Delirium and pain in patients in the immediate postoperative period of cardiac surgery: prevalence and associated risk factors

Delirium e dor em pacientes no pós-operatório imediato de cirurgia cardíaca: prevalência e fatores de risco associados

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ABSTRACT

BACKGROUND AND OBJECTIVES: Delirium is an acute mental status change, with fluctuating course and high incidence in cardiac surgery (CS) post-operative (PO) period. Delirium can lead to short and long-term consequences. The aim of this study was to assess the prevalence of delirium and pain and their risk factors on the 1st PO day after CS.

METHODS: This was a cross-sectional analytical research. To determine the presence of PO delirium, the Confusion Assessment Method modified for Intensive Care Unit setting (CAM-ICU) and the Richmond Agitation Sedation Scale (RASS) were used. PO pain was analyzed using the Visual Analogue Pain Scale (VAS) and the presence of neuropathic components was analyzed using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale. After bedside analysis, patients were divided into Delirium (D) and Without Delirium (WD) groups.

RESULTS: The total number of patients was 79. The prevalence of delirium was 16.5% (95% CI = 9.06 - 26.49%) and the mean number of comorbidities in the preoperative period was a significant risk factor for the occurrence of delirium (D =4.15±2.37 *versus* WD=2.96±1.78, p: 0.04). Another significant risk factor was the group older than 65 years of age, with the occurrence of delirium 1.45 times higher (PR=1.12-1.88, p: 0.0014). Regarding pain evaluation, 72.15% (95% CI 60.93 - 81.65%) reported it in the 1st PO day.

CONCLUSION: The prevalence of delirium was similar to previous studies. The number of previous comorbidities and advanced age were risk factors for delirium. Pain was present predominantly over the sternotomy incision region.

Keywords: Delirium, Cardiovascular surgical procedures, Postoperative pain.

RESUMO

JUSTIFICATIVA E OBJETIVOS: *Delirium* é uma alteração aguda do estado mental, com curso flutuante e alta incidência no pós-operatório (PO) de cirurgia cardíaca (CC). O *delirium* pode levar a consequências a curto e longo prazo. O objetivo deste estudo foi avaliar a prevalência de *delirium* e dor e seus fatores de risco no 1º dia PO após CC.

MÉTODOS: Trata-se de um estudo transversal analítico. Para determinar *delirium* no PO, foram utilizados o *Confusion Assessment Method* modificado para ambiente de Unidade de Terapia Intensiva (CAM-UTI) e a *Richmond Agitation Sedation Scale* (RASS). A dor PO foi analisada por meio da Escala Analógica Visual (EAV) e a presença de componentes neuropáticos foi analisada por meio da Escala de Avaliação de Sintomas e Sinais Neuropáticos de Leeds (LANSS). Após análise, os pacientes foram divididos nos grupos *Delirium* (D) e Sem *Delirium* (SD).

RESULTADOS: Foram estudados 79 pacientes. A prevalência de *delirium* foi de 16,5% (IC 95% = 9,06-26,49%) e o número médio de comorbidades no pré-operatório foi um fator de risco significativo para a ocorrência de *delirium* (D=4,15±2,37 *versus* SD=2,96±1,78, p: 0,04). Outro fator de risco foi o grupo com mais de 65 anos, com ocorrência de *delirium* 1,45 vezes maior (RP=1,12-1,88, p: 0,0014). Em relação à avaliação da dor, 72,15% (IC 95% 60,93-81,65%) a relataram no 1º dia PO.

CONCLUSÃO: A prevalência de *delirium* foi semelhante à de estudos anteriores. O número de comorbidades prévias e a idade avançada foram fatores de risco para *delirium*. A dor estava presente predominantemente na região da incisão da esternotomia.

Descritores: *Delirium*, Dor pós-operatória, Procedimentos cirúrgicos cardiovasculares.

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HIGHLIGHTS

- 72.15% of the sample experienced pain on the 1st postoperative day.
- The prevalence of delirium was 16.5% in the postoperative period of cardiac surgeries.
- The presence of comorbidities and age over 65 years were associated with a higher prevalence of delirium in the studied population.

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INTRODUCTION

Delirium is a frequent, although under-reported, complication in the postoperative (PO) period of cardiac surgeries (CS), which is related to a significant functional decline in the patients' quality of life[1]. This condition is defined as an acute change in mental status, with a high variety of neuropsychiatric signs and symptoms, with a fluctuating course caused by disorders in cerebral homeostasis[2].

There are several predisposing and precipitating factors for delirium that patients may present. Among the predisposing ones, advanced age (>65 years), male gender, previous dementia and multiple comorbidities history may be mentioned. Among the precipitants, polypharmacy, hydroelectrolytic disorders, intraoperative hypotension, immobilization, and prolonged physical restriction are the ones that stands out. Thus, due to the high incidence of delirium in CS-PO, the analysis of patients' risk factors becomes relevant for both prevention and early treatment of these complications. PO delirium has been associated with several conditions that affect the patient functionally and cognitively, with both short and long-term consequences, such as PO mortality, prolonged hospital stay, nursing home placement, and increased health costs[3].

Another important factor to be analyzed in patients in CS-PO is pain, which is a frequent symptom that may expose the patient to undesirable risks. A particularly dangerous consequence of severe pain after cardiovascular procedures is respiratory system dysfunction. The pain causes reflex muscle tension and impairs the patient's activity or even immobilizes him, leading to dyspnea, and reduction in tidal volume, vital capacity, functional residual capacity, and lung compliance[4].

In this context, the post-surgical pain assessment is important since the success of the treatment largely depends on the adequate management of pain during the first days after the procedure. In CS, the incidence of PO pain is high, reaching more than 80% of the interventions, with the most frequent sites of pain being the sternal region and anterior chest, and a peak incidence on the 1st postoperative day[5]. Thus, the importance of an effective therapeutic approach is highlighted to avoid possible unnecessary adverse effects for the patient[5]. However, although this approach is necessary, 50% to 75% of patients do not receive appropriate analgesia, therefore, an efficient pain assessment is essential to ensure an adequate management of its intensity[6].

The aim of this study was to verify the prevalence of delirium and pain in the 1st PO day considering that, by concept, prevalence is the right choice in order to refer to the number of people currently diagnosed with a disease, in a specific moment. Other studies followed the patients during their length of stay in the hospital and therefore were able to verify the incidence of the same variables, since these studies were designed to research new cases being diagnosed over a period, which was not part of the scope of the present study.

Therefore, due to uncertain data, especially among research carried out in Brazil, the objective of this study was to assess the prevalence of delirium and pain and their risk factors on the 1st PO day after CS.

METHODS

This was an analytical cross-sectional study that analyzed the prevalence of delirium and its risk factors (International Classification of Diseases [ICD] code F05) and pain after CS in a tertiary hospital, between January of 2020 and June of 2022. Through a questionnaire, the clinical-epidemiological data and delirium risk factors were obtained from the electronic medical record TASY®, provided by the clinical and scientific board of the hospital.

To determine the presence of delirium on PO period, the Confusion Assessment Method modified for Intensive Care Unit setting (CAM-ICU) and the Richmond Agitation Sedation Scale (RASS) was used. Initially, it was evaluated if the patient was awake and out of intense sedation, according to the RASS scale. Subsequently, the patient's fluctuating mental state was determined with the multidisciplinary team, which accompanied the patient throughout hospitalization. Once the patient was considered in an acute and fluctuating mental state, inattention, altered level of consciousness and, if necessary, disorganized thinking, was assessed following the CAM-ICU. PO pain analysis was performed with the patient at rest and its location and intensity was assessed using the Visual Analogue Scale (VAS), while the presence of a neuropathic component was assessed using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale. After data collection, it was tabulated and submitted to statistical analysis using Excel 2010® and EpiInfo™ software. After bedside analysis, patients were divided into Delirium (D) and Without Delirium (WD) groups.

This study selected adult patients (>18 years old), undergoing CS by sternotomy or minimally invasive surgery. All patients were analyzed on the 1st PO day and were in accordance with the approved Free and Informed Consent Term (FICT). Patients with a percutaneous surgical approach, in severe sedation, in coma or who had incomplete data in the medical records were not included in the analysis.

This study was carried out through a cross-sectional observational survey on patients referred to the participating service for CS. There was no interference by the research team in the indication of cardiac surgery or in its technique, being the research restricted to the application of questionnaires to whom underwent the procedures on the recommendation of their assistant physician.

This research was approved by the Research Ethics Committee of the Goiás Emergency Hospital under CAAE: 38630920.7.0000.0033.

Statistical analysis

Tabulation and statistical analysis were performed using Microsoft Excel®, version 2010. Quantitative variables were presented as means and standard deviations, including minimum and maximum. The distribution of these variables was analyzed using the Kolmogorov Smirnov test, when necessary, to calculate normality. This study used a measure of relative association to quantify the relationship between a given exposure and a consequence. To indicate such a relative association, the prevalence ratio (PR) was used. Qualitative variables were presented in absolute numbers and proportions. Data were evaluated by Student's *t* and Chi-square tests,

adopting a confidence interval of 95% and a significance level of 5% (p<0.05). For such calculations, EpiInfo™ software was used.

RESULTS

During the analyzed period, the total number of patients was 79, and approximately 53% of them were men. The clinical and epidemiological data of the sample are represented in table 1. The prevalence of delirium was 16.5% (95% CI = 9.06 - 26.49%), with approximately 54% of them occurring in males. Regarding the analysis of risk factors, it is noteworthy that clinical factors classically described in the literature, such as pre/postoperative polypharmacy and male gender, were not statistically significant in the sample when comparing D and WD groups. Alongside, the mean number of comorbidities in the preoperative period was shown to be a significant risk factor for the occurrence of delirium (D=4.15±2.37 *versus* WD=2.96±1.78, p: 0.04).

The most frequent comorbidities in the population of this study were arterial hypertension, followed by atrial fibrillation and diabetes mellitus, with 61.5%, 30.8% and 15.4%, respectively. Another risk factor that was significantly associated was age over 65 years, with a occurrence of delirium 1.45 times higher (PR=1.12-1.88, p: 0.0014). Regarding the intraoperative and postoperative management, five factors were analyzed: extracorporeal circulation (ECC) time, aortic clamping (CLAMP) time and use of opioids, statins, and benzodiazepines; none of these factors being statistically significant associated with delirium occurrence. All the analyzed elements and its relation to delirium are presented on table 2.

Regarding pain evaluation, among the 79 patients analyzed in the period, 72.15% (95% CI 60.93 - 81.65%) reported it in the 1st PO period. On average, patients reported 1.16±0.92 painful areas, with the sternal area being the most frequent, with approximately 40% of complaints. The mean postoperative pain intensity measured by VAS was 3.82±3.27 and no significant association was observed with the use of opioids for PO analgesia (VAS with opioids = 3.37±3.09 *versus* VAS without opioids = 4.01±3.36, p=0.42). In the investigation with LANSS scale, among those who reported pain, approximately 7.6% of the patients had a score greater than 12, suggesting a neuropathic component in PO pain. All the analyzed elements and its relation to PO pain are presented on table 3.

Table 1. Clinical-epidemiological characteristics of participants

Characteristics	N/SD (%)
All	79
Gender (Male/Female)	42/37
Body mass index (kg/m²)	27.4
Average number of comorbidities	3.2 /±1.9
Average number of drugs used at home	4.2 /±2.2
Average number of drugs used in the post-operative period	7.5 /±1.9
Surgical time	
ECC time (in minutes)	97.5 /±26.3
CLAMP time (in minutes)	69 /±22.1
Surgical procedure	
Valve replacement	46 (58.3%)
Coronary bypass	24 (30.38%)
Aneurysm	2 (2.53%)
Atrial septal defect	2 (2.53%)
Aortic dissection	1 (1.27%)
Others	4 (5.06%)

SD = Standard Deviation; BMI = Body Mass Index; ECC = Extracorporeal Circulation; CLAMP = Aortic Clamping.

Table 2. Risk factors between patients with delirium versus without delirium

Variables	Delirium (n=13)	Without delirium (n=66)	Prevalence ratio	p-value
Age				
≥ 65 years old	11	21	PR = 1.45 (CI 95% 1.12-1.88)	p<0.001
< 65 years old	2	44		
Gender				
Male	7	35	PR = 1.02 (CI 95% 0.37-2.18)	p=1.0
Female	6	31		
Average number of drugs used at home	4.84±2.33	4.03±2.12	NA	p: 0.21
Average number of drugs used in the post--operative period	7.69±2.75	7.42±1.71	NA	p: 0.64
Number of comorbidities	4.15±2.37	2.96±1.78	NA	p: 0.04
Surgical time (in minutes)				
ECC time	101.91(±30.16)	96.71(±25.73)	NA	p: 0.53
CLAMP time	70 (±26.06)	68.8 (±21.46)		p: 0.86
Statin use				
Yes	7	32	PR = 0.83 (CI 95% 0.3 -2.2)	p: 0.96
No	6	34		
Benzodiazepine use				
Yes	3	5	PR = 2.66 (CI 95% 0.91-7.7)	p: 0.07
No	10	61		
Opioid use				
Yes	10	45	PR = 0.68 (CI 95% 0.2-2.2)	p: 0.76
No	3	21		

ECC = Extracorporeal Circulation; CLAMP = Aortic Clamping; PR = Prevalence ratio; CI = Confidence Interval; NA = not applicable.

Table 3. Analysis of the prevalence and characteristics of pain

Variables	Total sample (n = 79)	
Prevalence of post-operative pain	57 (72.15%) (CI 95% = 60.93 – 81.65%)	
Mean pain intensity through VAS	3.82±3.27	
Mean number of painful regions	1.16±0.92	
Most reported areas (N)		
Sternal area	31	
Posterior thoracic region	13	
Right lateral-thoracic region	11	
Epigastric region	5	
Left lateral-thoracic region	4	
Other	22	
Neuropathic component analysis		
LANSS > 12	6 (7.6%)	
LANSS < 12	58 (73.4%)	
LANSS = zero (no pain)	15 (19%)	
Relationship between VAS and opioid use	With post-operative opioid use	Without post-operative opioid use
	VAS = 3.37 (±3.09)*	VAS = 4.01 (±3.36)*

*p: 0.42; VAS = Visual Analogue Scale; LANSS = Leeds Assessment of Neuropathic Symptoms and Signs; CI = confidence interval.

DISCUSSION

The present study obtained a prevalence of delirium of 16.46% (95% CI 9.06 - 26.49%). It also demonstrated that 72.15% (95% CI 60.93 - 81.65%) of the patients had some degree of PO pain. Unlike other studies, which followed patients for days postoperatively, thus being able to address the incidence of delirium and pain, this study carried out only one assessment, precisely on the 1st PO day, which characterizes it as a prevalence study. The incidence of delirium after CS can vary greatly depending on the study methodology used, but in general it ranges from 26% to 52%[7]. The three forms of delirium can be found in the patient after CS (hyperactive, hypoactive and mixed delirium), but the most found is the hypoactive form, in 92% of the time[3].

In a prospective German cohort study that analyzed 254 patients over 60 years of age undergoing CS, the incidence of delirium was 50%[8]. In a meta-analysis published in 2021, 13,286 patients over 18 years of age undergoing CS were evaluated, determining a wide range of incidence of PO delirium, between 4.1 and 54.9%[9].

One of the risk factors for PO delirium is gender, with males classically described as having the highest relative risk.

Currently, there is no consensus as to whether the patient's gender has a negative influence on the occurrence of delirium, with the most current references indicating it as a non-significant factor[10]. In the analyzed sample, the prevalence of delirium in males was approximately 54%, with 1.02 PR (95% CI 0.37 - 2.18, NS), being non-statistically significant and in line with current literature.

The age, in turn, is a risk factor well established in the literature, which shows a higher prevalence of delirium among the seniors, but higher mortality when it occurs in the youngest[10]. In a cohort study who prospectively followed more than 5,000 patients, the incidence of delirium in the age group older than 65 years was 9%, while in those younger than 65 years the incidence was 3%[11]. In the present study, the mean age of the patients was 59±12.6 years. Comparing the groups aged less than 65 years and those aged greater than or equal to 65 years, delirium was more frequent among the seniors, thus being in line with what is currently established.

When evaluating the relationship between ECC time and delirium, none of the studies found demonstrated relationship between them. In a study which compared delirium in ECC times greater than one hour, there was no statistical difference between more and less than 1 hour[12]. The present study agrees with previous researches, presenting no statistical significance when comparing the ECC times of patients with and without delirium.

The relationship between multimorbidity and delirium is already well established in the literature as an important predisposing factor for this complication, especially in CSs, which usually involve patients with several associated comorbidities. A prospective study, which aimed to evaluate preoperative CS predictors for delirium, was found that dyslipidemia was a factor with higher risk for the complication[13]. In another study, however, diabetes and peptic ulcer disease were the factors that increase the risk for PO delirium[14]. In this study, multimorbidity was a factor of higher prevalence of delirium in patients undergoing CS. The comorbidities more frequently associated with delirium were arterial hypertension, followed by atrial fibrillation and diabetes mellitus.

Polypharmacy, another predisposing factor discussed for patients with delirium, was not described with a significant increase in the risk of this complication in the PO-CS period. In a study published in 2021 that analyzed risk factors for PO delirium in seniors undergoing CS, evaluating 254 patients, the number of preoperative drugs was not a risk factor for the evaluated complication[8]. The current study agreed with these data in the literature.

It is well established in the literature that the use of opioids, especially in high doses, is associated with a higher incidence of delirium in patients. In a meta-analysis published in 2017 that sought to assess this association, tramadol and meperidine were the opioids that led to a risk factor for delirium.[15] In another multicentric study, which evaluated delirium after CS in children, patients with delirium received a higher amount of opioids when compared to children without delirium (group D=1.80 *versus* group WD=0.36)[16]. The present study showed discordant results from the literature, with no statistical significance of delirium between the groups that used opioid and non-opioid analgesics.

Another class of drug with an important relationship with delirium is the benzodiazepines. In a prospective longitudinal study published in 2018 that sought to assess several risk factors involved in delirium after CS, the use of benzodiazepines was considered an independent predictor factor for this complication[17]. However, this study did not demonstrate such data, and the use of benzodiazepines was not a risk factor for delirium.

Studies suggest that the use of preoperative statins may increase the risk of delirium in the PO period of surgeries in general. Other studies have already shown a protective effect of statins for this complication due to its neuroprotective effect. However,

in a study that sought to assess the prevalence of delirium in the PO-CS period comparing the home use of statins, there was no relationship between the groups[18]. The present study also did not show statistical significance comparing patients who used and did not use statins.

In retrospective questionnaires, similar to the one used in the current study, the prevalence or incidence of pain in the PO period of sternotomy was 38% to 56%[19]. In a prospective cohort that analyzed patients undergoing coronary artery bypass graft surgery via sternotomy during the first four PO days, 49% reported experiencing severe pain at rest on the 1st PO day[20]. At the same time, in a prospective study carried out in Brazil with 30 patients undergoing CS, it was observed that the prevalence of pain in the 1st PO period was 63.3%, corroborating this study. This research also evaluated pain intensity by VAS and found that the mean pain intensity was 2.6 on the 1st PO day[6]. In another prospective study with 200 patients undergoing CS, it showed an average of 3.9 points[21]. When comparing with the value found in this study, a similarity is observed, since the average of the present study was 3.82 points by VAS.

Pain control in the PO-CS period is of fundamental importance for the best recovery of the patient in the short and long term. Although opioids are classically described as potent analgesics, the current trend towards adherence to multimodal analgesia therapy ("opiod free") with lower doses of opioid and synergistic association with paracetamol is increasing. This strategy has been gaining ground in the context of CS, which allows for better pain control and lower risk of PO side effects[21]. In a prospective, randomized and controlled study in which 180 patients who underwent CS via sternotomy were evaluated, the multimodal analgesia regimen (dexamethasone, gabapentin, ibuprofen and paracetamol) was compared to the traditional regimen with morphine and paracetamol and was demonstrated that the multimodal regimen showed lower pain rates than the standard regimen[22].

According to the literature, the use of intravenous opioids, mainly morphine, is the most effective post-sternotomy pain control therapy when administered by the patient-controlled intravenous analgesia method, although there is no difference in the clinical significance of the efficacy on the specific opioid used[23]. In this study, there was no significant difference in pain intensity between patients who used opioids and those who underwent pain control with NSAIDs alone, with patients using opioids having a mean pain intensity of 3.37, while patients without opioid use had a mean of 4.01 (p: 0.42). Both classes of analgesics, in high doses, can lead to complications in the PO-CS period, since it is well discussed that the indiscriminate use of opioids can lead to nausea, constipation, urinary retention, pruritus, delirium and even respiratory depression, which can prolong the length of stay of the patient or prevent their surgical recovery, in addition to a greater risk of causing chemical and respiratory dependence[24]. In addition, excessive use of NSAIDs after CS is known to increase the risk of acute kidney injury and myocardial infarction[23].

Regarding the neuropathic aspect of pain after CS, in a study that evaluated the presence of neuropathic pain 6 months after surgery, it was observed that 10 patients (8.1%) out of a total of 122 had a neuropathic aspect according to the LANSS scale[25]. This data corroborates the findings in the present study, since a prevalence of neuropathic pain of 7.6% was found in patients evaluated by the same scale.

The etiology and pathogenesis of delirium after surgeries are not fully understood. Drug-induced delirium has been reported, especially concerning drugs such as opioids, which have been associated with an increased risk of delirium. On the other side, undertreated acute pain is also a predisposing factor for delirium[26].

This study had important drawbacks. As this was an observational, cross-sectional study with data collection from medical records and questionnaires, the causality observed between exposure to risk factors and pain and delirium outcomes have not the same degree of evidence when compared to longitudinal studies. Moreover, the data was obtained through operator-dependent medical records, which is vulnerable to information bias. Furthermore, this was a study carried out in a center with a single team of surgeons, intensivists, and anesthesiologists, which can be biased when extrapolating data to other centers.

The reduction in surgical volume due to the pandemic of Covid-19 led to a small number of patients evaluated in the study, which hampered the statistical analysis and limited the possibility of making more significant inferences. In addition, analgesic drugs were prescribed at medical discretion, which may have hampered pain assessment, as only patients who reported having more intense pain received opioids, reducing the pain intensity of these patients at the time of analysis.

Another important limitation is related to the fact that this study only evaluated the prevalence of delirium, since a single approach was performed to the individuals studied, on the 1st PO day. It would have been ideal if this research could have also assessed the incidence of delirium in this population carrying out follow-up during hospitalization, which was not possible considering the logistics established for data collections.

Finally, the dosage of drugs used in analgesia was not verified to assess the difference between the doses of patients who used opioids and those who did not use them to control pain, impairing the analysis and possible inference of this study regarding this topic.

CONCLUSION

Delirium in the postoperative period of cardiac surgery has a significant prevalence in the patients evaluated in this study, with results similar to previous studies involving this complication and this population. The number of previous comorbidities and advanced age (greater than 65 years) were risk factors for postoperative delirium. Pain was present in more than 70% of evaluated patients, predominantly over the sternotomy incision region, with no relationship of lower pain intensity between the use of opioids and non-opioids. Pre- and postoperative assessments of the patient's risk factors, followed by early assessment and management of both delirium and postoperative pain, may play an important role in reducing cardiac surgery complications.

AUTHORS' CONTRIBUTIONS

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