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Evaluation of factors associated with postoperative delirium in patients undergoing complex orthognathic surgery: An original research

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Abstract--Purpose: Postoperative delirium (PD) is a common and severe complication, following extensive surgery and prolonged stays in intensive care units (ICU). The study aimed to estimate the frequency of and identify risk factors for PD in a unified orthognathic surgery patients. Methods: A retrospective cohort study composing of patients undergoing Maxillary and Mandibular orthognathic surgeries over 2 year. The predictor variables were identified as 146 general and periprocedural parameters. The primary outcome variable was PD (+ or -). Descriptive and bivariate statistics were performed to identify existing correlations between the predictive factors and PD and the P-value was set at 0.05. A logistic regression model (LRM) was created to adjust for possible confounding factors and reveal possible independent prognostic factors for the onset of PD. Results: 200 patients (36 with PD+, 164 without PD in patient history) undergoing Orthognathic Surgery [130 males, 70 females, mean age = 20 (range 18-40 years)] surgery were recruited. 15 variables that were statistically associated with PD were identified. In the LRM, after adjusting for age, diabetes status and preoperative TSH, Orthognathic surgery was associated with an risk for PD (Odds Ratio (OR) 6.3 (1.6-25.7, p=0.01). Conclusion: The investigators identified 15 variables associated with risk of developing PD, 1 of which was also associated statistically significant after adjusting for other variables in an LRM. Future research efforts should be devoted to assessing the use of these variables for predicting PD further. Since the Maxillary and Mandibular Surgery showed to be an independent prognostic parameter for the development of PD in this study, patients undergoing Extensive Surgery should get special attention in the first days after surgery to prevent PD and associated complications such as increased mortality and prolonged hospital stays.

Keywords--postoperative delirium, risk factors, reconstructive surgery, orthognathic surgeries, predictive factors, risk factors, intensive care unit.

Introduction

Delirium is a common postoperative psychiatric disorder that can occur at any age. Postoperative delirium (PD) is defined as a reversible neurological deficit with a change in cognition and disturbance of consciousness in the acute or late postoperative period. It is characterized by the acute onset of fluctuations in neuropsychiatric function and inattention, combined with altered levels of consciousness or disorganized thinking. While various forms of acute delirium can manifest postoperatively at any time from 1 to 30 days, PD usually occurs within 24 to 48 hours of surgery. Delirium is not a disease, but rather a clinical syndrome affecting cognitive functions such as consciousness, orientation, perception, attention, short-term memory, judgment and abstract thinking. It is a temporary condition with a sudden or gradual onset over a period of hours or days, while a single episode can last for up to 1 week. The incidence of PD varies

between 0 and 73% depending on the field, type and extent of surgery, patient age and gender, along with multiple separate cofactors. Various studies have been performed to clarify the underlying causes and risk factors of PD. A number of risk factors have been identified as being associated with a higher incidence of PD. Age, Gender, extensive surgery, high ASA class, low social status, amount of blood transfusion, elevated laboratory values (such as C-reactive protein, hemoglobin and liver enzymes) and preexisting comorbidities were just some of the most commonly identified risk factors in a large number of studies. Since the risk factors identified differ so widely, it becomes obvious that the etiology of delirium is very complex and usually dependent on multiple factors. Many PD details remain unclear. Since delirium is often associated with problems during postoperative management, long hospital stays, poor functional recovery, high healthcare costs, and high rates of morbidity and mortality, the early identification of individuals with a high risk of developing PD would be of great importance. As the type and extent of surgery may play a role in the development of PD, patients undergoing major Orthognathic Surgeries are considered to be at high risk. In these patients, a quick postoperative recovery is important for rehabilitation of speech and swallowing functions. The purpose of this study was to identify possible risk factors for PD in patients undergoing major Orthognathic surgery. It is the largest single study based on a homologous group of patients undergoing surgery. Many studies focused on a small number of possible predictive parameters for PD. It was hypothesized that increasing information and awareness of PD risk factors can help to establish preoperative risk assessment scores and provide guidelines in management and decision-making for at-risk patients. The null-hypothesis is that the parameters screened in the study are not associated with the development of PD. Modifiable factors may receive more attention and be optimized pre-, intra- and postoperatively. It is further hypothesized that this knowledge could reduce the incidence and the morbidity associated with PD, resulting in improved postoperative management, shorter hospital stays, faster recovery periods and lower healthcare costs. However, since the development of PD has been shown to be of a very complex and confusing nature, the specific aims of the study were to include as many potential causative screening factors as possible, including general patient parameters and preoperative, intraoperative and postoperative factors, thus gaining a broad knowledge of as many parameters possible that may influence PD development. Apart from this, this study focuses on parameters that showed to be responsible for PD in previous studies.

Materials and Methods

To address the research purpose a retrospective cohort study was obtained to identify PD risk factors in patients undergoing major Orthognathic surgery. Patients were identified and they were provided with the questionnaire. The inclusion criteria for the study were an age of 15 to 40, minimum operation time of 5 hours. All study participants were transferred to the ICU postoperatively. Exclusion criteria were a stay in the ICU within 1 years prior to surgery, any evidence of prior delirium, alcohol withdrawal syndrome or any pre-existing psychotropic long-term medication, the reconstruction of jaw or soft tissue defects with surgical techniques, synchronal tumors at the time of initial diagnosis, and previous surgical or non-surgical oncologic treatment. All patients

underwent the same type of surgery under standardized pre-, intra- and postoperative conditions. All orthognathic surgeries were performed in a 2-team approach. The primary outcome variable was the development of clinical PD, coded as yes or no. To be diagnosed as having PD, the medical course and records must show clear documentation of clinically manifest delirium in the form of ICD-10 and/or DSM IV coding (Group 1). Further PD was verified by a structured psychiatric interview considering the criteria from the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, which remains the gold standard for diagnosing PD. Group 2 served as the control group, with patients not developing PD after surgery. The predictor variable was a set of heterogenous variables (n=146) grouped into the following categories: general, preoperative, intraoperative and postoperative factors recorded from each patient. General basic parameters included age, gender, BMI, smoking habits, alcohol consumption and social status, while preoperative parameters comprised the amount and type of premedication, pre-existing conditions, ASA physical status class and the results of standardized preoperative laboratory tests, including 15 laboratory parameters. Intraoperative parameters included the type and duration of surgery, fluid balance, blood gas analysis at 2 different time points during surgery (each including 12 blood gas analysis parameters) and the total amount of blood transfusion. Postoperative parameters included the length of the ICU stay, duration of artificial respiration, time point of decannulation, postoperative monitoring, complications, newly scheduled postoperative medication, percutaneous endoscopic gastronomy, postoperative radiation and the results of laboratory tests on the first and fourth postoperative days. For all parameters obtained, each parameter was viewed individually as a separate predictor variable to screen for its potential influence on PD. The outcome variable was the development of PD. As there was a direct context to surgery and the stay in the ICU, a time limit for the development of PD did not exist and was not seen as a criterion. All the patients had a follow up over a minimum of 6 months.

Statistical analysis

After exporting a database into an Excel spreadsheet, it was transferred to the open-source statistical package R for statistical analysis. After checking the entire dataset, a dedicated script was written. To test the statistical significance of differences in parameters between the 2 subgroups, categorical data was investigated using the Chi-squared test (with Yates continuity correction) or Fisher's exact test. Quantitative data was analyzed using Welch's 2 sample t-test or a Wilcoxon rank sum test with continuity correction. In addition, a logistic regression model was created using 4 different baseline parameters that proved to be statistically significant with a p-value < 0.05

The level of statistical significance was defined as $p < 0.05$.

FACTORS	SIGNIFICANCE
1. AGE	P< 0.05
2. DIABETES	
3. TSH	
4. TYPE OF SURGERY	

5. HOSPITAL STAY

Results

A total of 200 patients were included in the study, 130 males and 70 females, with a mean age of 20 Years (range 18–40 years). The majority of patients (75%) were classified preoperatively as ASA 2. Fifty percent of the patients underwent Maxillary Surgery. Fifty percent of the patients underwent Mandibular Surgery. 88% of patients were tracheostomized. Duration of surgery was 4 ± 2 hours in both groups, with a range 4.35 - 10.21 hours. In Group 1, PD occurred 32 ± 6.7 hours (mean \pm SD) after surgery. No patient developed any form of PD later than 10 days after surgery. Detailed descriptive and statistical results of 146 parameters (general, preoperative, intraoperative and postoperative) recorded in this study for both groups. The following parameters showed a statistically significant difference between Group 1 (PD) and Group 2 (non-PD). Age: The mean age of Group 1 was 18, while the mean age of Group 2 was 20. The youngest patient in Group 1 was 14, while the youngest patient in Group 2 was 18. Preexisting conditions: diabetes: 8% of patients in Group 1 had diabetes. 7% of patients in Group 2 had diabetes. Oral anti-diabetics was taken on the day of surgery. Preoperative thyrotropic hormone (TSH): In Group 1 and Group 2, no patient was having Thyroid. Total hospital stay(mean, days): Patients in Group 1 had an average total hospital stay of 6 days, while the Group 2 patients stayed for 6.5 days on average. Duration of treatment/monitoring at intensive care unit (ICU): Patients in Group 1 spent an average duration of 3.8 days in ICU, while this was 4.2 days for Group 2. Transfer from ICU to ward on first postoperative day: 56% of patients in Group 1 were transferred from ICU to the ward on the first postoperative day, 88% for Group 2. Duration of postoperative monitoring (mean, days): Patients in Group 1 had to be monitored for 6.7 days after surgery, while patients from Group 2 were monitored for 6.9 days on average. New medication postoperatively (prior to onset of PD): psychotropics: Postoperatively, 94% of patients in Group 1 received new medication that they had not taken before surgery, compared to 49% of the patients in Group 2. Eighty-one percent of patients in Group 1 received psychotropics postoperatively, compared to 27% in Group 2. Postoperative thrombocytes: The mean count of postoperative thrombocytes of patients of Group 1 was 143.28/nL, while the mean count of patients in Group 2 was 181.7/nL. Postoperative Quick-value (International normalized ratio (INR)): The mean postoperative Quick-value (INR) of patients in Group 1 was 95.12 (1.1), while for Group 2 this was 102,25 (1.0). Postoperative partial thromboplastin time (PTT): The mean postoperative PTT in Group 1 was 39.06s, while in Group 2 it was 34.13s.

Discussion

This retrospective cohort study was performed to screen for and identify significant parameters from 4 subcategories, defined as the predictor variables associated with PD after complex orthognathic surgery. The primary outcome parameter was occurrence of PD. The null-hypothesis of the study is that there is no association between the screened parameters and the occurrence of PD. The study identified numerous factors as being significantly related to PD, so the null-hypothesis could be rejected and the alternative hypothesis could be

confirmed by the data. Among others, the following parameters proved to be associated significantly with PD: the application of new medication postoperatively (especially psychotropic medication), the number of thrombocytes on the first postoperative day, the PTT on the third postoperative day, and being transferred from the ICU to the general ward on the first postoperative day. The number of thrombocytes and the PTT are indicators for the amount of intraoperative transfusion due to bleeding, blood loss and dilution. From the large number of screened factors, several other parameters showed a significant association with the occurrence of PD. However, the causality between those factors and PD was not always obvious, such as the prolonged duration of postoperative monitoring on the ICU. In some cases, this could also be a result of the development of PD. In the present study setting, this question remains open and can only be answered by an exclusive prospective design. 36% percent of the patients included in this study developed clinically manifest PD with fluctuating clinical signs of impaired neuropsychiatric function and inattention as well as altered levels of consciousness or disorganized thinking. PD in these patients was identified objectively by a standard psychiatric interview based on ICD-10 and/or DSM IV coding. The incidence of PD within a surgical collective in this study is consistent with the results of previous studies investigating PD after surgery which report a range of 20-72%. Subclinical forms of PD without clinically manifest evidence of neuropsychiatric dysfunction were not considered. Psychological was found to be a very common factor in 95.4% of studies regarding the development of PD in different patient collectives according to a meta-analysis. Age has also been confirmed as a risk factor for PD in patients. They usually require significantly more aftercare in the ICU resulting in prolonged sedation. Elderly patients also tend to show pre-existing cognitive impairment, which has been identified as a predictive PD factor. These factors might contribute to an increased risk of PD. In this study, patients with PD were significantly older in group 2 than those in Group 1. Thus, results agree with those of previous studies identifying age as a risk factor for PD. However, patients who developed PD in our study were 2 years below the threshold identified in a prediction model for the development of PD by Marcantonio et al (1994). 12 out of 18 patients would have not been identified as having a higher risk of PD as they were younger. It becomes clear that even well-established predictive parameters cannot be used as individual indicators for developing PD, but would have to be considered in relation to other parameters. In this study, an LRM was created, showing that age was a significant risk factor for PD. In the following multivariate LRM this possible risk factor did not prove to be associated statistically significant with developing PD. While some studies have identified a longer duration of surgery as a risk factor. In our study, there was no significant difference in duration of surgery between patients with PD (with an average length of 4.08 hours of surgery) and patients without PD (with 4.09 hours). However, both the group were statistically significant in the development of PD. This is especially the case if the number of predictors exceeds $m/10$ where m is the limiting sample size of the minimum response variable. In our case $m=36$, representing the number of patients who developed PD, which means the maximum number of predictors in the model is 3.2. Therefore, since our data set is rather small, the resulting regression model has to be regarded critically. Diabetes was highlighted as a preexisting condition and relevant risk factor for PD by Makiguchi et al, but this has not been investigated any further. Analysis

found that patients with preexisting diabetes which are being treated with oral anti-diabetics are at a significantly higher risk of developing PD. However, after adjusting to other variables in a LRM, diabetes was not statistically associated with PD. In 1994, Marcantonio et al identified postoperative psychotropic medication as an important PD risk factor. In this study, patients under postoperative psychotropics were at a higher risk of developing PD than those who were not. The psychotropics given to patients undergoing surgery were benzodiazepines, typical antipsychotics (such as haloperidol) (Makiguchi et al). The patients with preexisting diabetes which are being treated with either oral anti-diabetics were at a significantly higher risk of developing PD.

However, after adjusting to other variables in a LRM, diabetes was not statistically associated with PD. It remains unclear and of great interest whether diabetes not being treated with medication is also a risk factor for PD. In our study, patients under postoperative psychotropics were at a higher risk of developing PD than those who were not. Due to the retrospective design of this study, indications for the use of psychotropics cannot be determined with certainty for all cases. Benzodiazepines, however, are commonly required by patients who suffer from anxiety and sleep deprivation after extensive surgery. Since various psychotropics were used, the effect of different substances on the development of PD after extensive surgery remains unclear. Social background factors like marital status and profession were considered as predictive. Both were obtained in this study, neither showed any significant impact on developing PD. However, these factors should be included in further studies about PD as well, as social background can be an important factor in recovery from and thus avoidance of PD. The most important strength of the current study lies in the size of the homologous collective and the total number of parameters implemented in the risk analysis. While many studies have considered a broad variety of parameters, this study evaluated general, pre-, intra- and postoperative parameters, covering a large selection of possible underlying risk factors. All study participants had identical pre-, intra- and postoperative conditions. While the retrospective nature of this study comes with some limitations, another small drawback is the protocol by which delirium was diagnosed. PD was screened with a standardized questionnaire, but all patients suspected of having developed PD were examined by mental health professionals as a standard protocol. However, in order to be seen by those mental health professionals, PD had to be sufficiently evident to be noticed by the supervising doctor, ICU staff or general ward nurses. The disadvantage of this approach is that hypoactive delirium which was not clinically evident might have gone undetected in its initial stage, resulting in a lower incidence of PD. However, this standard method selects cases of PD that are evident enough to become clinically significant and thus alter the course of recovery essentially. Without exception, patients undergoing surgery were screened and treated for psychiatric disorders prior to surgery where necessary. Homogeneity, as a basic requirement for objective comparison of the sub-collectives (PD vs. nonPD), was thus guaranteed. Although many studies have the aim of developing prediction models for PD, these can only be established once certain risk factors have been clearly identified. Various studies have obtained numerous risk factors that are inconsistent with one another. Multiple testing may also lead to unexpected findings of statistical significance. It becomes clear that retrospective study

settings are limited by their nature, and that in order to reliably identify indicators for PD, controlled prospective studies are needed. Based on the findings of these studies, a reproducible prediction model can then be developed. These can be in the form of a scoring system or a nomogram (similar to nomograms in oncology which have been developed to predict the accuracy of diagnostic tests and treatments). Existing models like Marangoni's prediction model can be used as guidelines. However, they have to be either confirmed or reconsidered by using data from prospective studies. The reason for prediction models being especially important in surgery is because these patients have a particularly high risk of developing PD. Orthognathic surgeries are extensive and complicated procedures. A quick recovery after surgery in the sense of "fast-track surgery" is especially important in these patients, in order to continue with necessary treatment and the rehabilitation of speech and swallowing. Even though the extensive surgeries proved to be a significant risk factor in the development of PD, it was shown that other parameters, such as age, diabetes, total hospital stay, length of ICU stays, transfer from ICU to ward on first postoperative day, duration of postoperative monitoring and postoperative psychotropic medications have an influence regarding the onset of PD after extensive surgery. The clinical presentation and outcomes of PD will also have to be investigated further. Although this study was based on a large homologous collective of patients that have undergone interventions of comparable complexity, and every patient has been treated and monitored according to the same guidelines, this study drawbacks outcome and reduced the validity of the results. Given the study setting, it was difficult to extract confounders and clarify the causality of some parameters that might have been the result of PD, such as the duration of postoperative monitoring. Controlled prospective multi center studies that include a consistent system of diagnosing PD are needed to identify further risk factors and develop reliable predictive models. Such models would allow patients to be placed into categories according to the risk of developing PD, with standardized protocols for pre-, intra- and postoperative procedures for anesthesiologists, surgeons and nurses.

Conclusion

PD is a common and severe condition with increased incidence after surgery. This results in long hospital stays, high healthcare costs, and high rates of morbidity and mortality. Several risk factors for PD could be identified in this study. However, due to the study setting, the interaction of some parameters could not be clarified as the PD itself could have caused a significant association. Prospective multi center studies are necessary to exclude all confounders and gain further knowledge of the interaction of risk factors. By identifying specific indicators for PD in homogenous collectives and settings like this study protocol, it would be possible to establish reliable prediction models. Thus high-risk patients could be identified and their periprocedural management could be optimized accordingly. In this way, even cases of clinically non-evident PD could be detected and treated more reliably at an early stage.

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