesthesia). Preoperative (morning of surgery) and postoperative (24 hours after surgery) blood samples were obtained. Statistical analysis was done, and the results were analyzed. **Results:** Demographic profile and pre-operative parameters were comparable between both groups. We did not find any statistically significant difference in the Post-operative levels of TGF-β, neutrophil-lymphocyte ratio (NLR), Monocyte Lymphocyte Ratio (MLR), platelet lymphocyte ratio (PLR), *IL-6*, IL-10, and T-helper cell profile (IFN-γ, IL-17A, and IL-4 as surrogate markers) among the three study groups. However, it was noted that the overall Opioid consumption was markedly reduced in Group C without any major adverse effects being noted.

Keywords: Oral cancer- Anesthesia- Anti-Tumor Immunity- TGF-β

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Introduction

Cancers of the oral cavity account for one of the most common types of cancers in the Indian population. Among males in India, oral cancer accounts for one of the most common cancer sites, and in 2020, it was among the five most common cancers in India [1]. Oral cancer is defined as cancer of the lips, mouth, and tongue. This definition confirms the definition of oral cavity cancers as per the International Classification of Diseases for Oncology [2].

Among the approaches to the treatment of oral cancer is surgery. In resectable tumors, surgery is superior to all alternative therapies [3]. The high burden of head and neck cancer has increased the responsibilities of anaesthesiologists, not only during the perioperative period but also in the management of chronic pain in these patients. Surgical stress, along with neuroendocrine and inflammatory responses, aggravates the attenuation of cell-mediated immunity and favors tumor metastasis and recurrence [4].

Recurrence of any solid malignancy after surgical removal of the primary mass has been attributed to incomplete removal, already metastasized status, and adequacy of anti-tumor immunity in the body. Anti-tumor immunity consists of CD8+ T-helper cells and Natural Killer cells involved in the identification and killing of cancer cells, as well as priming other anti-tumor cells [5]. Macrophages also undergo differentiation into M1 (anti-tumor) and M2 (pro-inflammatory) lineages, which play a role in suppressing tumor cells and promoting the growth of tumors respectively [6]. M2 lineage cells are a part of Tumor-Associated Macrophages (TAMs) that secrete cytokines such as Tumor Growth Factor-β (TGF-β) and Interleukin-6 (IL-6) (causes immunosuppression), Vascular Endothelial Growth Factor (VEGF) (promote tumor angiogenesis), and Matrix Metalloproteinase (MMP) [7, 8].

Although not fully understood, other leucocytes also

*All India Institute of Medical Sciences, New Delhi, India. *For Correspondence: rakeshdeepak2008@gmail.com*

play essential roles in cancer suppression. Neutrophils are chief inflammatory response leucocytes, and a high level of neutrophilia and a higher neutrophil/lymphocyte ratio is associated with adverse prognoses for various cancers [9, 10]. Pharmacological agents used to provide anesthesia during cancer surgery have been investigated at length for their propensity to suppress anti-tumor immunity and contribute to recurrence. Contemporary research has begun focusing on the impact that perioperative factors, such as the type and method of anesthesia used, may have on cancer recurrence and outcomes. Retrospective studies and meta-analyses suggest that particular anesthetic techniques may reduce cancer-related mortality and recurrence by decreasing immunosuppression after surgical treatment for certain types of cancer [11]. The agents used to induce anesthesia and the depth of anesthesia play a role in suppressing the Hypothalamo-pituitary axis (HPA) and sympathetic activity. Inadequate suppression of the two during cancer surgery leads to the release of catechol amines, pro-inflammatory factors (TGF-β, *IL-6*, VEGF), and suppression of cell-mediated immunity [12-14]. The use of opioids, like Morphine, for perioperative pain management in patients undergoing surgery for Oral cancer has been a standard technique for many years. However, opioids usually inhibit T-lymphocyte proliferation, and Morphine suppresses NK cell activity and T cell differentiation, promotes lymphocyte apoptosis, and decreases toll-like receptor 4 (TLR4) expression on macrophages [15]. Research has suggested that the implementation of an ERAS protocol for head and neck cancer patients can successfully decrease overall length of stay, postoperative pain scores, and narcotic use. To this effect, several agents have been investigated, such as ketamine, lignocaine, dexmedetomidine, ketorolac, and gabapentin [16]. Among these, lignocaine and dexmedetomidine have shown promising results [17-19].

Lignocaine is a tertiary amine that is an amide derivative of diethylaminoacetic acid and is a local anesthetic agent that can be used intravenously. Due to its sizeable therapeutic margin, strong anti-inflammatory properties, and potentially beneficial impact on the innate immune surveillance system, lignocaine might be an ideal candidate for drug repurposing in cancer, which may potentially affect the patient outcome dramatically. Besides the already proven favorable effects of perioperative IV lidocaine, patients with oral cancer might also benefit from an ant-metastatic effect [17].

Dexmedetomidine is an α2-adrenergic receptor agonist with analgesic, sedative, anxiolytic, and anti-sympatholytic properties. Several studies have indicated that dexmedetomidine can regulate the perioperative immune response in radical surgeries of breast, colon, and gastric cancer [19-21]. Nevertheless, the influence of dexmedetomidine on immune response in patients with oral malignant tumors during operation remains unclear. Several studies have been carried out to test the validity of the above hypothesis, using pre and post-operative levels of different pro-tumor cytokines and soluble factors such as *IL-6*, 10 and VEGF, TGF-β in surgery for breast cancer, surgery for lung cancer, and surgery for colon cancer [22-24].

Literature regarding the effect of drugs like lignocaine and dexmedetomidine on anti-tumor immunity and its markers in cases of oral cancer undergoing surgical treatment and the effect on recurrence and long-term survival is conflicting. Our study has compared these two drugs for their impact on postoperative levels of TGF-β, *IL-6*, and T-helper cell profiles in patients of oral cancer undergoing surgery receiving lignocaine infusion and dexmedetomidine infusion-based anesthesia. Moreover, we have compared the total opioid consumption in the perioperative period among the study groups.

Materials and Methods

Design of the study

Prospective, Randomized trial (Figure 1).

Place of the study

After getting approval from the institutional ethical committee, this study was performed at the Department of Onco-Anesthesiology, B.R.A.I.R.C.H, AIIMS, New Delhi and National Cancer Institute, AIIMS Jhajjar, Haryana.

Inclusion criteria

1. Age18 -70 years.
2. Patients undergoing surgery for Oral cancer.
3. ASA I, II, III.

Exclusion criteria

1. Patient refusal.
2. Allergy to any of the study drugs.
3. Chronic kidney and liver disease.
4. Blood transfusion in the perioperative period. (30 days before surgery and Up to 24 hrs postoperative period)
5. Atrioventricular conduction disorders. (Either with a pacemaker or on an Antiarrhythmic drug)
6. Heart failure on treatment with beta-blockers.
7. Patients with chronic pain preoperatively already receiving Opioids.

Sample Size Calculation

After thorough search on PubMed and Medline, to the best of our knowledge we could not find any article or study with comparison of anti-tumour immunity pre and post-surgery as assessed by TGF-β levels in oral cancer surgeries with respect to lignocaine and dexmedetomidine based anaesthesia technique. Hence, we decided to perform a pilot study, and included 30 patients in each group (total 90) as per the feasibility of case numbers at our institution.

Preoperative visit

Recruitment of the patients for the study was done after getting approval from the institutional scientific and ethics committee. Informed written consent was obtained. All the selected patients underwent a routine pre-anesthetic check-up. The demographic data like age, sex, comorbidities, related drug details, details of preoperative chemotherapy, radiotherapy, any surgery, and preoperative opioid use, etc., were noted. All the routine investigations of anesthesia management were done.

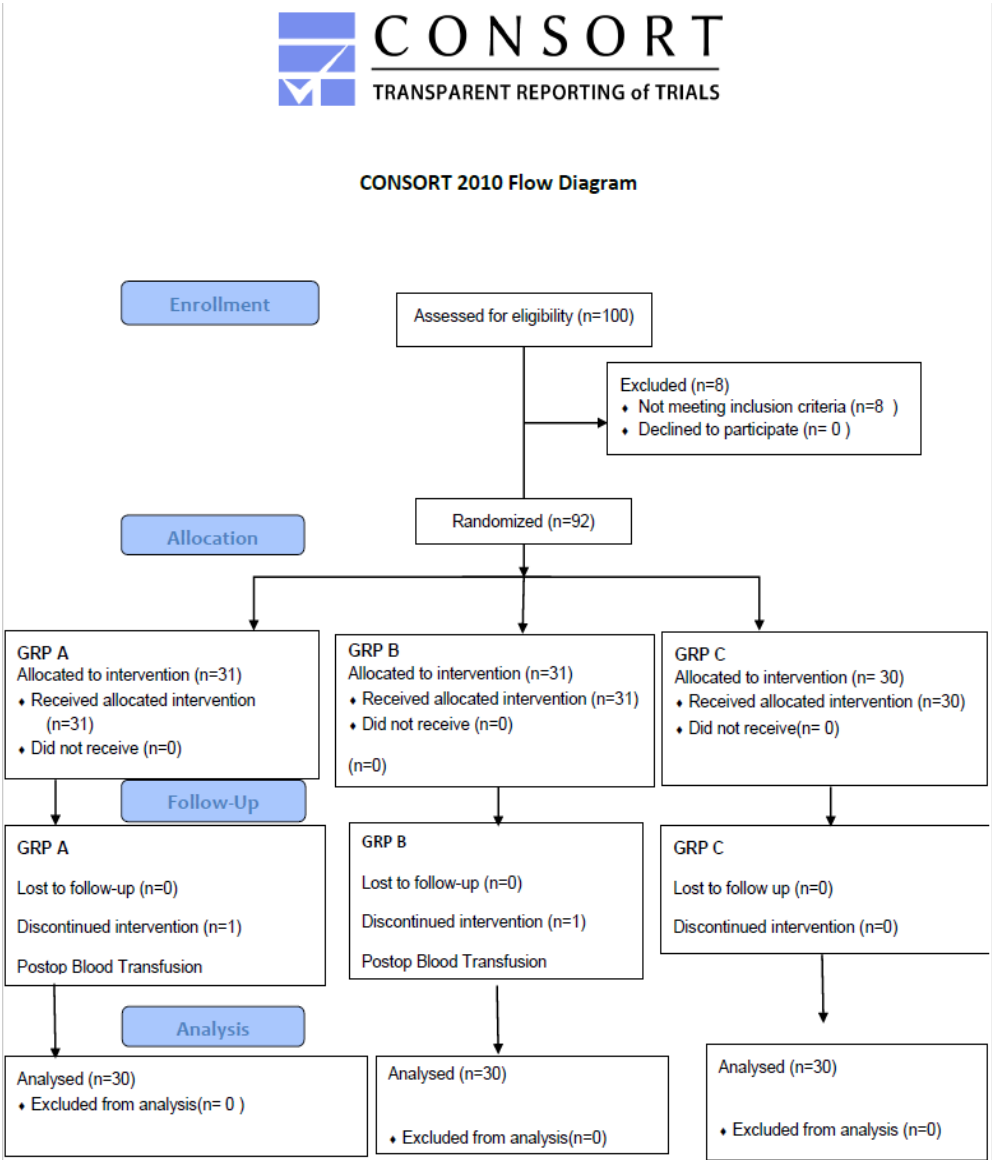

Figure 1. Graphical Abstract

Upon arrival at the operation theatre, the I.V. line was secured on the day of surgery, and routine monitors (Spo2, NIBP, and E.C.G.) were attached. Baseline heart rate (HR) and blood pressure (BP) were noted. A blood sample for preoperative neutrophil-lymphocyte ratio (NLR), Monocyte Lymphocyte Ratio (MLR), platelet lymphocyte ratio (PLR), *IL-6*, and TGF beta with T-helper cell profile was collected.

Randomization and allocation concealment

Patients were randomly allocated into three groups, "A," "B," and "C," using a computer-generated random numbers sequence and allocation concealed in a sequentially numbered opaque envelope.

Intraoperative Management

For Group A, after adequate preoxygenation, an initial bolus dose of opioid Injection fentanyl (2 µg/kg) was administered. Anesthesia was induced with an injection of propofol (2-2.5 mg/kg titrated to the effect of loss of consciousness) and followed by muscle relaxant Injection rocuronium (0.6 mg/kg I.V bolus) after checking ventilation. The intubation plan and technique were per the anesthesia provider attending the case. For patients of this group, intraoperative sedo-analgesia was provided with Inj. fentanyl (1 µg/kg bolus) as required. Total opioid consumption was noted.

For Group B, after adequate preoxygenation, an initial bolus dose of opioid Inj. fentanyl (2 µg/kg) was administered. Anesthesia was induced with i.v propofol (2-2.5 mg/kg titrated to the effect of loss of consciousness and followed by muscle relaxant rocuronium (of 0.6 mg/kg I.V bolus). The intubation plan and technique were as per the anesthesia provider attending the case. This was followed by starting Injection lignocaine (preservative-free, trade name –XYLOCARD) 2% intravenous infusion at the rate of 1.5 mg/kg/hr. If heart rate and/or blood pressure rose from baseline by 20%, Inj. Fentanyl (1 µg/kg) was given for sedo-analgesia. Total opioid consumption was noted.

For Group C, after adequate preoxygenation, an initial bolus dose of opioid Inj. fentanyl (2 µg/kg) was administered. Anesthesia was induced with i.v propofol (2-2.5 mg/kg) titrated to the effect of loss of consciousness and followed by muscle relaxant rocuronium (0.6 mg/kg

Table 1. Demography and Baseline Characteristics

Variable	Category	Group A	Group B	Group C	P value
Age (years)		54± 12.01	55± 9.37	53± 7.71	0.8936
Gender	Female	5 (16.67%)	5 (16.67%)	6 (20%)	
	Male	25 (83.33%)	25 (83.33%)	24 (80%)	0.927
Height (cm)		159.63±7.5	158.56±10.87	161.83± 9.27	0.8959
BMI (kg/m^2)		23.48±3.39	23.67±3.93	22.89± 4.12	0.4011
Weight (Kg)		59.4±5.88	58.7±5.55	59.26±6.88	0.7158
Duration of surgery (min)		174.33±14.46	174.26±13.84	176.43±12.92	0.7867

Table 2. Pre-Operative Laboratory Values

Pre-operative Lab values	Group A	Group B	Group C	p value
Urea (mg/dL)	23.09±7.60	24.32± 6.62	25.74±8.34	0.124
Creatinine (mg/dL)	0.69±.22	0.68±0.16	0.77±0.165	0.125
Sodium (mmol/L)	139.43± 3.67	139.36± 2.91	137.6±4.87	0.805
Potassium (mmol/L)	4.39±0.40	4.53±0.40	4.0±.44	0.586
Haemoglobin (g/dL)	11.75±1.96	12.13±1.54	11.75± 1.33	0.786
Platelets (Lac/µL)	2.10± 0.89	2.37±0.82	2.11± 0.69	0.944
Total Leucocyte Count (/µL)	7761± 2850	7605±2268	7777±932	0.068
Lymphocytes (%)	24.36± 9.88	26.48±8.03	26.71±7.13	0.471
Monocytes (%)	5.63±1.72	5.57±1.71	5.75±1.01	0.43
Neutrophils (%)	64.44±11.59	58.23± 10.16	55.34±9.84	0.645
NLR	2.85 (1.72-4.18)	2.66 (1.48-2.92)	2.22 (1.71-2.79)	0.061
MLR	0.22 (0.16-0.30)	0.20 (0.13-0.25)	0.18 (0.13-0.22)	0.122
PLR	84.75 (58.66-123.03	82.59 (56.17- 121.4)	79.77 (52.15-108.250	0.747

I.V bolus). The intubation plan and technique were as per the anesthesia provider attending the case. An infusion of Inj followed this. Dexmedetomidine (loading dose 1 µg/kg over 10 minutes followed by maintenance dose 0.5 µg/kg/hour). If heart rate and/or blood pressure rose from baseline by 20%, Inj. Fentanyl (1 µg/kg) was given for sedo-analgesia. Total opioid consumption was noted.

For all the patients, intraoperative maintenance of anesthesia was done with Oxygen + air + sevoflurane + rocuronium infusion. All patients received Inj. paracetamol 15mg/kg I.V. and Inj. diclofenac 1.5 mg/kg I.V. as part of multimodal analgesia towards the end of the surgery. For patients of groups B and C, the respective infusions were continued for 24 hours and then stopped.

Intraoperative HR, Spo2, ECG, invasive/non-invasive BP, and temperature were measured, and urine output was monitored. Patients were mechanically ventilated in a volume-controlled mode to maintain tidal volumes of 6-8 ml/kg at respiratory rates (10- 14 breaths/min) to maintain a target end-tidal carbon dioxide (EtCO2) partial pressure of 35- 40 mmHg with a positive end-expiratory pressure of 5 mmHg. Any hypotensive episodes, defined as a decrease in mean arterial pressure by 20% of the baseline value, were treated by i.v bolus doses of 6 mg of Phentermine. Blood loss was replaced as per institutional protocol. The pain was managed by multimodal analgesia.

Table 3. Vasopressor Requirement

Vasopressor usage	Group A	Group B	Group C	p value
Number of patients in each group	2 (6.67%)	2 (6.67%	1 (3.33%)	0.613

Table 4. Pre-Operative Inflammatory Markers

Pre-operative Inflammatory markers	Group A	Group B	Group C	p value
IFN-γ (pg/ml)	180.19 ± 128.53-361.2	189.20 ±116.87-453.15	218.22 ± 181.88-231.40	0.4012
IL-4 (pg/ml)	90.93 ± 51.52- 199.89	111.62 ± 40.82 - 205.24	147.10 ± 55.46 - 371.07	0.1049
IL-6 (pg/ml)	612.81 ± 372.81-799.75	360.28 ± 251.92- 673.31	484.00 ± 143.88- 1007.35	0.2502
IL-10 (pg/ml)	21.24 ± 11.66 - 27.57	21.52 ± 7.32 - 33.73	34.36 ± 31.56 - 35.9	0.0001
IL-17A (pg/ml)	60.62 ± 34.35- 133.26)	74.41 ± 27.21- 136.82	110.08 ± 44.10 - 247.38	0.0282
TGF-β (pg/ml)	20.32 ± 10.92- 33.84	25.59 ± 11.92 - 41.58	33.67 ± 23.53 - 45.18	0.0111

Table 5. Post-Operative Inflammatory Markers

Post-operative Inflammatory markers	Group A	Group B	Group C	p value
IFN-γ (pg/ml)	246.641 ± 55.65-358.45	283.20 ± 207.71-345.67	244.15 ± 168.66-320.94	0.4283
IL-4 (pg/ml)	189.995 ± 107.45- 357.99	153.50 ± 88.28- 330.99	248.78 ± 150.92-354.48	0.1477
IL-6 (pg/ml)	278.95 ± 177.78- 350.15	293.40 ± 200.14 - 464.70	315.89 ± 236.66 - 842.50	0.1477
IL-10 (pg/ml)	11.601 ± 6.24-14.33	10.29 ± 5.77 - 14.57	9.45 ± 6.008 - 15.29	0.9244
IL-17A (pg/ml)	159.2 ± 71.63 - 259.54	37.97 ± 19.78 - 76.85	63.26 ± 28.52 - 152.8	0.9244
TGF-β (pg/ml)	27.20 ± 16.01 - 32.67	22.91 ± 13.01- 33.15	22.91 ± 14.58 - 34.1	0.7533

Table 6. 24 Hour Opioid consumption

Perioperative Opioid Consumption (over 24 hours)	Group A	Group B	Group C	p value
FENTANYL(µg)	2466±235	2521±230	1937±189	<0.01

Postoperative Management

The patients were shifted to the ICU and electively mechanically ventilated as per the institutional protocol. ICU sedation was provided with Inj. Midazolam infusion (0.5mg-2mg /hr) and Inj fentanyl (0.5µg-2µg/kg/hr). Sedation was switched off before planned extubation. The pain was managed with multimodal analgesia required to keep an NRS score <3/10. In the postoperative period, all patients received Injections of paracetamol (15mg/kg) intravenous TDS as part of postoperative analgesia. Inj. Diclofenac 1.5 mg/kg was used to rescue analgesia if needed.

Incidence of pruritus, nausea, vomiting, bradycardia, hypotension, and any other complication/event were noted in all the study groups and treated as per institutional protocol. Total 24-hour consumption of opioids was noted. 24 hours after the surgery, a blood sample was sent for post-operative neutrophil-lymphocyte ratio (NLR), Monocyte Lymphocyte Ratio (MLR), platelet lymphocyte ratio (PLR), CRP, *IL-6* and TGF beta with T-helper cell profile.

TGF-beta and IL-6 were evaluated by an ELISA-based assay technique, whereas T-helper cell profile was evaluated based on levels of IFN-gamma (for Th-1), TNF-alpha (for Th-2) and IL-17 (for Th-17) by an ELISA-based assay.

Results

The three groups were comparable in demography (age, gender), height, weight, body mass index, and duration of surgery (Table 1).

Pre-operative laboratory values pertaining to hemoglobin, hematocrit, total leucocyte count, percentages of neutrophils and monocytes, platelet count, urea, creatinine, serum electrolytes (sodium and potassium), monocyte-lymphocyte ratio and platelet-lymphocyte ratio were found to be comparable in both groups (Table 2).

Number of incidences of hypotension requiring vasopressor support was comparable in all the groups. There were nil episodes of bradycardia in either group (Table 3).

Preoperative inflammatory markers, cytokines, and T-helper cell profile were comparable in all the groups. It is worth noting that the preoperative TGF-β levels were found to be significantly higher in Group C by applying the Analysis of Variance test (ANOVA). However, further analysis has shown that after applying the covariance test (ANCOVA) analysis, the results become insignificant (Table 4).

Post-operative assessment reported no significant difference in cytokine levels of I*L-4, IL-6, IL- 10, IL-17A* and IFN- γ. The post-operative levels of TGF- β were also not found to be significantly different among any of the groups (Table 5). 24 hour total Opioid consumption was significantly lessor in Group C (Table 6).

Discussion

Several studies have compared the type of anesthesia technique concerning its effect on anti-tumor immunity, cytokines, and inflammatory markers over the past few years. Most of these are either exclusive or a mix of propofol-based, inhalational-based, or regional anesthesia-based techniques. However, we could not find any studies comparing the effects of lignocaine and dexmeditomidine infusions in patients with Oral cancer.

Inflammatory markers studied were *IL-6* and *IL-10* – both implicated in increased localized inflammation and angiogenesis. Signature cytokines were studied for the T-helper cell profile – IFN-γ for Th1, *IL-4* for Th2, and *IL-17A* for Th17 cells. TGF-β was studied as a separate marker, having been proven to a certain degree to increase the metastatic potential of oral cavity malignancy.

Looney et al. [22] conducted a study comparing a propofol-paravertebral anesthetic (PPA) technique with balanced general anesthesia (GA) and morphine analgesia in women undergoing surgery for primary breast cancer and found the mean postoperative change in TGF-β concentration among GA patients was -163 (decrease) as compared to +146 (increase) pg/ml for patients in PPS group. The difference was significant. In another study, Xu et al. [23] compared thoracic-paravertebral plus propofol-based anesthesia with Sufentanil and inhalational-based general anesthesia in colon cancer patients and found that there was no difference between pre-operative and post-operative values of *IL-6*, 10 and TGF-β in GA group. This result is similar to the results of our study.

A study conducted by Lili Huang et al. suggested that dexmedetomidine can attenuate immunosup¬pression in

patients undergoing radical and reconstructive surgery for oral cancer [18]. Another study by Yulan Wang et al. [21] concluded that Dexmedetomidine had been shown to reduce surgical stresses and maintain Th1/Th2 balance. It has been shown to reduce inflammatory responses and exert an immunoprotective effect. A similar study by Kun Wang et al. [20] observed that the application of dexmedetomidine during anesthesia in patients receiving radical operation of colon carcinoma has a better clinical treat¬ment effect, which can reduce the secretion of inflammatory factors, decrease the inhibition of immunity and reduce the use of fentanyl. In our study, we were able to replicate this result, as in Group C patients with Dexmedetomidine infusion, it was shown that Fentanyl consumption was significantly lower (p-Value <0.01).

In our study, we observed that the use of lignocaine infusion did not reduce the Opioid consumption in Group B patients. Similarly, IV lignocaine failed to confirm an opioid-sparing effect after breast cancer surgery in two studies by Terkawi AS et al. and Grigoras A et al. [25, 26]. The complex role of the type of cancer, use or complete omission of opioids, pain management techniques, and interaction with other drugs may also affect anti-cancer immunity. More in-depth studies will be required to effectively unmask the role of anesthetic modality on anti-cancer immunity in specific cancers and their effect on metastasis and survival.

Rigg et al. [27] showed that there was no significant difference in mortality or morbidity between patients undergoing surgery under general anesthesia with intraoperative and postoperative epidural therapy or general anesthesia with other anesthetic and analgesic regimens for major abdominal or thoracic surgery (MASTER trial). A sub-study of this MASTER trial was done to check cancer-free survival and all-cause mortality differences between the two arms. The authors could not detect any difference in 5-year recurrence and mortality rates [28]. In a recent narrative review on the role of dexmedetomidine on cancer recurrence, Cai Q et al. opined that the conclusions on whether dexmedetomidine would influence cancer recurrence could not be currently drawn for the lack of strong clinical evidence. Therefore, this is still a new area that needs further exploration [29].

As of today, evidence and data linking the choice of anesthetic modality and anti-tumor immunity are conflicting, and it would be improper to base any recommendations based on current literature and study results. Our own study has failed to show a linkage between anesthesia technique and an inhibitory effect on cancer recurrence based on the levels of the tumor markers investigated.

A pilot randomized control trial was conducted in patients undergoing surgery for oral cavity malignancy under three different arms-Opioid technique, Lignocaine infusion, and Dexmedetomidine infusion, to study their effect on anti-tumor immunity and inflammatory markers.

We found that there was no significant difference between the three groups with respect to anti-tumor immunity, cytokines, and inflammatory markers. The comparison of Pre and post-operative levels of neutrophil-lymphocyte ratio (NLR), Monocyte Lymphocyte Ratio (MLR), and platelet lymphocyte ratio (PLR), *IL-6*, *IL-10* with T-helper cell profile, and TGF-β did not yield any statistically significant results.

Several Preclinical and retrospective studies have recently focused on the potential benefit of anesthetic techniques in reducing cancer-related mortality and recurrence by attenuating immunosuppression following surgical treatment in patients with specific types of cancer. However, data is conflicting, and currently, available data do not provide any definitive answers to the hypothesis that using a particular anesthesia technique can reduce perioperative immunosuppression, angiogenesis, and, eventually, cancer recurrence to prolong patient survival. Further adequately powered studies are required, especially prospective Human Randomized controlled trials. Limitations of the study includes, Ours was a pilot study done on a relatively smaller sample size at a single center, hence the study may not be adequately powered to study the outcomes.

The study was conducted only on patients undergoing surgery for Oral cavity cancer. Thus, the applicability of the results to other cancers or general patient population might not be valid.

Our study included limited number of indicators. Many other markers such as VEGF, TNF etc. may also provide valuable information. The inflammatory markers and anti-tumor immunity is a relatively new field of research. More studies with larger sample size will be required to make recommendations.

Author Contribution Statement

The work reported in the paper has been performed by the authors as follows: Tanmay Mathur: Formal analysis, Methodology, Writing – original draft. Sachidanand Jee Bharati: Funding acquisition, Project administration. Lata Kumari: Conceptualization, Writing – review & editing. Shivani Kaushik: Conceptualization, Writing – review & editing. Brajesh Kumar Ratre: Investigation, Project administration, Supervision. Sushma Bhatnagar: Project administration, Supervision. Seema Mishra: Formal analysis, Supervision. Nishkarsh Gupta: Conceptualization, Validation, Visualization. Rakesh Garg: Investigation, Project administration. Vinod Kumar: Investigation, Validation. Mahroof Ahmad Khan: Investigation, Validation, Visualization. Sunil Kumar: Project administration, Software, Supervision. Rakesh Deepak: Data curation, Funding acquisition, Resources, Visualization.

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How the ethical issue was handled

All India Institute of Medical Sciences, New Delhi's ethics committee approved this study. Written Consents were taken from patients who participated in the study

willingly.

Clinical trial registration number

CTRI/2022/03/040751

Availability of data

The data supporting this study's findings are available from the corresponding author upon request.

Any conflict of interest

There is no conflict of interest.

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