Anesthesia and Immune Response in Cancer Patients

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Abstract

Background: This study was designed to evaluate the immunity condition of cancer patients and to assess the efficiency of combined bilateral superficial and deep cervical plexus blocks with general anesthesia in patients undergoing total laryngectomy with respect to the immune response.

Method: The patients (40) were allocated randomly to one of two groups: General Anesthesia Group (GA) (n=20) and Combined Group (regional and general anesthesia) (n=20). After assessment of the airway, propofol was titrated slowly until loss of verbal contact is achieved, after assessment of adequacy of ventilation, vecuronium 0.1mg/Kg was given for muscle relaxation, fentanyl was given in a dose 1ug/kg and then a cuffed endotracheal tube was inserted. The maintenance of anesthesia in both groups was achieved by sevoflurane with fresh gas flow 5 L/min. In combined group, after achieving satisfactory level of anesthesia, the patients received combined bilateral superficial and deep cervical plexus block. The hemodynamic goals were to maintain the mean arterial pressure (MAP) at 60-65mmHg by adjusting the sevoflurane concentration and the use of esmolol. The consumption of sevoflurane and the Frequency of use of esmolol were evaluated in both groups. Intraoperative blood loss was assessed. Venous blood samples for measurement of serum SIL-2R and IL-2 levels were obtained before induction of anesthesia, at the end of surgery, and in the mornings of 1st and 5th postoperative days. In addition, serum samples also were collected from 40 healthy volunteers (mean age 39 yr, 30 male and 10 female) for comparison.

Results: The number of patients requiring supplemental fentanyl, and the mean end tidal sevoflurane concentration were significantly increased in GA group. All patients in GA group required supplemental esmolol to achieve the target MAP, in contrast only 5 patients in the combined group required supplemental esmolol (p<0.001). A reduction in blood loss was observed in the combined group during the surgical procedure (p<0.05). As regards, the immune response, Serum SIL-2R were significantly elevated (p<0.005), whereas the serum IL-2 levels were significantly reduced (p<0.005) in both groups as compared with the preoperative values. The mean serum levels of SIL-2R had increased (p<0.05), whereas IL-2 levels had declined (p<0.01) but there was less significant increase in the mean serum SIL-2R levels and less significant decrease in the mean serum IL-2 levels in the combined group than in the GA alone group (p-value 0.001).

Conclusion: Cancer larynx is associated with a state of immuno-suppression. surgical procedure performed with GA combined with regional anesthesia had less depressant effects on the immune response in the immediate postoperative period.

Key Words: Deep and superficial cervical blocks – Cancer larynx – Immunity – Total laryngectomy.

Introduction

An immune system is a system of biological structures and processes within an organism that protects against disease by identifying and killing pathogens and tumor cells. It detects a wide variety of agents, from viruses to parasitic worms, and needs to distinguish them from the organism's own healthy cells and tissues in order to function properly [1].

The immune system composed of innate and adaptive systems.

The innate immune system, also known as non-specific immune system and secondary line of defence, comprises the cells and mechanisms that defend the host from infection by other organisms in a non-specific manner [2].

The adaptive immune system evolved in early vertebrates and allows for a stronger immune response as well as immunological memory, where each pathogen is "remembered" by a signature antigen. The adaptive immune response is antigen-specific and requires the recognition of specific
“non-self” antigens during a process called antigen presentation [3].

Cancer is a major health problem worldwide and one of the most important causes of morbidity and mortality in children and adults. Cancers arise from the uncontrolled proliferation and spread of clones of transformed cells. From an immunologic perspective, cancer cells can be viewed as altered self-cells that have escaped normal growth-regulating mechanisms [4].

Immunosuppression associated with neoplasm results mainly from T-cell dysfunction and is characterized by impaired synthesis of interleukin-2 (IL-2) [12]. It has been shown that T-lymphocyte-produced IL-2 has an antineoplastic effect through stimulation of self-induced proliferation and lymphokine secretion of the T-lymphocytes themselves, intensification of both proliferation and differentiation of natural killer (NK) cells, induction of r-interferon expression and direct or indirect stimulation of the production of immunoglobulins by B-lymphocytes [5].

The main response of the immune system to tumors is to destroy the abnormal cells using killer T-cells, sometimes with the assistance of helper T-cells [6].

Cancer immunosurveillance appears to be an important host protection process that inhibit carcinogenesis and maintains regular cellular homeostasis [7]. The important role of the immune system is to identify and eliminate tumors. The transformed cells of tumors express antigens that are not found on normal cells. To the immune system, these antigens appear foreign, and their presence causes immune cells to attack the transformed tumor cells [8].

Immuoediting is a process by which a person is protected from cancer growth and the development of tumor immunogenicity by their immune system. It has three main phases: Elimination, equilibrium and escape [9].

An intact cellular immune system is the critical host defence against the development of metastases [10]. Natural killer (NK) cells are the primary defence against cancer cells. They are a subpopulation of large granular lymphocytes that spontaneously recognize and lyse tumour cells. Multiple studies show an inverse relationship between NK cell activity at the time of surgery and the development of metastatic disease. Patients with a low level of NK cell activity have been reported to have a higher incidence of cancer [11].

General anaesthesia may influence immune function. The inhibitory effects of thiopental, ketamine and midazolam on neutrophil functions have been well documented [12].

The potential effects of drugs used in anaesthesia on host defences have been studied using in vitro and animal models and in some human studies.

Current literature suggests that anesthetic agents have immuno-modulatory effects on both the specific and non-specific components of the immune response. Very few published studies are available as regards the independent effect of the anesthetic agents on cytokine level in human [13,14].

Also major surgery suppresses cellular immunity for several days. There is a measurable decrease in the production of cytokines that favour cellular mediated immunity such as IL-2, IL-12, and IFN-g, and an increase in the production of cytokines that interfere with cell mediated immunity, such as IL-10. There is a decrease in the number of circulating natural killer (NK) cells, cytotoxic T-lymphocytes, dendritic cells and T-helper cells [15].

**Material and Methods**

This study included 40 patients with range of age 46–69 year (ASA II-III), with malignancy of the larynx scheduled for total laryngectomy, in El-Kasr El-Aini Hospital from 2011-2012.

The patients were allocated randomly to one of two groups; General Anesthesia group (GA) (n=20), and Combined Group (regional and general anesthesia) (n=20). The study was approved by our Institutional Ethics Committee and informed consents were obtained from all patients. Exclusion criteria included ASA physical status IV, age <40 or >65 years, previous allergy to local anesthetics, drug abuse, or receiving drugs that affect blood coagulation.

Anesthetic management:

All patients were monitored by (ECG, pulse oximetry, capnography, NIBP and 20 gauge intra-arterial cannula for direct blood pressure measurement). After assessment of the airway, all patients were ventilated with 100% oxygen for 3 minutes. After oxygenation, propofol was titrated slowly until loss of verbal contact is achieved, after assessment of adequacy of ventilation, vecuronium
0.1mg/Kg was given for muscle relaxation, fentanyl was given in a dose 1ug/kg and then a cuffed endotracheal tube was inserted.

Tube position and equality were confirmed by auscultation of both sides of the chest followed by fixation of ETT.

The patient’s lungs were mechanically ventilated with 100% O\textsubscript{2} to get an end-tidal CO\textsubscript{2} concentration of 35-40mm Hg. The maintenance of anaesthesia was achieved by sevoflurane with MAC 2% with fresh gas flow 5 L/minute. Vecuronium 0.01mg/Kg every 15-20 minutes was given for muscle relaxation.

In combined group, after achieving satisfactory level of anaesthesia, the patients received regional blockade in the form of bilateral superficial and deep cervical plexus block. With the patient in the supine position, the head was turned to the side opposite to the block. Superficial cervical plexus block was done after identification of the midpoint of the posterior border of the sternomastoid muscle. A skin wheal was made at this point and a 22 gauge, 4-cm needle was advanced. 5ml of local anesthetic solution was injected along the posterior border and medial surface of sternomastoid muscle. The deep cervical plexus block was performed with single injection of 10-20ml of local anesthetic solution at the C4 transverse process. The superficial and deep cervical plexus blocks were repeated on the opposite side. The blocks were carried out with a mixture of equal volumes of 0.25% bupivacaine and 1% of lignocaine with epinephrine 1:200,000.

In both groups, The haemodynamic goals were to maintain the mean arterial pressure (MAP) at 60-65mm Hg by adjusting the sevoflurane concentration and the use of esmolol. The consumption of sevoflurane and the frequency of use of esmolol were evaluated in both groups intraoperative blood loss was assessed.

Neuromuscular blockade was antagonized with neostigmine 0.05mg and atropine 0.01mg/Kg the end of the operation.

Immunity assay:

Venous blood samples were obtained before induction of anaesthesia, at the end of surgery, on the mornings of the 1\textsuperscript{st} postoperative and 5\textsuperscript{th} postoperative days. The samples were centrifuged rapidly and stored at \(-70^\circ\text{C}\) until assayed. In addition serum samples were also collected from 40 healthy volunteers for comparison.

Detection of the IL-2 concentration and SIL-2R were performed by means of common enzyme-linked immunosorbent assay (ELISA) double-antibody sandwich technique using kits supplied by BioVendor-Laboratorni medicina.

Statistical analysis:

Data were statistically described in terms of mean±standard deviation (±S.D), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student \(t\)-test for independent samples. Within group comparison of numerical variables was done using paired \(t\)-test for paired (matched) samples. For comparing categorical data, Chi square \(\chi^2\) test was performed. Exact test was used instead when the expected frequency is less than 5.

For cytokine data Comparison of numerical variables between the study groups was done using Student \(t\)-test for independent samples in comparing 2 groups when normally distributed and Mann Whitney U test for independent samples when not normally distributed. Within group comparison of numerical variables was done using paired \(t\)-test in comparing 2 groups when normally distributed and Wilcoxon signed rank test for paired (matched) samples when not normally distributed. \(p\)-values less than 0.05 was considered statistically significant.

Results

Patient data

There was no significant difference between the two groups in age, weight, duration of surgery and preoperative mean arterial Hood pressure. all of our patients in this study were males, owing to the higher incidence of cancer larynx in males than females. The operative time was comparable in the two groups. (Table 1).

Intraoperative variables

All patients in GA group required supplemental esmolol to achieve target MAP, in contrast only 5 patients in the combined group required esmolol \((p<0.001)\). Table (2).

Most of patients in GA group required supplemental fentanyl \((n=16)\), while only 5 patients in Combined group required supplemental fentanyl \((p<0.002)\). Table (2).

No patients required blood transfusion in both groups. A reduction in blood loss was observed in the Combined group during the surgical procedure.
Mean blood loss (ml) in GA group was (688 ± 125), while in combined group (445.5 ± 91). Table (2).

Mean end tidal sevoflurane concentration were significantly increased in GA group in comparison to combined group. Fig. (1). p-value <0.001.

There were no complications detected from the regional block failure of the block was suspected in five cases.

Cytokine data:
Serum SIL-2R and IL-2 levels of the 40 patients (T1 and 5th day postoperatively (T4)) in both groups (Fig. 2).

Serum SIL-2R levels were significantly elevated (568.18 ± 67.840 versus 280.53 ± 90.456) p-value <0.001 in cancer patients compared with those of healthy volunteers.

There was no significant difference in IL-2 levels at the end of operation (T2) and preoperatively (T1) in both groups (Fig. 2).

But on the morning of 1st postoperative day (T3) and 5th day postoperatively (T4) there was significant decrease in the levels of IL-2 from preoperative values (T1) p-value <0.001 in the GA group (T3=1.925 ± 0.42 and T4=2.44 ± 0.44 while T1=4.43 ± 0.647).

On the other hand, in the combined group less significant decrease was observed between IL-2 levels in T3 and T4 in comparison to T1 values (T3=626 ± 39.92 and T4=613 ± 40.74 while T1=593 ± 47.362).

By analyzing data from Fig. (3) we can conclude that T3 and T4 levels of SIL-2R in the GA group (T3=700 ± 55.15 and T4=661.50 ± 48.588) are significantly higher than T3 and T4 levels in the combined group (T3=626 ± 39.92 and T4=613 ± 40.749) (p-value <0.001) which means that the combined group patients are immunologically better than the GA group in the postoperative period.

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But in the morning of 1st postoperative day (T3) and 5th day postoperatively (T4) there was significant increase in the levels of SIL-2R from preoperative values (T1) p-value <0.001 in the GA group. (T3=700 ± 55.15 and T4=661.50 ± 48.588 versus T1=590.95 ± 52.827).

On the other hand, in the combined group less significant increase was observed between SIL-2R levels in T3 and T4 in comparison to T1 values (T3=626 ± 39.92 and T4=613 ± 40.74 while T1=593 ± 47.362).

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Table (1): Demographic data and duration of surgery [values are mean±S.D or ratio as appropriate].

<table>
<thead>
<tr>
<th>GA group (n=20)</th>
<th>Combined group (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.1±4.5</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>20/0</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>76.3±7.4</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>145±15</td>
</tr>
</tbody>
</table>

Table (2): Anaesthetic requirements and intraoperative variables values are mean±S.D or number of patients as appropriate.

<table>
<thead>
<tr>
<th>GA group (n=20)</th>
<th>Combined group (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplemental fentanyl (no.)</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Supplemental muscle relaxant (no.)</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Supplemental esmolol (no.)</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Intraoperative blood loss (ml)</td>
<td>688±125</td>
<td>445±91</td>
</tr>
</tbody>
</table>

Table (3): Comparison of IL-2 levels and SIL-2R levels between healthy volunteers and patients with cancer values are mean±S.D p-value <0.001.

<table>
<thead>
<tr>
<th></th>
<th>Healthy volunteers</th>
<th>Cancer patients</th>
</tr>
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<tbody>
<tr>
<td>IL-2 (pg/ml)</td>
<td>6.73±0.979</td>
<td>3.56±0.786</td>
</tr>
<tr>
<td>SIL-2R (u/ml)</td>
<td>280.53±90.456</td>
<td>568.18±67.840</td>
</tr>
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</table>
Discussion

Although anesthesia for total laryngectomy may appear quite simple, it is surprising that when GA is used alone, a relatively deep plain of anesthesia is required. This is probably related to the stress of surgery, together with the frequent tracheal stimulation by movement of endotracheal tube during surgical manipulations. The use of regional anesthesia may lighten the level of GA required and provide prolonged postoperative analgesia. Many studies have addressed the clinical interest of plexus blocks for surgery of the neck [16].

The experience with use bilateral superficial and deep cervical blockade in total laryngectomy was defective, but its use with many surgical neck interferences was reported.

In our study, there was significant decrease in end tidal sevoflurane concentration in the combined group compared to the GA group correlates with the results of Shin et al. [17].

In our study, 80% of the patients in GA group required supplemental fentanyl while only 25% of the patients in combined group required supplemental fentanyl during the surgery. (GA n=16 versus combined group n=5) which is closed to the results of the studies of Shin et al., and Aunac et al. [18].

In our study, there was significant decrease in blood loss in combined group (688.5 ± 124.8 in GA versus 445.5 ± 91 in combined group) intraoperatively confirm the findings of Prasad et al. [19] but contradicts the findings of Rui Celso Martins Mamede, et al. [20] which found no significant difference in blood loss between BSCPB and GA groups during thyroidectomy. They believed that the surgical technique, the type of instrumentation, the tumor type and volume, the presence of systemic disease, and knowledge of the cervical anatomy explain increased or decreased bleeding, and is independent of the technique used for anaesthesia.

Immunosuppression associated with neoplasm results mainly from T-cell dysfunction and is characterized by impaired synthesis of IL2 [21].

Interleukin-2 is an anti-inflammatory cytokine released from the lymphocytes after IL-1 stimulation, causes the rapid proliferation of effector cells, and is decreased after major surgery [22-23]. The severity of injury and depressed IL-2 production are correlated. Interleukin-2 is also an important cytokine produced by activated CD4+ lymphocytes, and plays critical roles in various immunologic cancer phenomena.
The main functional roles of IL-2 pertain to the development and maintenance of cytotoxic responses by NK cells and cytotoxic T lymphocytes, which are especially expressed in cancers. The NK cells are believed to play an important role in host defenses against certain cancers. They are a subpopulation of large granular lymphocytes that spontaneously recognize and lyse tumour cells [23].

Soluble IL-2R is part of a membrane receptor for interleukin-2, which can be localized on the cell surface of different lymphoid cell lines including activated T and NK cells, monocytes, eosinophils and on some tumor cells. This membrane receptor is important for cell stimulation with interleukin-2 (IL-2), which is one of the most significant interleukins in the immune system [24]. Thus these cytokines (IL-2 and SIL-2R) were chosen for the present study.

In our study, the immune function in cancer larynx was impaired, as shown by the reduced serum level of IL-2 and the increased serum level of SIL-2R preoperatively in comparison to their levels in healthy volunteers. These results had many supporting studies and observations.

In a study done by Lai et al. [25] there was a marked decrease in the serum level of IL-2 and NK cell activity and increase in the serum level of SIL-2R in patients with early stages of cancer larynx compared with healthy volunteers. In other studies, high serum concentrations at time of diagnosis were highly correlated with shorter survival. [26].

On the other hand, low levels of the soluble receptor point to a reduced chance of metastasis development by cancer patients within a 3-year period. Tartour et al. [26] postulated that serum sIL-2R can be employed in head and neck cancers as an independent prognostic marker of distant metastases development and as a marker of the patient's survival.

In our study, both types of anaesthesia suppress IL2 level and increase level of SIL-2R in the immediate postoperative period. But in the Combined group patients there was less suppression of IL2 and less increase in SIL-2R in the 1st day postoperative and 5th day postoperative which correlates with the findings of Deegan et al. [27] they pointed out the effect of paravertebral blocks and propofol on cytokine response during breast cancer surgery and noted a decrease in tumorigenic and an increase in antitumor cytokine.

Our results also agree with the study done by Beilin et al. [28] who reported that preemptive epidural bupivacaine and fentanyl were associated with an attenuated production of proinflammatory cytokines (IL-1 and IL-6), and with decreased suppression of anti-inflammatory cytokines (IL-2) after gynecologic non-cancer surgery. Akural et al. [29] reported that preemptive epidural sufentanil treatment had minor effects on the immune depressive response after abdominal hysterectomy.

Our findings close to the study done by Longas et al. [30] who postulated that the use of mixture of local anesthetics and opioids exhibited reduced suppression of lymphocyte proliferation and an attenuated proinflammatory cytokine response in the post-operative period following radical prostatectomy.

In conclusion, cancer larynx is associated with a state of immunosuppression. surgical procedure performed with GA combined with regional anesthesia had less depressant effects on the immune response in the immediate postoperative period.

References


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