Original Paper

Association Between Oxidative Stress Markers and Postoperative Delirium in Elderly Patients Undergoing Oncologic Surgery

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ABSTRACT: Introduction: Postoperative delirium is a frequent complication associated with various types of surgery, particularly among older adults. It is thought that postoperative delirium is the result from an imbalance caused by the overproduction of free oxygen radicals. Objective: To determine an oxidative stress marker that can predict the onset of postoperative delirium in patients undergoing laparoscopic urological surgery for malignant conditions. Materials and Methods: The study involved 29 male and female patients who underwent transperitoneal laparoscopic radical surgery for localized kidney cancer between 2021 and 2024. Blood samples were collected at three intervals: before general anesthesia induction, immediately after surgery, and 24 hours postoperatively. The levels of malondialdehyde (MDA), glutathione peroxidase (GSH) and superoxide dismutase (SOD) were measured. The occurrence of postoperative delirium was evaluated using the Confusion Assessment Method for the ICU (CAM-ICU). Results: All cases of postoperative delirium emerged within the first seven days after surgery. Out of 29 patients, 11 developed postoperative delirium. Patients in the delirium group exhibited significantly higher malondialdehyde levels at the end of surgery compared to those without delirium ($p<0.05$). Additionally, superoxide dismutase levels measured before anesthesia induction differed significantly between the delirium and nondelirium groups ($p<0.05$). Also, glutathione peroxidase (GSH) at the end of surgery significantly decreased in delirium group ($p<0.05$). Conclusion: The likelihood of developing postoperative delirium in patients undergoing laparoscopic urological surgery for malignant conditions can be anticipated by evaluating oxidative stress markers levels.

KEYWORDS: *Postoperative delirium, superoxide dismutase, malondialdehyde, glutathione peroxidase.*

Introduction

Postoperative delirium is named also acute cognitive dysfunction, and is referred to a postoperative complication.

Postoperative delirium is most frequent in older adults, with incidence rates of 15-53%, and up to 80% in elderly patients requiring intensive care.

One study shows that among elderly patients, one-fourth of those diagnosed with postoperative delirium do not survive more than 6 months after onset of this complication [1].

Although the precise causes for the high frequency of postoperative delirium in older patients are not well understood, numerous mechanisms have identified.

These mechanisms include decreased blood flow or oxygen to the brain tissue, imbalances in main neurotransmitters, such as noradrenaline and acetylcholine, abnormal amino acid metabolism, antecedent of different cognitive impairments, and low antioxidants levels [2].

Oxidative stress, which is defined as an imbalance between prooxidative species and antioxidants, has been proposed as a causative risk factor.

The levels of serum markers such as malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPX) reflect lipid peroxidation and antioxidant defences, respectively [3].

This study assesses the correlation between these markers and postoperative delirium incidence in patients undergoing laparoscopic surgeries for early-stage renal neoplasms.

Our study aims to identify oxidative stress markers that could predict the onset of postoperative delirium in major oncological urological surgery patients.

Methods

This study was conducted at the Clinical Emergency Hospital of Craiova over three years (2021-2023).

Ethics committee approval no. 81/07.04.2020 was obtained prior to study start.

After written informed consent was obtained, we enrolled 29 patients aged ≥65 years, diagnosed with early-stage renal malign tumours, scheduled for laparoscopic surgeries.

Study Design: the study is prospective, randomized clinical trial.

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Inclusion Criteria: age ≥65 years, ASA score I-III, elective laparoscopic surgery for renal neoplasms.

Exclusion Criteria: severe comorbidities or pre-existing cognitive impairments.

Patients underwent standardized general anesthesia and were monitored for hemodynamic and ventilation parameters.

Blood samples were drawn at three intervals: preoperatively, immediately postoperatively, and 24 hours postoperatively.

Malondialdehyde (MDA) was measured via HPLC (µmol/L), superoxide dismutase (SOD) was assessed using photometric methods (U/g Hb), and glutathione peroxidase (GPX) was evaluated through enzymatic assays (U/L).

Postoperative delirium (POD) was diagnosed using the Confusion Assessment Method for ICU (CAM-ICU), with assessments conducted thrice daily postoperatively.

Statistical analysis included t-tests for parametric data and correlations between oxidative stress markers and POD incidence.

Results

Demographics

The study included 29 patients with no significant differences in baseline demographics, such as age, BMI, sex, living area, or medical history, between groups (Table 1).

Table 1. Demographic data of patients (data expressed as mean±SD or percentage).

Parameter	Non delirium group (n=18)	Delirium group (n=11)	p
Age(years)	68,16±2,61	67,90±2,50	ns
Height (cm)	171,05±7,76	167,81±7,93	ns
Weight (kg)	78,38±14,07	73,00±10,87	ns
BMI	26,67±4,10	26,33±2,40	ns
Sex (M/F)	62,5%/37,5%	66,7%/33,3%	ns
Rural/Urban	62,5%/37,5%	66,7%/33,3%	ns

There were no significant differences among the delirium or nondelirium groups regarding surgery time, heart rate, mean arterial pressure, end-tidal carbon dioxide, peripheral oxygen saturation, duration of anesthesia, and intraoperative complications (p=ns) (Table 2).

Table 2. Parameters monitoring perioperative (data expressed as mean±SD).

Parameter	Non delirium group (n=18)	Delirium group (n=11)	p
Heart rate(beats/min)	94,83±10,53	91,72±10,23	ns
MAP (mmHg)	96,85±7,64	97,75±5,94	ns
EtCO2 (mmHg)	39,44±3,83	40,90±2,77	ns
SpO2 (%)	99,55±0,70	99,45±0,82	ns
Operation time (min)	158,33±9,54	159,54±12,54	ns
Anesthesia time (min)	182,22±8,44	187,27±15,71	ns
Intraoperative complications	2/18	1/11	ns
Length of stay (days)	5,44±1,91	8,90±1,75	p<0,01
Postoperative delirium incidence (N/Y)	62,07%	37,93%	ns

All patients with delirium from both groups developed the condition on the first and 7 postoperative days.

Incidence of postoperative delirium in our study was 37,93%.

Oxidative Stress Markers

MDA Levels

In nondelirium group preoperative MDA was 3,24±0,78µmol/L (non-delirium) and 3,18±0,52µmol/L (delirium).

Levels rose significantly postoperatively to 6,50±1,00µmol/L (non-delirium) and 7,51±0,85µmol/L (delirium) and gradually decreased to 5,29±1,20µmol/L and 5,83±1,05µmol/L, respectively, at 24 hours (Table 3).

Table 3. Malondialdehyde levels (MDA) (data are expressed as mean±SD).

Marker	Non delirium group (n=18)	Delirium group (n=11)	p
MDA preop (µmol/l)	3,24±0,78	3,18±0,52	ns
MDA end of surgery (µmol/l)	6,50±1,00	7,51±0,85	p<0,05
MDA postop 24h (µmol/l)	5,46±1,15	6,47±0,98	ns

SOD and GPX levels

Both SOD and GPX activities decreased postoperatively in both groups, with the lowest levels observed in patients with POD.

Superoxide dismutase levels in the nondelirium group before anesthesia induction were 2202,5±100,72U/g Hb.

Superoxide dismutase levels in the delirium group before anesthesia induction were lower but not significantly statistic, 2008,72±92,36U/g Hb.

The SOD levels decreased at the end of surgery for both groups, nondelirium and delirium, to 1967,50±125,96U/g Hb, respectively 1820,27±59,32U/g Hb, and increased after 24 hours to 2077,94±96,20U/g Hb, respectively 2063,64±118,30U/g Hb (Table 4).

Table 4. Superoxide dismutase levels (SOD) (Data expressed as mean±SD).

Marker	Non delirium group (n=18)	Delirium group (n=11)	p
SOD preop (U/g Hb)	2202,5±100,72	2008,72±92,36	p<0,01
SOD end of surgery (U/g Hb)	1967,50±125,96	1820,27±59,32	p<0,01
SOD postop 24h (U/g Hb)	2077,94±96,20	2063,64±118,30	ns

Glutathione peroxidase (GPX) levels in the nondelirium group before anesthesia induction were 4460,61±428,13U/l.

Glutathione peroxidase levels in the delirium group before anesthesia induction were lower but not significantly statistic, 4330,55±300,48U/l.

The GPX levels decreased at the end of surgery for both groups, nondelirium and delirium, to 3286,78±205,39U/l, respectively 3572,00±238,51U/l, and increased after 24 hours to 3865,22±157,57U/l, respectively 3857,55±249,21U/l (Table 5).

Table 5. Glutathione peroxidase (GPX) (Data expressed as mean±SD).

Marker	Non delirium group (n=18)	Delirium group (n=11)	p
GPX preop (U/l)	4460,61±428,13	4330,55±300,48	ns
GPX end of surgery (U/l)	3286,78±205,39	3572,00±238,51	p<0,01
GPX postop 24h (U/l)	3865,22±157,57	3857,55±249,21	ns

POD was diagnosed in 11 patients with an incidence of 37,93%.

Patients with POD had significantly higher postoperative MDA levels and lower SOD and GPX activities compared to non-delirium counterparts (p<0.05).

Patients with POD had extended hospitalizations (9,09±0,83 days) compared to non-delirium patients (6,28±1,27 days), (p<0.05).

Among all oxidative stress markers, the one with the best correlations, as well as the highest specificity and sensitivity, is preoperatively determined superoxide dismutase, which most accurately indicates the risk of a high-risk patient developing postoperative delirium (Figure 1).

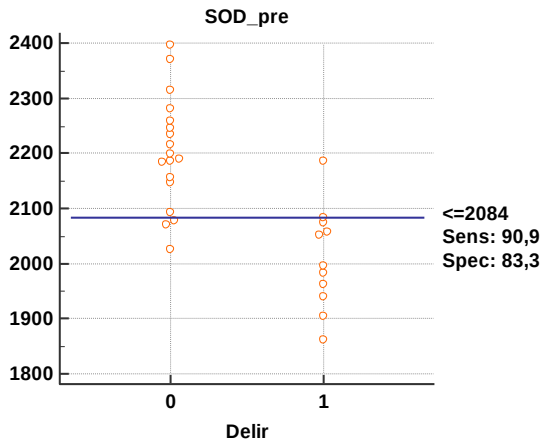

Figure 1. Correlation between preoperatively superoxide dismutase (SOD) and preoperative delirium.

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Our findings suggest that preoperative SOD measurement can be a valuable predictor for identifying patients at risk of developing postoperative delirium, with a high degree of accuracy and reliability based on the provided sensitivity and specificity values.

The cut-off value for preoperative superoxide dismutase (SOD) in predicting postoperative delirium is established at ≤2084U/g Hb with a sensitivity of 90.9% and a specificity of 83.3%.

Significant ROC comparisons between oxidative stress markers and the occurrence of postoperative delirium reveal that the preoperative determination of superoxide dismutase, or the immediate postoperative measurement of superoxide dismutase, malondialdehyde, and glutathione peroxidase, can indicate the relative risk of developing this syndrome in high-risk patients (Figure 2).

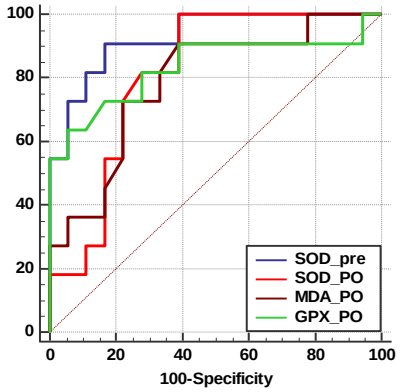

Figure 2. ROC curves comparisons between oxidative stress markers and the occurrence of postoperative delirium.

The ROC curves demonstrate that preoperative superoxide dismutase **(**SOD_pre) is the most effective oxidative stress marker for predicting postoperative delirium, with immediate postoperative superoxide dismutase (SOD_PO) also showing strong performance.

For early diagnosed postoperative delirium, postoperative malondialdehyde (MDA_PO) and postoperative glutathione peroxidase (GPX_PO) are less effective but still contribute.

The ROC curve of preoperative superoxide dismutase (SOD) may prove a high AUC, indicating it is a strong predictor of postoperative delirium.

The relative risk of the immediate postoperative levels of malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione peroxidase (GPX) indicates the same issue with variable sensitivity and specificity.

Discussion

The results of our study demonstrate that oxidative stress has an important role in the pathophysiology of postoperative delirium (POD), especially the biomarkers malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione peroxidase (GPX).

The levels of malondialdehyde (MDA) in this study are high, showing high level of lipid peroxidation that occurs during surgery especially in the early postoperative period.

The products of lipid peroxidation, such as malondialdehyde (MDA), are toxic and lead to cellular dysfunction, inflammation, and neuronal injury and are associated with postoperative delirium.

This is correlated with previous research that has identified oxidative stress as a cause of cognitive decline and neuroinflammation in the perioperative period [4].

This is especially true for elderly patients since postoperative delirium is a common problem in surgical care, which is characterized by prolonged hospital stays, increased dependency, and higher rates of morbidity and mortality.

It usually comes on hours to days after surgery and is often reversible [5,6,7].

Delirium has three subtypes: hyperactive, hypoactive, and mixed.

Hyperactive delirium is manifested by agitation, and violence, patients trying to remove even medical tubes or lines.

Hypoactive delirium is characterized by lethargy, apathy, and decreased responsiveness.

Mixed delirium includes a combination of these two types of delirium [8,9,10].

The high prevalence of postoperative delirium in elderly patients is not yet fully understood, but several mechanisms have been proposed.

One potential mechanism involves an imbalance between oxidative stress and antioxidant defense systems [11,12,13].

Research on the incidence of postoperative delirium in laparoscopic major urologic surgeries is limited.

These minimally invasive techniques have gained popularity over the last few decades for treating renal and uterine cancers.

Laparoscopic surgery is favored over traditional open surgery because of its numerous benefits, including less physical stress on the patient [14].

Operative stress, which can lead to oxidative stress, is less pronounced in laparoscopic techniques compared to open surgical methods.

This reduced stress response has been associated with lower oxidative damage in laparoscopic procedures used for renal surgeries [15,16,17].

Oxidative stress occurs when the production of reactive oxygen species exceeds the capacity of antioxidant defenses, leading to cellular damage.

It represents an imbalance between oxidant and antioxidant biomarkers [18].

Measuring both oxidative and antioxidant markers provides a comprehensive evaluation of oxidative stress [19].

In our study, malondialdehyde (MDA) was used as a marker of oxidative stress, while superoxide dismutase (SOD) and glutathione peroxidase (GPX) represented antioxidant activity.

The relationship between these markers, and the occurrence of postoperative delirium in laparoscopic surgeries for urological malignancies was examined.

MDA levels rose significantly immediately after surgery in both delirium and non-delirium patients, followed by a gradual decrease.

These findings are consistent with studies such as those by Rifat Karlidag et al., who examined predictors of delirium in patients undergoing cardiopulmonary bypass surgery [11] and Mu-Huo Ji et al., who studied postoperative delirium in orthopaedic surgery patients [20].

Preoperatively, SOD and GPX levels were lower in patients who developed postoperative delirium.

Postoperatively, SOD and GPX levels showed a significant decline in all patients.

At 24 hours post-surgery, both levels improved across all groups, suggesting a recovery of antioxidant defenses.

These results highlight the role of oxidative stress in the development of postoperative delirium.

Patients with delirium exhibited lower preoperative antioxidant defenses, as indicated by reduced SOD levels.

The study also confirms the findings of Konstantinos Kalimeris [21].

Assessing preoperative SOD levels may help predict the risk of developing postoperative delirium.

Patients identified as high-risk could benefit from prophylactic interventions such as low-dose haloperidol, the standard treatment for delirium.

Additionally, administering antioxidant agents preoperatively may further reduce the risk of delirium by enhancing the body's ability to counter oxidative stress [3].

The observed correlation between elevated postoperative MDA levels and POD aligns with hypotheses suggesting a link between oxidative damage and neuroinflammation.

Surgery-induced stress can disrupt the blood-brain barrier, allowing systemic inflammatory mediators and ROS to enter the central nervous system (CNS).

This results in neuroinflammation, microglial activation, and neuronal apoptosis, processes implicated in the development of POD [22].

The reduction in SOD and GPX activity, observed predominantly in patients with POD, further emphasizes the vulnerability of the elderly population.

Age-related declines in antioxidant capacity, coupled with the increased oxidative burden of surgery, create a "double-hit" scenario that predisposes this group to cognitive dysfunction [12].

The findings highlight several actionable strategies for managing POD risk in elderly patients, such as: perioperative administration of antioxidants such as N-acetylcysteine or vitamin C could potentially mitigate oxidative stress, as supported by earlier studies on antioxidant therapies.

Also, close monitoring of oxidative stress markers and adjustments in ventilation strategies (e.g., limiting CO2 insufflation during laparoscopy) may help reduce ROS production.

Study Limitations and Future Directions

While this study offers valuable insights, several limitations should be acknowledged: the small cohort size limits the generalizability of the findings.

Larger studies are needed to validate these results. The study only evaluated oxidative stress markers up to 24 hours postoperatively.

Longitudinal studies examining the persistence of oxidative stress and its long-term cognitive impacts are warranted.

While MDA, SOD, and GPX are robust markers of oxidative stress, incorporating additional markers (e.g., 8-isoprostanes or advanced oxidation protein products) may provide a more comprehensive picture.

Future research should focus on exploring the molecular pathways linking oxidative stress and neuroinflammation, as well as the efficacy of targeted interventions in reducing POD risk.

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Conclusions

This study emphasizes the impact of oxidative stress, on the development of postoperative delirium (POD).

Postoperative delirium incidence can be predicted by preoperative superoxide dismutase levels assessment in older patients undergoing laparoscopic surgery for malignant urologic pathologies.

In conclusion, this study underscores the importance of oxidative stress in postoperative delirium and suggests practical approaches for its prevention.

Conflict of interest

None to declare.

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