



Which is the Prognostic Value of the Mini Mental State Examination Test in Surgical Oncology?

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Abstract

Introduction: Cancer patients are usually subjected to numerous surgeries during their course of treatment. Recent studies suggest that anesthetic drugs such as propofol, benzodiazepines, and opioids are linked to cognitive impairment.

Aim: The aim of the study was to show and compare the cognitive function of oncology patients who have undergone surgery and have been sedated with propofol, fentanyl and benzodiazepines.

Materials and methods: In order to determine whether the cognition of oncological patients is being impaired, a mini-mental state examination (MMSE) test was obtained 6 to 24 hours pre- and postoperatively for the duration of one month from 8 eligible oncological patients and 7 non-oncological ones. Afterwards, the data were statistically processed with SPSS version 25.0 (Chicago, Ill. the USA).

Results: The analysis shows that there is statistically significant difference in the preoperative MMSE scores between oncological and non-oncological patients.

Conclusions: Oncological patients compound a sensitive group for cognitive dysfunction, and indeed, MMSE test could be useful for cognitive evaluation. The present sample, however, is small, and the results could not be generalized. Therefore a more extensive study is needed.

Keywords

benzodiazepines, MMSE, oncology, propofol, surgery

INTRODUCTION

Oncology patients, more often than not, have to undergo numerous surgical interventions. However, the way each patient perceives surgery is exceptionally subjective. The mental activity of understanding and perception is known

as cognition, and it is defined as “a mental action or process of acquiring knowledge and understanding through thought, experience, and the senses”. It encompasses many aspects of intellectual functions and processes such as attention, the formation of knowledge, memory and working memory, judgment and evaluation, reasoning and

“computation”, problem-solving and decision making, comprehension and production of language.

Cognitive evaluation could be done by applying different examination methods, one of which is the Mini-Mental State Examination (MMSE). During the performance of an MMSE test, an individual is answering several questions covering the entire spectrum of the cognitive evaluation. Based on the final score, the cognitive function of the participant could be intact, mild, moderate or severely impaired. Recently, studies have been reporting an effect of propofol, benzodiazepines and opioids on the cognitive function of the patients.

Propofol is one of the most commonly used sedation drugs used for anesthesia. Its primary mechanism of action is to create unconsciousness, by stimulating γ -aminobutyric acid type A (GABA A) receptors, thus increasing the affinity for GABA and permeating the passage of chloride ions. The latter provokes hyperpolarization of the cell, causing a delay of the deactivation and metabolism of GABA.¹ Benzodiazepines also stimulate GABA ARs receptors in the same way as propofol does. Since GABA is an inhibitory neurotransmitter, involved in brain signalling and regulating, including network’s synchronization, behaviour, and memory, its activation results in sedation and amnesia.²

On the other hand, opioids are substances stimulating different receptors such as M, D and K receptors, located in the brain, spinal cord, lungs, heart, etc. Fentanyl is an opioid drug stimulating the Mu receptors, and it is often used for pain management, even during surgical operations. These receptors are linked to reward brain circuits, emotion and behavior.

These drugs are commonly used in surgery and until recently it is believed to cause cognitive impairment. However, there is a lack of published data on the cognitive function of the cancer patients postoperatively.

AIM

The current study has the aim to show the role of the MMSE in the evaluation of the cognitive function of the on-

colony patients who have undergone surgery and have been sedated with propofol, fentanyl and benzodiazepines.

MATERIALS AND METHODS

Data collection and data selection

The study was conducted in the Second Department of Surgical Oncology at Metaxa Anti-Cancer Hospital. Surgical oncology patients are usually referred to our clinical department and rarely non-oncological patients with benign pathologies requiring surgical treatment.

From the initial sample of 32 patients, two patients died, one had a tracheostomy, one patient was admitted to the intensive care unit (ICU), three were treated with a local anesthetic, seven were lost for the postoperative MMSE, and three refused to take the test postoperatively, and therefore, were excluded from the study. Fifteen patients were included for the final analysis, 8 of whom were operated because of malignancy and 7, operated due to other pathology (**Table 1**).

In order to answer the stated question whether the general anesthesia has any impact on the cognitive function on the patients, a Mini-mental State Examination (MMSE) test was applied pre- and postoperative. The choice of the MMSE test was based on the physician/author’s familiarity with the test.

MMSE is a clinical test used to detect cognitive impairment and to evaluate cognitive function. Typically, it is used to detect dementia. In the current study, MMSE was used to detect cognitive impairment of the patients who underwent surgery with general anesthesia with propofol and benzodiazepines.

The enrolment of patients was performed for a period of 1 month (October 2018 - November 2018). Inclusion criteria were patients who agreed to proceed with the MMSE; patients who underwent general anesthesia with propofol; patients who received benzodiazepines as pre-anesthetic medication, and patients over 18 years of age.

In order to provide the same conditions of examination for the patients, the same health provider performed the

Table 1. MMSE scores pre- and post-operatively

	Group statistics				
	Group	N	Mean	Std Deviation	Std Error Mean
Post-op MMSE	1	7	25.29	3.861	1.459
	2	8	27.50	2.000	0.707
Pre-op MMSE	1	7	24.14	3.288	1.243
	2	8	28.25	1.982	0.701
Age	1	7	53.43	23.720	8.965
	2	8	64.63	12.961	4.582

Group 1: oncological group; Group 2: non-oncological group; Pre-op: preoperative scores; Post-op: postoperative scores

procedure 6 to 24 hours before surgery and 6 to 24 hours after surgery, taking under consideration that propofol needs up to 24 hours to wash out of the organism.

Fifteen patients were included for analysis. They were divided into non-oncological and oncological group (7:8) or group A and group B. Furthermore, the sample was divided into a female and male group (8F:7M) and age groups >65 years and ≤65 years, respectively. Mean age of the participants was 59.4 years. The oncological group included breast cancer and stomach cancer patients, while the non-oncological: cholelithiasis and herniation.

All of the participants received propofol as a sedation drug and the same pre-anesthetic medications (opioid, anti-emetic and benzodiazepines). The entire sample received the same analgesics postoperatively, and no one received morphine.

Statistical analysis

The data were analyzed with SPSS version 25. The α for the p-value was set up at 0.05.

RESULTS

Mean MMSE score preoperatively and postoperatively was 26.33 and 26.47, respectively. The MMSE scores are illustrated in **Table 1**.

Mann Whitney U test

Mann-Whitney U test was performed on the selected categories. Initially, it was made for the comparison of the two basic categories – A and B. The results, as illustrated in **Table 2**, are showing a significant difference in the preoperative MMSE scores.

The same analysis was performed for the comparison of the categories divided by age and sex, showing no significant difference between the preoperative, or the postoperative MMSE scores.

Wilcoxon signed-rank test

Wilcoxon ranked test was initiated on the categories, as mentioned above, showing no significant difference between preoperative and postoperative MMSE scores.

Correlation analysis

The correlation analysis for the entire sample showed a statistically significant positive correlation between pre- and postoperative MMSE score in the younger female age group (**Table 3**).

For the oncological and non-oncological groups, there was no statistically significant correlation.

Table 2. Mann Whitney U test for an independent sample. Group A vs. Group B

	Independent Samples Test							
	Levene's test for equality of variances		t	df	Sig. (2-tailed)	Mean difference	Std. error difference	Lower
	F	Sig.						
POST OP	1.689	0.216	-1.424	13	0.178	-2.214	1.555	-5.575
			-1.366	8.736	0.206	-2.214	1.621	-5.899
PRE OP	0.224	0.644	-2.977	13	0.011*	-4.107	1.379	-7.087
			-2.879	9.591	0.017	-4.107	1.427	-7.304
Age	5.257	0.039	-1.156	13	0.268	-11.196	9.684	-32.118
			-1.112	9.017	0.295	-11.196	10.068	-33.966

*Significant p-value

Table 3. Correlation analysis

		Preoperative MMSE score females<65	Postoperative MMSE score females <65
Postoperative MMSE score females < 65	Pearson's <i>r</i>	0.926	—
	<i>p</i> value	0.012	—
Age females<65	Pearson's <i>r</i>	0.029	-0.130
	<i>p</i> value	0.482	0.582

DISCUSSION

Cognition is a higher form of mental activity and perception, where the self is separated from the surroundings, though synchronously receiving information, thus creating solutions or plan for potential actions.³ It comprises six essential functions and processes, including concentration, awareness, memory, language skills, learning, and a process known as reflective cognition. It is believed that with age, there is a decline in the cognitive functions, including vocabulary, measurement and speed.⁴

Mini-Mental State Examination was introduced in 1975, and since then, it is continuously used for the assessment of the cognitive function.⁵ In the clinical practice, it is used to detect impairment, response to treatment and for evaluation of the course of the disease. The test can estimate a few parameters of the individual cognition – orientation, attention, memory, language and the ability to follow commands. Based on the answers given by the individuals, there are four established categories. The first category with scores equal to or greater than 24 points indicates normal cognition. The second category with scores ranging between 19 and 23 indicates mild cognitive impairment, followed by moderate cognitive impairment with scores between 10 and 18, and severe cognitive impairment with scores equal or below 9.

It has been observed that with age, there might be a decline of the cognitive ability.⁶ There are also studies supporting the fact that the cognitive function is more impaired among females than males.⁶ Moreover, people with declining cognitive function are also prone to develop dementia. Regarding the postoperative MMSE scores, Lingehall et al.⁷ suggests that declining postoperative scores are linked to increased incidence of dementia in the upcoming five years. Moreover, there is an association of the declining MMSE score to the existence of different diseases, including heart problems, diabetes and anemia.

In the current study, we observed that the preoperative MMSE scores between oncological and non-oncological patients were significantly different. This finding is supported by several studies, which report the impact of cancer itself on the cognitive function.⁸⁻¹¹ Moreover, it is estimated that around 11% to 35% of the affected patients before any other therapy suffer from breast cancer.^{8,12-14}

On the other hand, the MMSE scores among males and females for the entire sample were statistically equal, as well as the scores between both age categories. However, we observed a statistically significant correlation between pre- and postoperative MMSE scores in the younger female age group. A similar result was reported by Boos et al.¹⁵, who suggested that the only predictor of the postoperative scores are the preoperative ones.

Generally speaking, the cognitive recovery time after anesthesia depends on multiple factors. Propofol, fentanyl benzodiazepines, and N₂O are among the drugs that cause cognitive impairment.^{16,17}

Current concerns include the use of propofol as anesthetic drug for operations and its impact on cognition. It is believed that the neurotoxicity of the anesthetic drugs is tolerated better among younger patients because of their expectable better general condition, while others suggest that propofol is inducing developmental neurotoxicity in children.^{17,18} Brain metabolizes mainly glucose and lactate to pyruvate acid in the mitochondrial citric acid cycle (CAC) producing adenosine triphosphate (ATP) for its energy needs.¹⁹ Bains et al.²⁰ suggested that propofol induces mitochondrial depolarization by inhibiting the complex I-IV of the respiratory chain, thus reducing the manufacture of ATP. In this regard, Berndt et al.¹⁹ reported from his experiment that propofol inhibits complex II of the respiratory chain, leading to decrease in the rate of metabolism of oxygen consumption in the brain, decrease of the incidence and strength of gamma fluctuation and increase in the adenine dinucleotide (FAD) oxidation, thus producing toxicity. Qin et al.²¹ made a study where the enrolled sample was divided into propofol and sevoflurane sedation groups. In his study, the propofol group had at 24 hours after surgery higher levels of oxidative stress, measured by the levels of nicotinamide adenine dinucleotide phosphate (NADHP) subgroups in the peripheral blood. Moreover, the same group of propofol had lower rates of pulmonary activity, including vital capacity (VC), forced expiratory volume 1 (FEV1) and forced vital capacity (FVC) and lower MMSE scores, compared to the sevoflurane group.

The clinical effect of the drug is short, but it requires 2 to 24 hours to be fully eliminated from the body. According to the study conducted by Hoecker et al.²², there is no correlation between preoperative and postoperative MMSE score and propofol after 1 hour. Goswami et al.²³, in a comparative study of propofol and sevoflurane, reported that the MMSE scores were significantly different 1 hour immediately after surgery between the groups, and not significantly different after that. The current study observed no statistically significant difference in the MMSE scores 6 to 24 h after surgery.

Midazolam (benzodiazepine) and fentanyl are commonly used as premedication before different invasive procedures. Cok et al.²⁴ suggest that their combination is unnecessary because of the overly extensive sedation that they are causing. On the other hand, Prakash et al.²⁵ report that the combination of fentanyl, midazolam and propofol provides better conditions for anesthesia with no change in the MMSE scores.²⁶

The current study observed no statistically significant difference in the MMSE scores 6 to 24 h after surgery. However, we observed that the oncological group had an increase of the MMSE scores from 24 preoperatively to 25 postoperatively, while the non-oncological group had unchanged pre- and postoperative MMSE scores (mean MMSE = 28). A result implying that the cancer itself might be affecting the cognitive ability, while the anesthesia is unrelated factor for the cognitive function of the patients.

The study, however, presents a few limitations. Main limitation is the small study sample, discouraging the generalization of any of the results. Another limitation represents the small duration of patients' enrollment. For that reason, larger studies are highly needed.

CONCLUSIONS

The current analysis proposes that the cognitive function in oncological patients is indeed affected and MMSE test has for certain place in the evaluation of the cognitive function in surgical oncology. Whether the equality of the postoperative MMSE scores was due to the removal of the primary cancer, or due to the anesthesia could not be generalized in the present study; therefore, more substantial research is needed.

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Какова прогностическая ценность краткого теста психического состояния в хирургической онкологии?

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Резюме

Введение: Больные раком обычно подвергаются многочисленным операциям во время курса лечения. Недавние исследования показали, что анестетики, такие как пропофол, бензодиазепины и опиоиды, связаны с когнитивными нарушениями.

Цель: Целью исследования было показать и сравнить когнитивные функции онкологических больных, перенёвших операцию и получавших седативные препараты пропофолом, фентанилом и банзидиазепинами.

Материалы и методы: Чтобы определить, были ли нарушены когнитивные способности онкологических больных, тест на минимальное психическое обследование (ТМПО) проводился от 6 до 24 часов до и после операции в течение 1 месяца на 8 подходящих онкологических и 7 здоровых пациентах. Затем данные были статистически обработаны с помощью SPSS версии 25.0 (Чикаго, Иллинойс, США).

Результаты: Анализ показал, что существует статистически значимая разница в предоперационных результатах теста ТМПО между онкологическими и не онкологическими пациентами.

Заключение: Больные раком составляют чувствительную группу с точки зрения когнитивной дисфункции, и действительно, тест ТМПО может быть полезен для оценки когнитивной функции. Однако текущая выборка мала, и результаты нельзя обобщать. Это требует дополнительных исследований.

Ключевые слова

бензодиазепины, ТМПО, онкология, пропофол, хирургия
