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Evaluation of the safety profile of conscious sedation with inhaled mixture in ASA II patients

PhD thesis

- SUMMARY -

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Introduction

Although anesthetic procedures used in ambulatory conditions are increasingly used over the past decade, global morbidity and mortality compared to those of 30 years ago have not improved a lot, as the written domain studies point out.

In this context, knowing the risk factors for the morbidity associated with the therapeutic interventions practiced under conscious sedation may allow a better selection of patients, a more coherent counseling on the risk-benefit ratio of the procedure and the self-evaluation of one's own results, with a medical performance value, but also a forensic one.

This approach proved extremely difficult, the results of the various studies available in the specialized literature being difficult to compare, due to the lack of homogeneity of the study samples and the therapeutic protocols applied in conscious sedation.

In the international medical literature, the studies on the topic chosen by me – addressing the impact of therapeutically compensated comorbidities on the effectiveness and safety of inalosedation – are limited.

My PhD thesis presents for the first time in the specialized literature results with a high character of novelty and originality regarding the use of inhaled conscious sedation in patients with associated general conditions, controlled therapeutically.

Overall, through the assumed research objectives, my goal was for the results I obtained would lead to a better understanding of the practical value of conscious sedation in the dental therapy of patients with compensated comorbidities.

CURRENT STATE OF KNOWLEDGE

CHAPTER 1. GENERAL CONSIDERATIONS ON CONSCIOUS SEDATION

Sedation is obtained by means of medicinal substances (sedatives), which have the ability to induce a state of controlled depression of the state of consciousness, under the conditions of maintaining unchanged the respiratory function and maintaining cardio-vascular stability.

ASA defines sedation as a progressive decrease in the level of consciousness, ranging from minimum to maximum in the case of moderate sedation, deep sedation and general anesthesia, patients being able to continuously move from one level of sedation to another [1].

The fact that there is no strict delimitation between the levels of sedation, makes it compulsory to take account of this phenomenon, especially in the case of patients with comorbidities or in the case of extreme ages, since there is a risk that the degree of depth of sedation will increase and the patient will pass from one lower degree of sedation to a more advanced one, with the associated risks - the most important being hypoxia/apnea and bradycardia.

In this context it should be emphasized that the sedative agents have a wide variability of the pharmacological effect, which is why the transition from anxiolysis to deep sedation directly depends both on the doses of the medicinal substance administered, but also on the individual response of the patient to the sedative that is used [2].

Conscious inhaled sedation

It consists in the use of a gaseous mixture consisting of nitrous oxide in subaesthetic doses and 100% oxygen. The administration of the inhaler mixture is carried out by means of a flexible tubing circuit, provided with a nasal mask.

Data from the specialized literature show that theoretically the inhaled mixture of nitrous oxide and oxygen does not exert significant depressing effects on ventilation, nor on the cardiovascular apparatus.

PERSONAL CONTRIBUTION

CHAPTER 2. WORKING HYPOTHESIS AND GENERAL OBJECTIVES

The interest of the international dental community in conscious sedation methods based on volatile general anesthetics has made it possible to extend the range of indications for inhalation, which has in turn led to concerns about the risks of administering the inhalation mixture to anxious or odontophobic patients, that also present comorbidities, in order to improve the safety of the medical act performed in ambulatory conditions, without benefiting from the material endowment and the human resources of an ATI service.

In this regard, my approach is part of the effort to investigate the safety of conscious sedation with inhaled mixture in ASA II patients, the most important category of people who could benefit from this medical procedure, considering as a priority the identification of risk factors that can influence both the immediate post-procedural evolution, but also the prognosis on medium and long-term.

Studying the literature of the last two decades, we noticed the lack of statistical data on the occurrence of cardiovascular and respiratory depression post-conscious sedation with volatile mixture, after a unique and short-term exposure to nitrous oxide.

However, we must emphasize that the impact on medical practice of these studies is small, as they are performed almost exclusively on the pediatric population, the results of a possible causal relationship between inhalation and changes in general condition can not be validated by extrapolation. on adult patients with comorbidities, even when these are therapeutically controlled.

In this regard, I emphasize that the doses of nitrous oxide used in clinical trials in children and the variable exposure time exceed the clinical correspondent in the adult patient.

On the other hand, the risk of cardiovascular and respiratory changes is difficult to be clinically quantified in minor patients, given that conscious sedation is mainly used in children with special care needs, who frequently have associated systemic conditions and who are repeatedly sedated by inhalation, which equates to a longer duration of exposure to the gaseous sedative mixture.

My working hypothesis in this research was the existence of differences with statistical value, from a safety point of view, between ASA II patients who benefited from inhalosedation and those who did not receive the volatile sedative mixture before dental treatment, under local anesthesia.

Given that specialized studies in the psychomedical field have revealed that high levels of anxiety and stress have an unfavorable impact in maintaining/aggravating hypertension [3], I also turned to the separate evaluation of hypertensive ASA II subjects to establish the risks related to the administration of conscious volatile sedation.

Last but not least, the purpose of my research was to assess the level of satisfaction of patients undergoing conscious sedation with gaseous mixture of nitrous oxide and oxygen, compared to the individuals included in the study, who have not benefited from inhalosedation.

***2.1. The main objectives of the doctoral research**:*

a. research of hemodynamic and respiratory changes determined peri-procedurally, in case of use of inhalosedation, respectively in the situation when conscious sedation is not administered;

b. determination of the correlation between possible hemodynamic or ventilatory changes and the type of anesthesia administered – simple local anesthesia or in combination with inhaled sedation with nitrous oxide;

c. interpretation of the degree of agitation / sedation in inhalosedated subjects, respectively in patients who do not receive volatile sedative mixture;

d. determination of the efficiency of analgesia in case of administration of nitrous oxide, compared to local anesthesia;

e. determining the degree of satisfaction of patients undergoing inhalosedation, compared to those who do not benefit from this method.

2.2. Study 1

In the first study we aimed to establish the differences between the main hemodynamic constants that occur during the peri-surgery period in a sample of patients with comorbidities, classified in class ASA II, in order to perform dental treatments.

Given that theoretically the effect of general anesthetic gases (including nitrous oxide) on the cardiovascular system and the respiratory system is moderate in individuals without general disorders, we have identified this first direction of research to validate the indication for inhalation application to patients with drug-controlled comorbidities.

2.3. Study 2

In the second study, we evaluated the quality of multimodal analgesia compared to local anesthesia and the measurement of patient satisfaction in the two investigated categories.

The patients were registered in a database in which general identification data, personal pathological history, clinical data and instrumental measurements of vital signs were recorded.

Descriptive statistical analysis methods were used to carry out the analysis.

The exact Fisher or chi-square test was conducted in order to identify possible associations between categorical variables and a p-value.

CHAPTER 3. GENERAL RESEARCH METHODOLOGY

The protocol of the study was approved by the Ethics Commission of the Clinical Hospital of Oro-Maxillofacial Surgery "Prof.dr. Dan Theodorescu" Bucharest, Romania (no.3616/06.05.2021).

All participants in the clinical trials carried out at the OMF Surgery Clinic of the University of Medicine and Pharmacy "Carol Davila" Bucharest expressed their consent and signed the informed consent.

As the author of this study, I fully assume the anonymization of the data used to write the thesis, all the data of the patients that participated in this study respecting the confidentiality agreement.

The data collection was carried out in collaboration with the team of the OMF Surgery Clinic of the "Carol Davila" University of Medicine and Pharmacy Bucharest, under the coordination of Prof.Univ.Dr. Alexandru Bucur.

Characteristics of the study batch

The study group consisted of a number of 54 patients, of which 30 (55,56%) were of male gender.

The average age of the subjects included in the study group was 65.02 years (+/- 15.97; range 20-89).

The average height of the patients included in the study group was 167.54 cm (+/- 10.28; range 145-191).

The average body mass of the individuals included in the study group was 78.89 kg (+/- 15.19; range 50-109).

Control batch characteristics

The control group consisted of 60 patients, of which 28 (46,67%) were of male gender.

The average age of the patients in the control group was 65.43 years (+/- 13.45; range 27-86).

The average height of the subjects included in the control group was 164.32 cm (+/- 9.43; range 137-185).

The average body mass of the individuals included in the control group was 73.6 kg (+/- 16.3; range 40-110).

No statistically significant differences were recorded between the two lots on the prevalence of HTA (p>0,05).

CHAPTER 4. COMPARATIVE STUDY OF HEMODYNAMIC AND VENTILATORY PARAMETERS, PERIOPERATORY DETERMINED IN ASA II PATIENTS

4.1. Introduction

The purpose of the study is to evaluate changes occurring at the cardio-vascular and respiratory level in ASA II classified patients who are sedated using an inhaled mixture consisting of oxygen and nitrous oxide in subanesthetic doses, compared to patients classified in the same anesthetic risk class, to which conscious volatile sedation was not applied before administration of local anesthesia.

Under the conditions of maintaining spontaneous breathing under conscious sedation, ventilatory dysfunction that could be induced by the sedative (nitrous oxide) takes on a clear importance.

Also, in case of hypotension, there is a risk of decompensation of patients with increased sympathetic tone.

4.2. Objective of the study

The aim of this first study in the doctoral research was to determine the hemodynamic and ventilatory changes that occurred before and after inhalation of patients with ASA II anesthetic risk, compared to subjects in the same risk category and who did not receive conscious sedation with protoxide azote.

4.3. Material and method

The study was a monocentric, prospective, analytical one, carried out between 2021-2022 within the Oro-Maxillofacial Surgery Clinic of the "Carol Davila" University of Medicine and Pharmacy in Bucharest.

The participation of the patients enrolled in the study was voluntary, all subjects expressing their informed consent before the procedures carried out in the present research.

The patients from the study group were inhalosedated according to the protocol used in the Oro-Maxillofacial Surgery Clinic of the U.M.F. "Carol Davila" Bucharest , according to *Bucur A. and collab*. [4] :

The patients were monitored for 6 hours after the procedure by the medical staff of the OMF Surgery Clinic.

At the end of the procedure, all data related to the sedation procedure were recorded.

Statistical analysis of the study data

All statistical data was registered in a database, in which all the recorded variables were included. The statistical analysis was performed with the Stata/IC 16 program (*StataCorp*), using descriptive analytical methods, univariation and multivariation statistical analytical methods. The distribution of continuous variables was rendered by using standard means and deviations.
Distribution of categorical variables was rendered using frequencies and percentages. The exact Fisher or chi-square test was conducted to evaluate the associations between categorical variables and a p value of less than 0.05.

4.4. Results

Changes in heart rate

In the study group, made up of subjects who were given an inhaled mixture of nitrous oxide and oxygen, the pulse values decreased after performing local anesthesia. The resulting differences between the values recorded in the two stages of treatment have statistical significance (p<00,0001; t-test for 2 dependent samples).

In the case of patients in the control group who were not given the inhaled mixture based on nitrous oxide, the pulse value decreased after administration of local anesthesia.

The resulting differences between the values thus determined showed statistical significance (statistically (p<0,0001; t test for 2 dependent study lots).

The decreases in the recorded pulse values were higher in the case of the subjects in the study group, compared to the individuals registered in the control group (5.40 vs. 3.7).

The differences between the measured values of the pulse for the patients in the study group, respectively the values determined for the persons included in the control group, showed statistical significance (p=0.065; t test for 2 independent study lots).

Changes in systolic blood pressure

In the study group, the result was after administration of the inhaled mixture of nitrous oxide and oxygen, a decrease in the values of systolic blood pressure measured after local anesthesia.

The differences from the pre-surgery values of systolic blood pressure had no statistical significance (p<0,0001; t test for 2 dependent study lots).

With regard to the measurements made for the control group, represented by patients who did not benefit from conscious sedation with nitrogen and oxygen anesthetic gases, a decrease in systolic blood pressure values resulted after administration of local anesthesia.

The differences obtained did not show statistical significance (p<0,0001; t-test for 2 dependent study lots).

The decrease in the systolic blood pressure values recorded in the patients included in the study group, who benefited in addition to local anesthesia and inhalosedation with nitrous oxide and oxygen, was higher compared to the decrease recorded in the control group (12,54 vs 5,57), with statistically significant differences (p=0,002; t test for 2 independent study lots).

The tendency to decrease in the measured values of systolic blood pressure was observed globally, during the dental therapeutic procedure, both in the patients included in the study group and also in the case of individuals who were included in the control group.

Decreases in systolic blood pressure values in inhalosedated hypertensive patients were higher compared to hypertensive individuals who did not receive inhaled conscious sedation (12.37 vs. 6.11), with statistically significant differences (p=0.025; t test for 2 independent samples).

M diastolic blood pressure odifications

In the study group, it resulted after administration of the inhaled mixture of nitrous oxide and oxygen, a decrease in the values of diastolic blood pressure measured after local anesthesia.

The differences from the pre-suregry values of diastolic blood pressure had statistical significance (p=0.0001; t pen-test 2 dependent samples).

With regard to the measurements made for the control group, represented by patients who did not benefit from conscious sedation with nitrogen and oxygen anesthetic gases, a decrease in diastolic blood pressure values resulted after administration of local anesthesia.

The differences obtained have no statistical significance (p=0,05; t-test for 2 dependent study lots).

The decrease in diastolic blood pressure values recorded in patients included in the study group, who benefited in addition to local anesthesia and inhalosedation with nitrous oxide and oxygen, was higher compared to the decrease recorded in the control group (2.85 vs. 1.08), without significant statistical differences (p=0.07; t-test for 2 independent samples).

The tendency to decrease in the measured values of diastolic blood pressure was observed globally, during the dental therapeutic procedure, in the patients included in the study group.

Decreases in diastolic tension values in hypertensive patients who benefited from inhaled conscious sedation were higher compared to hypertensive subjects who were not inhalosed (2.58 vs. 0.98), with no significant statistical differences (p=0.14; t test for 2 independent study lots).

Changes in arterial saturation in oxygen

In the study group, it resulted after administration of the inhaled mixture of nitrous oxide and oxygen, an increase in arterial saturation in oxygen measured after local anesthesia.

The differences from the pre-surgery values of arterial saturation in oxygen, had statistical significance (p<0,05; t test for 2 dependent study lots).

Regarding the measurements made for the control group, represented by patients who did not benefit from conscious sedation with nitrogen and oxygen anesthetic gas, an increase in the values of arterail saturation in oxygen resulted after administration of local anesthesia.

The differences from the pre-surgery values of arterial saturation in oxygen, had statistical significance (p<0,05; t test for 2 dependent study lots).

The increase in oxygen saturation recorded in the patients included in the study group, who benefited in addition to local anesthesia and inhalosedation with nitrous oxide and oxygen, was significantly higher compared to the increase in saturation recorded in the control group (0.008 vs. 0.004), with statistically significant differences (p=0.04; t test for 2 independent study lots).

The tendency to increase the measured values of arterial saturation in oxygen was observed globally, during the dental therapeutic procedure, both in the patients included in the study group and also in the case of individuals who were included in the control group.

The increase in oxygen saturation in hypertensive patients receiving inhaled mixture was higher compared to hypertensive individuals who did not benefit from conscious sedation with nitrous oxide and oxygen (0.008 vs. 0.005), with no significant statistical differences (p=0.2; t-test for 2 independent samples).

CHAPTER 5. STUDY ON THE EFFECTIVENESS OF INHALOSEDATION IN ASA II PATIENTS

5.1. Introduction

The purpose of this direction of research was to establish the objective and subjective result of the association of local anesthesia with the administration of inhaled mixture of oxygen and nitrous oxide (in subaesthetic doses) in patients with therapeutically compensated comorbidities, who are subjected to dental treatment in ambulatory conditions.

5.2. Objective of the study

The objective of this study within the Phd research was to analyze the efficacy of inhaled sedation in ASA II patients, compared to the people included in the study, who were given only local anesthesia.

Also, the present study aimed at evaluating the physical and psycho-emotional comfort of ASA II inhalosedated patients, compared to subjects who did not benefit from inhaled analgosedation.

5.3. Material and method

5.3.1. Material

The study performed was a monocentric, prospective one, carried out between 2021-2022 within the Oro-Maxillofacial Surgery Clinic of the "Carol Davila" University of Medicine and Pharmacy in Bucharest.

The participation of the patients enrolled in the study was voluntary, all of whom expressed their informed consent before the procedures carried out within the framework of the research.

The study group and the control group were identical to those described for the study recorded in the previous chapter.

5.3.2. Metodes

In order to evaluate the effectiveness of the therapeutic procedure we used the following methods:

a. Ramsay scale

b. Richmond (RASS) scale

c. Motor evaluation scale (MAAS)

d. Visual analogue scale (VAS)

e. Post-surgery satisfaction

Statistical analysis

In order to collect the data, a database file was created, in which we registered all the parameters considered to be studied. The primary processing of data resulted from the analysis was carried out using the Microsoft Excel module from the Microsoft Office Professional software package. The data was processed and analyzed statistically using the Stata/IC 16 program (*StataCorp*), specialized in scientific statistical calculations. The comparative analyses for the continuous variables were done using the t-Student test. For the comparison of the averages of the quantitative variables corresponding to two independent groups, the Student test (t-test) was used if the variables were normally distributed. The Fisher Exact test was used to compare qualitative variables. The accepted error threshold considered was 0.05.

5.4. Results

Ramsay scale - pre-anesthetic phase :

Of the 54 patients in the study group, 38 (70.37%) were anxious and agitated (Ramsay scale = 1), and 16 (29.63%) patients - cooperative, oriented and relaxed (Ramsay scale = 2).

Of the 60 patients in the control group, 17 (28.33%) were anxious and agitated (Ramsay scale = 1), and 43 (71.67%) patients - cooperative, oriented and relaxed (Ramsay scale = 2).

In the preanesthetic stage, the patients in the study group were significantly more anxious and agitated than the patients in the control group (70,37% *vs* 28,33%, respectively; $p<0,001$).

In the preanesthetic stage, hypertensive patients in the study group were significantly more anxious and agitated compared to hypertensive subjects in the control group (73.17% *vs*. 36.36%, respectively; $p=0.001$.

Ramsay scale - intra-anesthetic phase:

Among the 54 patients in the study group, 0 patients were anxious and agitated (Ramsay scale = 1), 50 (92.59%) patients - cooperative, oriented and relaxed (Ramsay scale = 2), and 4 (7.41%) patients only responded to orders (Ramsay scale = 3).

Of the 60 patients in the control group, 36 (60%) patients were anxious and agitated (Ramsay scale = 1), and 24 (40%) patients - cooperative, oriented and relaxed (Ramsay scale = 2), and 0 patients only responded to orders (Ramsay scale = 3).

In the intra-anesthetic stage, the patients in the study group were significantly more cooperative, oriented and quiet (Ramsay = 2) than the patients in the control group (92.59% *vs* . 40%, $p<0.001$), at the same time no patient was anxious or agitated (Ramsay = 1) in the study group compared to 36 agitated and anxious patients in the control group (0% *vs* 60%, respectively, p<0,001, Fisher's test exactly).

In the intra-anesthetic stage, hypertensive patients in the study group were significantly more cooperative, oriented and relaxed (Ramsay = 2) than hypertensive patients in the control group (90,24% vs 36,36%, $p<0,001$).

Ramsay scale - post-anesthetic phase:

Of the 54 patients in the study group, 2 (3.7%) patients were anxious and agitated (Ramsay scale = 1), and 52 (96.3%) patients - cooperative, oriented and relaxed (Ramsay scale = 2).

Of the 60 patients in the control group, 2 (3.33%) patients were anxious and agitated (Ramsay scale = 1), and 58 (96.67%) patients - cooperative, oriented and relaxed (Ramsay scale = 2).

In the post-synesthetic stage, there were no statistically significant differences between the study and control groups both in the case of patients associated with Ramsay = 2 (96.3% *vs*. 96.67%, p >0.05), and in the case of patients associated with Ramsay = 1 (3.7% *vs*. 3.33%, respectively; p>0.05).

In thepostanesthetic tapa, there were no statistically significant differences between hypertensive patients in the study group and hypertensive subjects in the control group, with a Ramsay score = 2 (97.56% *vs* . 95.45%, *p* >0.05).

Richmond scale - pre-anesthetic phase:

Of the 54 patients in the study group, 16 (29.63%) patients were alert and calm (Richmond scale = 0), 37 (68.52%) patients were restless (Richmond scale = +1), and 1 (1.85%) patient - agitated (Richmond scale = +2).

Of the 60 patients, 43 (71.67%) patients were alert and calm (Richmond = 0 scale), 17 (28.33%) patients were restless (Richmond = +1 scale), and 0 patients – agitated (Richmond scale = +2).

Patients in the study group were a lot more frequently associated with an RASS = +1 than patients in the control group (68.52% *vs* . 28.33%, *p*<0.001, Fisher's test exactly).

In the preanesthetic stage, the HTA patients in the study group were a lot more frequently associated with an RASS = +1 than the patients with HTA in the control group (70.73% *vs* . 36.36%, *p*=0.001, exact Fisher's test).

Richmond scale- intra-anesthetic phase:

Of the 54 patients in the study group, 2 (3.7%) patients had a level of mild sedation (Richmond scale = -2), 11 (20.37%) patients were slightly dizzy (Richmond scale = -1), 41 (75.93%) patients were alert and calm (Richmond = 0 scale), and 0 patients were restless (Richmond scale = +1).

Of the 60 patients, 0 patients had a mild sedation level (Richmond = -2 scale), 0 were slightly dizzy (Richmond = -1 scale), 24 (40%) patients were alert and calm (Richmond scale = 0), and 36 (60%) patients were restless (Richmond scale = +1).

In the intra-anesthetic stage, the patients in the study group were a lot more frequently associated with RASS = 0 (alert and calm) than the patients in the control group (75.93 *vs* . 40%, $p<0.001$, Fisher's test exactly), at the same time no patient was restless compared to the control group (0% *vs* . 60%).

In the intra-anaesthetic stage, patients with HTA in the study group were a lot more frequently associated with RASS = 0 (alert and calm) than patients with HTA in the control group (73.17 *vs* . 36.36%, $p<0.001$,7 exact Fisher's test).

Scale Richmond - post-anesthetic phase:

Of the 54 patients in the study group, 1 (1.85%) patients were slightly dizzy (Richmond = -1 scale), 52 (96.3%) patients were alert and calm (Richmond = 0 scale), and 1 (1.85%) patients were restless (Richmond scale = +1).

Of the 60 patients in the control group, 0 were slightly dizzy (Richmond = -1 scale), 59 (98.33%) patients were alert and calm (Richmond = 0 scale), and 1 (1.67%) patients were restless (Richmond scale = +1).

In the post-anesthetic stage, patients were alert and calm in both groups, with no significant statistical difference (96.3% *vs*. 98.33%; $p>0.05$) .

In the post-anaesthetic stage, patients with HTA were alert and calm in both groups, with no significant statistical difference (97.56% *vs*. 97.73%, respectively; $p>0,05$).

MASS scale - pre-anesesthetic phase:

Among the 54 patients in the study group, 17 (31,48%) patients were calm and cooperative (MAAS = 3), 37 (68,52%) patients were restless in bed but cooperative (MAAS = 4).

Of the 60 patients in the control group, 43 (71.67%) patients were calm and cooperative (MAAS = 3), 17 (28.33%) patients were restless in bed, but cooperative (MAAS = 4).

In the pre-anesthetic stage, patients in the study group were more frequently associated with an MAAS = 4 than patients in the control group (68.52% vs . 28.33%, $p<0.001$).

In the pre-anesthetic stage, patients with HTA in the study group were more frequently associated with a MAAS = 4 than patients with HTA in the control group (73.17% vs . 36.36%, *p*=0.001).

MASS scale - intra-anesthetic phase:

Of the 54 patients in the study group, 5 (9.26%) patients responded to touching or calling the name (MAAS = 2), 49 (90.74%) patients were calm and cooperative (MAAS = 3), 0 patients were restless in bed, but cooperative (MAAS = 4).

Of the 60 patients in the control group, 0 patients responded to touching or calling the name (MAAS = 2), 24 (40%) patients were calm and cooperative (MAAS = 3), 36 (60%) patients were restless in bed, but cooperative (MAAS = 4).

In the intra-anesthetic stage, the patients in the study group were significantly calmer and cooperative (MAAS = 3) than the patients in the control group (90.74% vs. 40%, $p<0.001$), at the same time no patient was restless (MAAS = 4) in the study group compared to 36 patients in the control group (0% *vs*. 60%, respectively; p<00,001, Fisher's exact test).

In the intra-anesthetic stage, patients with HTA in the study group were significantly calmer and cooperative (MAAS = 3) than patients in the control group (87.8% *vs*. 36.36%, p<0.001, Fisher's test exactly).

MASS scale - post-anesthetic phase:

Of the 54 patients in the study group, 54 (100%) patients were calm and cooperative (MAAS = 3), 0 patients were restless in bed, but cooperative (MAAS = 4).

Of the 60 patients, 59 (98.33%) patients were calm and cooperative (MAAS = 3), 1 (1.67%) patient was restless in bed but cooperative (MAAS = 4).

In the post-anesthetic stage, the patients were calm and cooperative in both groups, without significant statistical difference (100% *vs*. 98.33%, respectively; p>0.05, Fisher's exact test).

In the post-anesthetic stage, patients with HTA were calm and cooperative in both groups, with no significant statistical difference (100% *vs*. 97.73%, respectively; *p*>0.05, Fisher's exact test).

VAS Scale:

Intra surgery, the patients in the study group were a lot more frequently associated with VAS=0 than the patients in the control group (100% vs. 81.67%, *p*=0.001, Fisher's exact test).

Intra surgery, patients with HTA in the study group were a lot more frequently associated with VAS=0 than patients with HTA in the control group (100% vs. 84.09%, p=0.01, Fisher's exact test).

Post surgery, patients in the control group were a lot more frequently associated with VAS=0 than patients in the study group (43.33% vs. 14.81%, p=0.001, Fisher's exact test).

Post surgery, patients with HTA in the control group were a lot more frequently associated with VAS=0 than patients with HTA in the study group (36.36% vs. 14.63%, p=0.037, Fisher's exact test).

Post surgery satisfaction

Out of the 54 patients in the study group, 16 (29.63%) declared themselves satisfied and 38 (70.37%) very satisfied.

Out of the 60 patients in the control group, 46 (76.67%) declared themselves satisfied and 14 (23.33%) very satisfied.

Comparatively, patients in the study group were a lot more frequently associated with the "very satisfied" level than patients in the control group (70.37% vs. 23.33%, p<0.001, square chi test).

Patients with HTA in the study group were a lot more frequently associated with the "very satisfied" level than patients with HTA in the control group (73.17% vs. 15.91%, p<0.001, square chi test).

CHAPTER 6. DISCUSSIONS

6.1. Variations in hemodynamic parameters in conscious sedation with inhaled nitrous oxide/oxygen mixture

A. Heart rate assessment

In my study group, I found that the pulse value decreased during the inhalosedation procedure compared to the values recorded before the administration of the gaseous mixture of nitrous oxide and oxygen, the observed differences showing statistical significance [5,6].

At the same time, we found that the pulse value also decreased following the administration of local anesthesia, with significant statistical differences [5,6].

However, the decreases in pulse values were higher following conscious sedation with the gaseous mixture of nitrous oxide and oxygen compared to the control sample, in which patients received only local anesthesia, without associating sedation/anxiolysis [5,6].

I would point out that these differences observed during the study did not show statistical significance value, as the research batch had a relatively limited numerical size.

Taking this data into account, it can be considered that the lack of a tendency to increase the pulse values in the ASA II patients included in my study group could be explained by the existence of a reduced reaction to the possible sympathomimetic action produced by nitrous oxide.

Based on these observations, I believe that the intra surgery decrease in pulse values following the administration of the inhaled gaseous mixture, which I observed in the subjects in my study, is most likely the result of the action of nitrous oxide.

I emphasize that during a dental intervention, the increase in pulse values should be independent of the effect exerted by the inhaled gaseous mixture, but rather from the local anesthetic solution that is being used.

In this context, it is difficult to establish whether the decrease of pulse values after the administration of conscious sedation with inhaled mixture nitrous oxide nitrous oxide – oxygen could be directly related to the depth of the sedation state, but surely this phenomenon is related to the installation of sedation.

B. Evaluation of blood pressure values

In my study group, I noted the decrease in the value of systolic blood pressure in patients who benefited from conscious sedation with inhaled mixture with nitrous oxide and oxygen protoxide, the differences recorded from the pre surgery measured blood pressure values being statistically significant [5,6].

For the subjects in my study group, the measured values of systolic blood pressure followed a downward course following the administration of local anesthesia, the differences recorded being statistically significant [5,6].

The reduction in systolic blood pressure values was more important in patients who benefited from conscious sedation with inhaled gaseous mixture with nitrous oxide and oxygen, compared with

individuals in the sample who did not benefit from sedation before the administration of local anesthesia by infiltration, the observed differences being statistically significant [5,6].

As for the diastolic blood pressure values, they showed the same remarkable tendency of decrease compared to the pre-therapeutic levels, the resulting differences being also statistically significant this time [5,6].

Unlike the sample of patients who benefited from conscious sedation, in the case of the control group, the diastolic blood pressure measured values showed variations in the negative direction, but without them showing statistical significance [5,6].

In the case of the patients from the group who benefited from conscious sedation, there is a much more evident decrease in the diastolic blood pressure values, compared to those recorded in the subjects who were part of the control group, who did not benefit from the intake of inhaled sedation with nitrous oxide mixed with oxygen, without having statistical significance [5,6].

A first observation that I note from the evaluation of the results of my study on the impact of the inhaled mixture administrated to ASA II patients on blood pressure values is that they are not particularly impacted by the anesthetic gas used, with both systolic blood pressure and diastolic blood pressure showing no increase following conscious sedation.

The second important observation resulting from my study on the same direction of research refers to the fact that the decrease in the values of systolic blood pressure is certainly associated with conscious sedation with inhaled mixture of nitrous oxide and oxygen, the decrease in those values being much more important compared to those determined in the patients in the control group.

At the same time, diastolic tension values in patients who benefited from conscious sedation with inhaled mixture were much lower than the pre surgery values, a tendency also noticed in the study group, but with a much more limited amplitude [5,6].

6.2. Variations in oxygen saturation in conscious sedation with inhaled nitrous oxide/oxygen mixture

In the present study, in the lot of patients who received conscious sedation with inhaled mixture of nitrous oxide and oxygen, we noticed the retention of arterial saturation in oxygen, significantly higher compared to the values recorded in the sample subjects included in the sample of those who were not given the gas mixture [5,6].

As a result, it can be considered that inhalosedation with a mixture of nitrous oxide and oxygen, the risk of developing hypoxia appears to be low, which is a major advantage in the case of ASA II patients.

The practical impact of the observations of the study we conducted lies in the fact that they confirm the hypothesis of the possibility of nitrous oxide to counteract the hypoxic risk generated by the emotional and physical stress associated with the dental therapeutic intervention.

In my study, I did not establish differences related to the gender of the subjects enrolled in the study programe in terms of the occurrence of hypoxia following conscious sedation with gaseous mixture nitrous oxide – oxigen [5,6].

6.3. Variations in sedation and post-surgery satisfaction in conscious sedation with nitrous oxide/oxygen inhaler mixture

For this study, in order to determine the efficiency of sedation, we used Ramsay and RASS (Richmond) sedation scales, motor activity evaluation scale (MAAS), visual analog scale and subjective level of patient satisfaction [5,6].

For patients who benefited from inhalosedation with a gaseous mixture of nitrous oxide and oxygen, prior to the actual administration of the sedative, the degree of anxiety and agitation was significantly higher than the one established for the subjects in the control group [5,6].

This could be due on the one hand to the lack of control that patients feel before taking the inhaled mixture, and on the other hand to the feeling of fear of a possible lack of installation of the sedative effect.

After the installation of local anesthetics, patients who received inhalosedation with a mixture of nitrous oxide and oxygen showed in a significantly higher proportion, a Ramsay score = 2, compared to the subjects included in the control group.

At the same stage of the therapeutic intervention, no cases with Ramsay score = 1 were recorded in the study group, unlike the individuals in the working sample, in which most of them showed the same score.

These results are explained by the effect of nitrous oxide, which significantly reduced the degree of anxiety of the patients included in the study group, which did not happen in the control group, the local anesthetic substances not having a sedative or anxiolytic effect.

After the end of the treatment, we did not notice statistically significant differences between the study and control group, both in patients associated with Ramsay = 2 and in patients associated with Ramsay = 1 (3.7% *vs* . 3.33%, respectively; p>0.05).

When evaluating the RASS score (Richmond scale), the participants in the study group presented a score = +1 more frequently, compared to the subjects in the control group, the differences having statistical significance.

In the intra-anesthetic stage, the patients in the study group were a lot more frequently associated with RASS = 0 (alert and calm), compared to the patients in the control group, the differences being statistically relevant.

It is remarkable that at this intra-anesthetic stage, none of the patients in the study group were restless, unlike the patients included in the control group.

In the post-anesthetic stage, both the patients in the study group and those in the control group were alert and calm, without finding the existence of a significant statistical difference.

Assessing the motor scale (MASS), we found in this study that patients in the study group had a score = 4 more frequently, compared to individuals in the control group.

In accordance with the above results, in the intra-anesthetic stage, the patients in the study group were significantly associated with MASS score values = 3 (calm and cooperative), compared to the subjects in the control group.

At the same time, at the same intra-anesthetic stage, no patient in the study group showed a MASS score = 4 (restless patient), while in the control group, a number of 36 patients had a MASS score value of 4.

In the post-anesthetic stage, we noticed that both the patients in the study group and the patients in the control group were calm and cooperative, with no significant statistical difference between the RASS scores.

Regarding the effectiveness of relative, intra-surgery analgesia, patients in the study group were a lot more frequently associated with SV=0 than patients in the control group, which highlights that inhaled sedation in sub-anesthetic doses can cause relative analegesia in ASA II patients.

Also, post-surgery, the patients in the control group were a lot more frequently associated with SVA=0, than the patients in the study group, which confirms the analgesic efficiency of conscious sedation in ASA II subjects.

Remarkablely, patients in the study group were a lot more frequently associated with the "very satisfied" degree compared to patients in the control group.

CHAPTER7. CONCLUSIONS AND PERSONAL CONTRIBUTION

7.1. Conclusions

1. Our study showed the existence of a significant risk of post-extraction hemorrhage in patients who received treatment with the new oral anticoagulants, a result consistent with the current statistics available in the literature.
2. From the statistical correlations resulted the lack of a statistically significant association between the hemorrhage risk and the pathological history of atrial fibrillation with emboligenic risk, both in the case of the administration of coumarin derivatives and in the case of the use of new oral anticoagulants.
3. The presence of congestive heart failure in comorbidities present in oral anticoagulated patients influenced the presence of the risk of late postextractional hemorrhage.
4. The comparison between the two categories of oral anticoagulants showed significant correlations between the risk of post-extraction hemorrhage and patients with atrial fibrillation and congestive heart failure, treated with the new oral anticoagulants.
5. There is no statistically significant link between valvular insufficiency and the proportion of postextractional hemorrhagic incidents in patients with atrial fibrillation undergoing oral anticoagulation, regardless of the category of oral anticoagulant medication administered.
6. Our study found solid evidence of the existence of correlations between the concomitance of hypertension in patients with stable heart rhythm disorders and the risk of late postextractional hemorrhage.
7. We have not obtained statistically significant differences between the presence of late postextractional hemorrhage and the presence of the history of stroke in oral anticoagulated patients in the studied population group.
8. In the comparative analysis of the risk of late post-extraction haemorrhage in patients with a history of stroke who received coumarin anticoagulant medication and, respectively, subjects who were given the new oral anticoagulants for secondary prevention of cerebral ictus, no statistically significant differences between the two diagnostic groups were determined.

9. Statistical analysis indicated significant differences between hemorrhagic risk values and the presence of diabetes mellitus in history in patients with a history of stroke, orally anticoagulated, compared to subjects without diabetes.

10. As regards patients with a history of stroke and a history of diabetes mellitus, in the lot of subjects who received medication from the category of new oral anticoagulants, we encountered a tendency of significant association with the risk of post-extraction hemorrhage, compared to those who benefited from the new oral anticoagulants.

11. As regards the existence of a history of acute coronary syndrome, I have demonstrated that there is no significant association with the presence of post-extraction hemorrhage.

12. Also, we noticed in the lot of patients who received oral anticoagulant consecutive to an acute coronary syndrome, a higher frequency of post-extraction hemorrhage incidents in the case of the use of new oral anticoagulants, but this association was not statistically significant.

13. The data indicate a higher rate of late post-extractional haemorrhage when administered apixaban (*Eliquis*) to patients with atrial fibrillation, similar to that associated with ticagrelor (*Brilique*).

14. We have pointed out the existence of a significant association between hemorrhagic risk and the concomitence of congestive heart failure in patients with atrial fibrillation, in the case of administration of ticagrelor antiplatelet agents, compared to subjects who have undergone oral anticoagulant therapy.

15. We have concluded that in the case of hypertension concomitance in patients with atrial fibrillation, there is a significant association with the risk of post-extraction hemorrhage only in the case of subjects treated with antiplatelet, not among those with oral anticoagulants.

Personal contribution

This study is unique in the speciality literature because there are no publications about the correlations between post-extraction hemorrhagic risk in patients receiving oral anticaogulation, compared to the old generation of coumarin anticoagulants and the new oral anticoagulants.

The originality consisted in compiling a group of patients with a history of anticoagulant treatment and comparing the risk of late postextractional hemorrhage with the groups of general conditions that have an indication of anticoagulation and with the comorbidities that the subjects present.

The character of originality is also supported by the inclusion in the studied population of similarly numerical samples of subjects who are given medication from all categories of oral anticoagulants currently available at national level.

The innovative character of the research is given by the results obtained that make it possible to individualize the therapeutic attitude for each category of patients, depending on the class of oral anticoagulant medication they receive, corroborated with the associated comorbidities.

The current paper, by clarifying and establishing the risk of late postextracional hemorrhage in oral anticoagulated patients, represents a starting point in order to reduce the number of post-surgery complications in oro-maxillofacial surgery and promotes the practice of medical reasoning in approaching patients with complex general pathology, who require surgical interventions in our sphere of interest.

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