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**ARTIGO ORIGINAL**

# Role of Dexmedetomidine in the Perioperative Management of Head and Neck Neoplasms: A Retrospective Study

## *Papel da Dexmedetomidina na Gestão Perioperatória de Neoplasias da Cabeça e Pescoço: Um Estudo Retrospectivo*

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## ABSTRACT

**Introduction:** The incidence of head and neck neoplasms is increasing worldwide. Extensive surgical resection and reconstruction with a microvascular free flap is often proposed, challenging the maintenance of the airway patency.

**Methods:** After the implementation of dexmedetomidine in our anesthetic protocol, 95% of the patients maintained spontaneous ventilation in the early postoperative period, reducing therefore the need of mechanical ventilation.

**Results:** Only 25% of the group required admission in the Intensive Care Unit (ICU) and there was an overall reduction in the incidence of complications.

**Conclusion:** This strategy has proven to be especially valuable during the COVID-19 pandemic, since it allowed our team to maintain the surgical management for this cancer patients without burden de Intensive Care Unit.

## RESUMO

**Introdução:** A incidência de neoplasias da cabeça e pescoço tem vindo a aumentar. A ressecção cirúrgica seguida da reconstrução com retalho livre microvascular é uma opção terapêutica que pode comprometer a permeabilidade da via aérea.

**Métodos:** A introdução da dexmedetomidina no nosso protocolo anestésico permitiu manter a ventilação espontânea no pós-operatório imediato, reduzindo a necessidade de ventilação mecânica invasiva.

**Resultados:** Apenas 25% dos doentes foram admitidos na Unidade de Cuidados Intensivos e verificou-se uma redução da incidência de complicações.

**Conclusão:** Esta estratégia provou ser especialmente valiosa durante a pandemia a COVID-19, uma vez que permitiu manter a atividade cirúrgica sem sobrecarregar a Unidade de Cuidados Intensivos.

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## INTRODUCTION

Head and neck neoplasms are the sixth most common type of cancer worldwide, and their incidence is increasing. Tobacco and alcohol consumption and, more recently, the increasing rate of infections by oncogenic viruses, such as the human papillomavirus (HPV), are among the most relevant risk factors associated with their development. The treatment of these neoplasms often involves a surgical resection that is usually extensive and deeply deformative, with an immediate need for maxillofacial reconstruction with a microvascular free flap.[1] These procedures are laborious, require elective tracheostomy and a long period of anesthesia, which we typically induce and maintain using drugs like propofol or sevoflurane.

In our institution, after this complex procedure, these patients are usually admitted in an intensive care unit (ICU) for a progressive ventilatory support weaning, because the immediate awakening of these patients often causes emergence *delirium*, related not only to the magnitude of the procedure but, above all, to a desynchrony of the breathing-swallowing mechanisms caused by the presence of a non-physiological surgical airway. This constitutes a major stress factor for the patient which induces a sympathetic autonomous system response which can lead up to vasoconstriction

and uncontrolled hypertension. This greatly increases the bleeding risk. The resulting hematoma compresses the anastomotic blood vessels, thereby reducing the flap blood perfusion and compromising its short-term survival. In fact, this is a surgical emergency demanding immediate re-exploration to ensure flap survival.[2,3] During the year of 2019, we added dexmedetomidine to the anesthetic protocol. This drug is a highly selective alpha-2 agonist with sedative, anxiolytic, sympatholytic, and analgesic-sparing effects with minimal respiratory depression.Its specific hypnotic effect is different from that produced by other anesthetic agents, such as propofol, generating what resembles a sleep-like state and reducing delirium, enabling early ventilator weaning and avoiding long periods of mechanical ventilation.[4] This allows the postoperative period to take place in the post-anesthesia care unit, rather than the ICU. During the COVID-19 pandemic, with an unprecedented number of patients requiring intensive care, overwhelming the units' usual capacity, this protocol proved to be most useful and needed because it permitted for non-urgent head and neck cancer patients to keep being surgically treated, without the need of an intensive care stay. The aim of our study was to verify the impact of the use of this new protocol regarding the need of mechanical ventilation, admission to the ICU and length of stay and post-operative complications in patients undergoing microvascular free flap surgery.

## MATERIAL AND METHODS

To reach our aim, we carried out a retrospective analysis of the perioperative data of all the patients submitted to this procedure between January of 2016 and December of 2020 in our institution, a tertiary referral hospital which covers a resident population of almost 2.8 million habitants, representing 34.6% of the entire national population, according to the 2011 census. Ethics committee approval was obtained, and all patient or family members where contacted in order to acquire written consent.

The inclusion criteria defined were age above 18 years and the presence of head and neck neoplasm proposed for free flap surgery. The exclusion criteria applied were the inability to follow up and absence of informed consent. According to these criteria, all patients were included in our study.

The population was divided into two distinct groups: group A, which comprised patients undergoing surgery with intravenous infusion of propofol and remifentanil guided by target-controlled infusion and admitted in the ICU with the same drugs (the *standard* protocol at our institution); and group D, formed by the patients that additionally received a continuous infusion of dexmedetomidine (0.3 µg/kg/h) starting 30 minutes before the end of surgery and 15 minutes before stopping propofol and remifentanil (Fig.1). The perfusion was maintained for the next 12 hours.

Through consultation of the clinical files the following data was collected: sex, age, American Society of Anesthesiologists Physical Status Classification System (ASA-PS) categorization, airway approach and anesthetic technique used, type of surgical procedure and its duration, need of post-surgery invasive mechanical ventilation, number of days under invasive mechanical ventilation, days in the ICU, postoperative complications and mortality on the 28th day. Follow-up was carried out until the 28th day after surgery.

We defined the following variables as primary outcomes: need

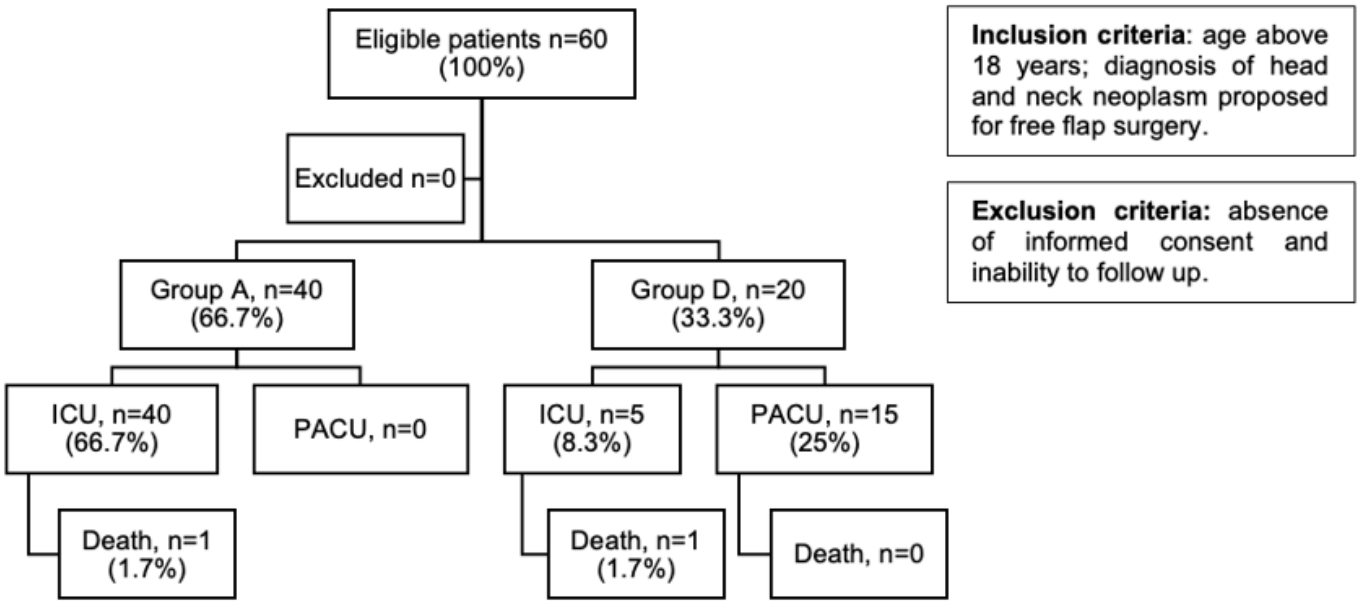


**Figure 1. Flow diagram: Eligible patients – all patients over 18 years of age with diagnosis of head and neck neoplasm proposed for free flap surgery between January 2016 and December 2020. Exclusion criteria applied: absence of informed consent and inability to follow up.**
Group A – pre-protocol group; Group D – pos-protocol group; ICU – Intensive Care Unit; PACU – Post-Anesthesia Care Unit.

of invasive mechanical ventilation after surgery, number of days under invasive mechanical ventilation, days in the ICU, postoperative complications and mortality on the 28th day.

Statistical analysis was performed using the Statistical Package for the Social Science (SPSS) program, version 22. The population was characterized by calculating the measure of central tendency and dispersion for quantitative variables and by determining absolute and relative frequencies for qualitative variables. To compare nominal variables, chi-square or Fisher's exact tests were used, according to the Cochrane rules. Regarding the ordinal and numeral variables, the t-student or Mann-Whitney U tests were performed after the application of a normality test. A significance level of 5% was considered.

This study followed the ethical principles for medical research in human beings enshrined in the Declaration of Helsinki of the World Medical Association.

## RESULTS

The analysis period prior to the protocol onset is set between January 2016 and March 2019. During this time, 40 patients underwent free flap surgery for head and neck cancer at our center.

The dexmedetomidine protocol was put in practice in April 2019. For our research we analyzed the patients treated with this new drug between April 2019 and December of 2020, summing up to 20 patients.

In Table 1, it is possible to observe a difference between groups regarding gender distribution ($p$=0.005, Chi-Square test) with a greater number of men in group A and a greater number of women in group D.

In addition to gender, there are also differences with regard to risk stratification through the ASA classification system ($p$=0.003, Mann-Whitney U test) with Group A presenting the highest scores, which suggest that patients in the group A have more comorbidities, although both groups have the same median ASA score (for more details regarding ASA PS classification see Table 2). Risk factors such as alcohol and smoking were present in half of the subjects and equally distributed between the two groups.

Considering the main variables regarding the pre- and intra-operative period, namely, duration of the procedure and airway approach (Table 3), we found no statistically significant differences. However, substantial disparities emerged in the pos-operative period in which concerns recovery, invasive mechanical ventilation after the procedure and number of days under this support, length of stay in the ICU and complications.

While all patients from group A went to the ICU sedated and under invasive mechanical ventilation, only 5 of the patients in group D (25%) required critical care, and only one (5%) was ventilated. This explains the differences found in the number of patients admitted in the ICU, the need for invasive mechanical ventilation and the number of days under this support and ICU stay between the two groups ($p$<0.001).

The median duration of invasive ventilation was 2 (IQR: 0 – 3) days and the length of stay in the ICU was 3 (IQR: 0 – 3) days. All patients admitted in PACU stayed there for less than 24 hours and then were transferred to the plastic surgery ward.

The incidence of complications followed a similar trend (Tables 4 and 5). In all, 36 complications were described and of these, 14 (38.9%) were surgical and the remaining 22 (61.1%) were medical. Five (13.8%) surgical complications were reported in patients sedated with dexmedetomidine and the remaining were verified in group A, (n=9; 25%). However, this difference was not statistically significant ($p$=0.736, Fisher's exact test).

Medical complications assume greater expression in Group A as no medical complications were reported in Group D.

Surgical complications were the most frequent (n=14), followed by respiratory complications (n=9) and renal and metabolic (n=5) as we can see in Tables 4 and 5.

During the study span, two deaths were reported, one in group A due to severe primary acute respiratory distress syndrome (ARDS) and the other in group D due to airway obstruction by mucus plugs and subsequent cardiorespiratory arrest. Deaths are not included in the study as part of complications.

## DISCUSSION

Sedation is usually given to promote tolerance to certain procedures and also promoting comfort of the patients. However, prolonged sedation contributes to immobility, weakness and perpetuation of invasive mechanical ventilation that may lead to further complications, such as nosocomial infection, agitation requiring physical restraints, pressure sores, critical illness neuropathy and myopathy, vascular thrombosis and even in some patients, sepsis, multiple organ failure and death.[5,6] For the last 15 years, research on this field has been focused on reducing depth of sedation as a means of reducing complications.

Our data shows that the implementation of dexmedetomidine in the anesthetic protocol decreased the need of invasive mechanical ventilation and intensive care admission in the immediate postoperative phase and this undoubtedly justifies the meaningful reduction of surgical complications and lack of medical adverse events, like respiratory distress syndrome, hypotension and *delirium*, in the treatment group. Some studies prior to ours had already showed that a protocolized approach to sedation and analgesia was associated with significant reduction in prevalence of deep sedation, ventilation time, ICU stay and a 6.5% absolute reduction in hospital mortality ($p$=0.009).[7] Also, in a randomized trial of daily interruption of sedation vs. standard practice, the first group had shortened median ventilation time by 2.4 days and

**Table 1. Demographic characteristics of the population**

| TABLE 1 | | Group A (N=40) | Group D (N=20) | Difference between groups *p value* | Statistical tests |
|---|---|---|---|---|---|
| Sex – no. (%) | Male | 30 (75) | 7 (35) | 0.005 | Chi-square |
| | Female | 10 (25) | 13 (65) | | |
| Age (average) | | 58,3±16,3 | 63,2 ±15,5 | 0.264 | T-Test |
| Risk factors – no. (%) | | 20 (50) | 10 (50) | 1.000 | Fisher's exact test |
| ASA PS (median (IQR)) | | II (IQR: 2 – 3) | II (IQR: 2 – 2) | 0.003 | Mann-Whitney U test |

**Legend:**
**Group A** – pre-protocol group; **Group D** – pos-protocol group; **RF** – presence of risk factors; **ASA PS** – American Society of Anesthesiologists Classification System; **IQR** – interquartile range.

**Table 2. Perioperative characteristics**

| TABLE 2 | | Group A (N=40) | Group D (N=20) | Difference between groups *p value* | Statistical tests |
|---|---|---|---|---|---|
| Duration of the procedure (h) (average) | | 10.9±2.3 | 10.2±2.1 | 0.63 | T-test |
| Patients submitted to surgical tracheostomy – no. (%) | | 33 (81.6) | 14 (71.9) | 0.537 | Chi-square |
| Recovery – no. (%) | ICU | 40 (100) | 5 (25) | <0.001 | Chi-square |
| | PACU | 0 (0) | 15 (75) | | |
| IMV after the procedure – no. (%) | Yes | 40 (100) | 1 (5) | <0.001 | Chi-square |
| | No | 0 (0) | 19 (95) | | |
| Days of IMV – (median (IQR)) | | 2 (IQR: 2 - 3) | * | <0.001 | Mann-Whitney U test |
| Days in the ICU – (median (IQR)) | | 3 (IQR: 3 – 4) | 2 (IQR: 2 – 3) | <0.001 | Mann-Whitney U test |
| Complications – no. (%) | Medical | 22 (61.1) | 0 (0) | 0.02 | Chi-square |
| | Surgical | 9 (25) | 5 (13.9) | | |

**Legend:**
**Group A** – pre-protocol group; **Group D** – pos-protocol group; **h** – hours; **IMV** – invasive mechanical ventilation; **ICU** – Intensive care unit; **IQR** – Interquartile Range.
*Only one patient who died on the third day of mechanical ventilation.

**Table 3. Surgical complications**

| TABLE 3 | Surgical complications (N=14, 100%) | |
|---|---|---|
| Group A | Tracheostomy hemorrhage – no. (%) | 2 (14.3) |
| | Vocal cord palsy – no. (%) | 2 (14.3) |
| | Graft dehiscence – no. (%) | 2 (14.3) |
| | Flap hemorrhage – no. (%) | 2 (14.3) |
| | Surgical site abscess – no. (%) | 1 (7.1) |
| | **Total – no. (%)** | **9 (64.3)** |
| Group B | Airway obstruction – no. (%) | 1 (7.1) |
| | Local hematoma – no. (%) | 4 (28.6) |
| | **Total – no. (%)** | **5 (35.7)** |

**Legend:**
**Group A** – pre-protocol group; **Group D** – post-protocol group.

ICU stay by 3.6 days comparing to the latter, which suggests that decreasing sedation depth may improve survival.[8]In our study, Group A registered a statistically significant higher number of surgical and medical complications than the group D ($p$=0.02, Chi-Square test). However, these complications do not seem to be directly related to invasive ventilation and the number of days under this support ($p$=0.961, Mann-Whitney U test) and the number of days in the ICU ($p$=0.969, Mann-Whitney U test). It should be noted that we found two different record systems available, with the ICU having a more exhaustive record of complications.

Furthermore, we think there might be an underreporting of clinical complications in the plastic surgery ward. This might lead to an inconsistency of the details documented and alter the incidence of complications. Patients in group A also had a higher ASA PS classification, which may also justify the worse primary outcomes seen in this group. Regarding surgical complications, which were higher in group A, the Plastic and Reconstructive Surgery Department considers that the early transfer of the patient to their ward guarantees a closer follow up, since the patient is closer to their surgical and specialized nursing team. This assures superior wound care and potential complications are identified earlier. There are 5 double-blind RCTs (SEDCOM[9]; MENDS[10]; DEXCOM[11],

**Table 4. Medical complications**

| TABLE 4 | | Medical complications (N=22, 100%) | |
|---|---|---|---|
| Group A | Neurological | Hiperkinetic delirium – no. (%) | 3 (13.6) |
| | | Delirium tremens – no. (%) | 1 (4.5) |
| | | **Total – no. (%)** | **4 (18.2)** |
| | Respiratory | Type 2 respiratory failure – no. (%) | 5 (22.7) |
| | | Pneumotorax – no. (%) | 1 (4.5) |
| | | Ventilator-associated pneumonia - no. (%) | 1 (4.5) |
| | | Severe ARDS - no. (%) | 1 (4.5) |
| | | Acute tracheobronchitis - no. (%) | 1 (4.5) |
| | | **Total – no. (%)** | **9 (40.9)** |
| | Cardiovascular | Hemodynamic instability - no. (%) | 2 (9.1) |
| | | Dysrhytmias - no. (%) | 2 (9.1) |
| | | **Total – no. (%)** | **4 (18.2)** |
| | Renal and metabolic | Acute kidney injury - no. (%) | 3 (13.6) |
| | | Rhabdomyolysis - no. (%) | 2 (9.1) |
| | | **Total – no. (%)** | **5 (22.7)** |

Legend:
**Group A** – pre-protocol group; **Group D** – post-protocol group; **ARDS** – acute respiratory distress syndrome.

**Table 5. ASA classification of the population studied**

| TABLE 5 – ASA classification of the population studied | | |
|---|---|---|
| **ASA PS** | **Grupo A - no. (%)** | **Grupo D - no. (%)** |
| **I** | 2 (5) | 1 (5) |
| **II** | 18 (45) | 18 (90) |
| **III** | 14 (35) | 1 (5) |
| **IV** | 6 (15) | 0 |
| **V** | 0 | 0 |
| **VI** | 0 | 0 |
| **Total** | **40** | **20** |

Legend:
**Group A** – pre-protocol group; **Group D** – post-protocol group

MIDEX and PRODEX[12]) that support our results. The MENDS study[10] concluded that dexmedetomidine reduces the incidence of coma and delirium. The SEDCOM study[9] supported these results and also observed a reduction in the time of ventilation. DEXCOM[11] and later MIDEX and PRODEX[12] published in 2012 proved, again, that dexmedetomidine reduces delirium, agitation and the time under invasive mechanical ventilation when compared with patients doing remifentanil, propofol and midazolam. Despite these encouraging results and its consistency with what is described by other authors, we acknowledge that there might be some confounding factors to contemplate. Improvement in surgical experience through the four years might justify the higher success rate, independently of the anesthetic protocol. The difference of ASA PS classification between the two groups and the different record systems available, with a more exhaustive database present in the ICU, should be kept in mind.

This study has some limitations. It is retrospective, unicentric and there is some missing data, which may justify the presence of statistically significant differences regarding gender distribution, ASA PS classification, and the absence of a relationship between complications, invasive ventilation and the number of days in the ICU. This makes our interpretation of the results difficult. We suggest further prospective studies with an adequate sample size in order to eliminate those bias and determine the best approach.

## CONCLUSION

Maintenance of invasive mechanical ventilation and the subsequent admission in the ICU, previously regarded as vital, is no longer mandatory for our patients since the introduction of dexmedetomidine in the anesthetic protocol. Instead, the post-operative period takes place in the post-anesthesia care unit where the patient remains in spontaneous ventilation, therefore reducing the incidence of complications, fulfilling the objectives of the ERAS protocol.[13] This reduction in ICU admissions proved to be crucial during the COVID-19 pandemic, as the demand for intensive care far exceeded its capacity, leaving these valuable resources for COVID-19 patients without postponing cancer surgery for head and neck neoplasms in our hospital.

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**Protection of Human and Animal Subjects:** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
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