ORIGINAL ARTICLE

Comparison of epidural analgesia combined with general anesthesia and general anesthesia for postoperative cognitive dysfunction in elderly patients

Günseli Orhun, M.D.,[1] Zerrin Sungur, M.D.,[1] Kemalettin Koltka, M.D.,[1]
Meltem Savran Karadeniz, M.D.,[1] Hacer Ayşen Yavru, M.D.,[1]
Hakan Gürvit, M.D.,[2] Mert Şentürk, M.D.[1]

[1]Department of Anesthesiology and Intensive Care, İstanbul University İstanbul Faculty of Medicine, İstanbul-*Turkey*
[2]Department of Neurology, Behavioral Neurology and Movement Disorders Unit, İstanbul University İstanbul Faculty of Medicine, İstanbul-*Turkey*

ABSTRACT

BACKGROUND: Cognitive dysfunction in the early postoperative course is common for the elderly population. Anesthetic management may affect postoperative cognitive decline. Effective analgesia, early recovery and modulation of the stress response are advantages of neuraxial blocks. This study aims to compare the effects of general anesthesia and the combination of general anesthesia with epidural analgesia for postoperative cognitive dysfunction (POCD). We hypothesized that neuraxial block combined with general anesthesia (GA) would have a favorable influence on POCD prevention.

METHODS: Patients above 60 years undergoing non-cardiac surgery were included in this randomized, prospective study and randomized into two groups. Patients in the first group (GI) were treated under GA, whereas in the second group (GII), epidural analgesia was combined with GA. Patients' cognitive function was assessed before and one week after surgery using a neuropsychological test battery. POCD was defined as a drop of one standard deviation from baseline on two or more tests.

RESULTS: A total of 116 patients were allocated for the final analysis. Demographic and operative data were similar between groups, except maximum pain scores, which were significantly higher in GI than GII (4.9±2.8 vs. 1.7±1.7; p<0.001, respectively). The incidence of POCD was comparable between groups (26% in GI and 24% in GII). Memory performance, visuospatial functions, and language skills tests were significantly higher in GII compared to GI.

CONCLUSION: General anesthesia and epidural analgesia combined with general anesthesia resulted in similar POCD in elderly patients undergoing abdominal surgery. However, in combined anesthesia group memory, language skills and visuospatial functions appeared to be better preserved. Effective pain control might contribute to preventing cognitive decline in some domains.

Keywords: Cognitive dysfunction; elderly; epidural analgesia; general anesthesia; postoperative pain.

INTRODUCTION

Postoperative cognitive dysfunction (POCD) is a common complication in elderly patients under general anesthesia, and also regional anesthesia.[1–3] POCD is commonly defined as some deficits in cognition and memory with a wide range of severity.[1,2] Patients may complain from mild impairment of concentration, difficulties in learning, decreased verbal abilities, and trouble in reasoning. The diagnosis is quite complicated and requires neuropsychological tests, although a unanimously accepted methodology is still lacking.[4] Cognitive decline may recover in early or late during the postoperative course or persist as a precursor of dementia, which will appear from months to years in susceptible subjects, without any recovery in the initial POCD phase.[5] Defined risk factors for patients are known as advanced age and lower educational

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Address for correspondence: Zerrin Sungur, M.D.
İstanbul Üniversitesi İstanbul Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, İstanbul, Turkey
Tel: +90 212 - 631 87 67 E-mail: zerrin_sr@yahoo.com

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level hence decreased cognitive reserve. Meanwhile, cardiac, major vascular, and hip fracture surgeries are generally associated with POCD.[5] The incidence of POCD for non-cardiac surgery varies from 5 to 40% in studies.[6] Moreover, it may reach 40 to 60% for cardiac and hip fracture procedures.[2,6]

The general etiology is currently unclear but seems probably multifactorial as established after the publication of the International Study of Postoperative Cognitive Dysfunction (ISPOCD) study twenty years ago.[1] Recent reports have pointed out an imbalance of the neurotransmitter system.[7] In the presence of decreased neurobiologic reserve (as may be seen in the elderly population), inflammatory mediators may contribute to the neurocognitive decline. Elevated postoperative cytokines are found to be associated with both early and mid-stage cognitive impairment for cardiac and non-cardiac surgery.[8] The effects of anesthetics have already been investigated in previous studies; general anesthesia was often compared to regional methods for appropriate surgery,[3,9] with the negligible incidence of POCD between two techniques. Volatile anesthetics were blamed for amplifying effects of cerebral insults, enhancing neuronal apoptosis, or even causing irreversible cerebral damage in experimental studies. However, results from human studies with inhalational anesthetics are controversial, some with favorable,[10] some with poorer outcomes.[11] Neuraxial blocks offer some advantages, such as adequate pain control, modulation of stress response triggered by surgery, early mobilization. Neuraxial block is-mostly investigated in hip replacement surgery and found to be associated with a similar prevalence of POCD compared to general anesthesia.[12,13] Epidural analgesia seems, however, suitable for the elderly population as it allows a reduction in both preoperative anesthetics and perioperative opioid use (which may affect cognitive decline via hyperalgesic effects, sleep disturbance), thereby allowing early discharge.

This study aims to compare the effects of general anesthesia and epidural analgesia-general anesthesia combination for elderly patients undergoing non-cardiac surgery on cognitive function. We hypothesized that neuraxial block combined to general anesthesia would have a favorable influence on POCD prevention compared to general anesthesia alone.

MATERIALS AND METHODS

After approval of the Institutional Review Board (2007/2607), patients undergoing non-cardiac elective surgery were enrolled in this prospective, double-blind, randomized study. Investigators who treated patients in the perioperative period (KK, MSK, AY) were unaware of cognitive results, and vice-versa two researchers (GO, HG) who were in the neurological evaluation did not participate in the perioperative course. The written informed consent was obtained from each participant after a full explanation of the procedure. Other inclusion criteria were as follows: patients above 60 years old; surgical procedures lasting more than one hour; and at least four days of hospital stay. The exclusion criteria were determined as history of major psychiatric disease and dementia or any disease of the central nervous system (meningitis and encephalitis, brain tumors, neurodegenerative, inflammatory, cerebrovascular disease) according to medical records; patients with a preoperative Mini-Mental State Examination (MMSE)[14] score below 23; prior neurosurgical, vascular or cardiac surgeries; drug or alcohol dependence; speech disturbances; vision and hearing impairment; inadequate use of native language; patient's refusal to participate to the study; and any contraindications for epidural analgesia. Any patient, who would require postoperative ICU stay, was also excluded from this study.

Patients' demographic data (age, gender, co-morbidities, education level) were recorded at the time of enrollment in the study. American Society of Anesthesiologists (ASA) physical status was also recorded. The ASA scale is the most commonly used system for the assessment of the physical status of patients undergoing surgery, as it is easy to perform and a good predictor of perioperative morbidity or mortality. No premedication was administered before surgery. In the operating room, eligible patients were randomly assigned into two groups via the sealed envelope technique. For the first group (GI), patients were treated solely under general anesthesia (GA), whereas in the second group (GII), epidural analgesia (EA) was combined with GA. Routine monitoring included ECG, noninvasive arterial pressure, and pulse oximeter (Horizon2000, Mennen Medical, Rehovot, Israel) for both groups. For GII, an epidural catheter (B. Braun, Melsungen, Germany) was inserted through the L2-3 or L3-4 intervertebral space, and placement of the catheter was verified by 3 ml of 2% lidocaine 1/200.000 adrenaline.

In both groups, anesthesia induction was achieved with propofol (2–3 mg/kg), sufentanil (0.15–0.2 μg/kg) and rocuronium (0.6–0.9 mg/kg). Desflurane was administered in a mixture of 50% O_2 with 50% NO_2 for maintenance with sufentanil and rocuronium bolus doses according to patients' requirements. Depth of anesthesia was monitored throughout surgery with bispectral index (BIS) (A-2000 BISTM monitor; System rev.2.1, AspectTM Medical Systems, Inc., Norwood, MA, USA). The desflurane concentration was adjusted to maintain a BIS value between 40 and 50.

Postoperative analgesia was achieved with an opioid via intravenous patient-controlled analgesia pump in GI (Abbott Pain Management Provider; Abbott Laboratories, Istanbul, Turkey). The same pumps provided postoperative analgesia in GII via the epidural route with a mixture of opioids and local anesthetic.

Operative data (type and duration of surgery, duration of anesthesia, transfusion requirement) were noted. Adverse events were defined as hypotension, hypoxia, serious bleeding, vasopressor therapy, and unplanned intensive care unit

stay. Emergent need for reoperation during the study period, removal of epidural catheter was determined as perioperative exclusion criteria. Pain evaluation with visual analogue scale (VAS), length of hospital stay, and multisystemic complications (such as pneumonia, dysrhythmia, myocardial ischemia, urinary infection, delirium) were followed during the postoperative period.

Neuropsychological Assessment

Initially, patients were evaluated with a preliminary MMSE to exclude subjects fewer than 22 points. If patients scored equal or more than 23 on the MMSE, they were considered eligible for this study and were assessed with a brief neuropsychological test battery, designed with the purpose of covering all cognitive domains, on the one hand, and easily applicable by a clinician, on the other hand, not necessarily demanding an expert neuropsychologist. Thus, the battery was composed of many bedside mental status tests and a number of practical formal neuropsychological tests: The Wechsler Memory Scale-Revised (WMS-R) - Logical Memory Subtest (as a measure of episodic memory, with two different stories (A and B) pre-and postoperatively), the Clock Drawing Test (as a measure of executive functioning),[15] the Word List Generation Test (as a measure of sustained attention and language), the WMS-R-Digit Span Subtest (as a measure of global attention and working memory), and the Interlocking Finger Test (as a measure of visuospatial functions).[16] The episodic memory measure, which is called the Logical Memory subtest in WMS-R, is comprised of two different short stories, thus preventing the learning effect when repeated post-operatively. They are identically scored according to the number of items recalled by the subject out of the total number possible. Short-term free recall is the number of recalled items from the story immediately after the examiner, long-term free recall the number of recalled items from the story after a twenty minutes delay-period, during which other tests were performed. Among the various scores, the delayed free recall score is used as the measure. WMS-R was standardized in Turkish, and normative scores for its various subtests are available.[17] The executive function measure, the Clock Drawing Test, is a practical bedside mental test, which is qualitatively evaluated in clinical practice according to the placement of digits within a circle and then the placement of arms showing the demanded time. However, quantified versions of it have been developed for research purposes. We used the 10-point version developed by Manos and Wu standardized in Turkish by Emek Savaş et al.[18] in this study. Category fluency is used as the Word List Generation Test. Our version was the naming of as many animals as possible within one minute. This version was standardized in Turkish by Tumac as a master's thesis.[19] WMS-R Digit Span Subtest is comprised of reciting of the heard random digits by the subject first in the same order (forward span-FS) and then in the reverse order (backward span-BS), and the last number of successfully recited digits makes the span. We used FS+BS as a measure. The Interlocking Finger Test is a practical bedside test for visuospatial functions. The subject is instructed to imitate the hand postures of the examiner. These postures are not certain gestures, do not convey any symbolic message, and thus they are seen for the first time by the subject. We used five such postures and scored each as 2, for a correct imitation, as 1, for not exactly correct, yet attempted and resembling imitation and as 0, for unattempted or having no resemblance. This test has not been standardized in Turkish.

Neuropsychological tests were first performed 2–3 days before surgery (baseline) and seven days after the operation. All evaluation was conducted by the same research investigator who was blinded to intraoperative anesthetic management (G.O.) and who was trained and supervised by the study consultant (H.G.) from the Department of Neurology during the entire study period. The neuropsychological test battery lasted approximately 45 minutes. All tests were administered at the same time of the day and the same location, a private room at surgical service.

Postoperative cognitive dysfunction is defined according to decline for more than one standard deviation from baseline on two or more neuropsychological tests, as described by Höcker et al.[20] in their study. The standard deviation (SD) of each preoperative test was calculated, and the number of patients who deteriorated or improved postoperatively was determined.

Statistical Analysis

The results of this study, SPSS 19.0 for WINDOWS software were used for statistical analysis. In assessing the study data, numerical values were shown as mean ± SD and compared via the student's t-test (cognitive test results for inter and intragroup analysis). Categorical data were expressed as number and percentage; compared with Fischer's exact test.

Sample Size

Our preliminary results showed that 41% of geriatric patients operated under general anesthesia fulfill this definition of POCD.[20] To detect a difference of at least 20% in this proportion at a significance level of 5% (α=0.05) and a probability of 90% (β=0.10), power calculations revealed a sample size of n=55 per group.

RESULTS

We included 129 patients meeting inclusion criteria, and 116 of them completed this study with 57 in GI and 59 in GII (Fig. 1). Demographic and perioperative data were similar between groups; except pain scores, which were significantly lower in GII ($p<0.001$) (Table 1). Perioperative hypotension was treated initially with the crystalloid bolus, and non-responder to volume therapy was treated with the vasopressor infusion. None of the hypotensive episodes lasted more than five minutes. Adequacy of pain therapy was evaluated with

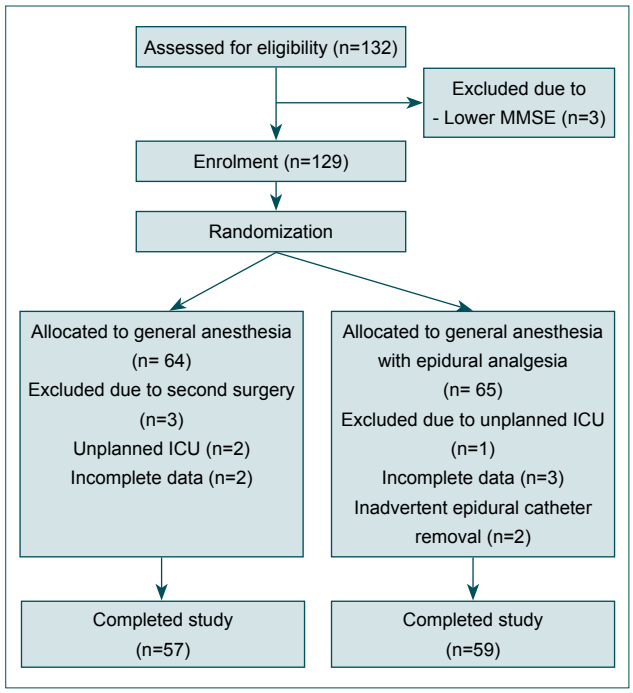

Figure 1. Flow diagram summarising patient enrolment and randomization. MMSE: Mini-Mental State Examination; ICU: Intensive care unit.

the worst score as maximum VAS.

Postoperative complications are summarized in Table 2. Cardiac complications were myocardial ischemia or supraventricular tachycardia. Complications did not show any difference between study groups (p>0.05). The incidence of POCD was not different among patients with or without complications (respectively 12 in 33 and 17 in 66; p=0.096).

Table 1. Patients demographic and perioperative data

	GI (n=57)	GII (n=59)
Age (years)	70.9±7.4	68.4±5.9
Gender (F/M)	18/39	13/46
ASA score I–II/III	32/25	25/24
Ischemic heart disease	12 (21%)	10 (17%)
Diabetes mellitus	10 (18%)	8 (14%)
Education (<8 years/>8years)	39/18	35/24
COPD	10 (18%)	7 (12%)
Operation time (min)	139.5±71.7	176.8±81.5
Peroperative hypotension	13 (23%)	17 (29%)
Transfusion requirement	18 (32%)	23 (39%)
Visual analogue scale (max)	4.9±2.8	1.7±1.7*
Surgery		
Urological	33 (58%)	37 (63%)
General surgery	24 (42%)	22 (37%)
Length of stay (day)	12±8.9	10.6±7.7

Quantitative data are presented as mean±standard deviation. Qualitative data are presented as frequencies and percentages. ASA: American Society of Anesthesiologists; GI: General anesthesia; GII: General anesthesia with epidural analgesia; M: Male; F: Female; COPD: Chronic obstructive pulmonary disease. *P<0.01 compared to GI.

Table 2. Comparison of complications between groups (p>0.05)

	GI (n=57)		GII (n=59)	
	n	%	n	%
Cardiac	4	7	2	2
Infection				
Urinary	6	11	7	12
Pneumonia	4	7	3	5
Miscellaneous	3	5	4	4

Neurocognitive test results are summarized in Table 3. Test results were compared between groups in both preoperative and postoperative periods. The comparison of individual test scores showed that patients in GII had significantly higher scores on memory, language, and visuospatial function tests (Table 3). In intragroup comparison, we did not find any significance between preoperative and postoperative values; except for MMSE in GI (p<0.05) (Table 3).

The incidence of POCD was similar between groups 15 (26%) in GI and 14 (24%) in GII (p=0.83).

DISCUSSION

In this prospective study, the incidence of POCD was similar between general anesthesia or general anesthesia combined with epidural analgesia groups in non-cardiac surgery. Compared to general anesthesia, its combination with epidural analgesia showed a trend of improvement in limited areas, such as short and long term memory, visuospatial functions, and language skills. To our knowledge, this is one of the rare studies comparing the effects of the combination of general anesthesia with epidural analgesia and general anesthesia alone for POCD after non-cardiac surgery in elderly patients.

The incidence of POCD is well defined and mostly studied in cardiac surgery. As non-cardiac procedures are quite heterogeneous, relevant literature reports a large variety of incidence concerning POCD.[6] Early POCD at first week appeared between 17.1–41.4% for general, orthopedic, thoracic, or urological surgery. We observed 25% (29/116) of POCD in the overall study population, which is concordant with previous studies.[6]

Although not completely clarified yet, postoperative cognitive dysfunction is a multifactorial phenomenon as a result of a combination of patient-related and surgery-related risk factors. Universally cited factors are older age, already impaired cognitive status, or generally lower education level, chronic

Table 3. Pre and postoperative neuropsychological test results comparing groups

Neuropsychiatric test	Preoperative GI	Preoperative GII	Postoperative GI	Postoperative GII
Mini Mental test	27.02±2.04	27.88±1.84	25.7±3.84$^{\delta}$	27.11±2.55
WMS-R Logical Memory (short-term free recall)	6.79±3.05	7.71±2.88	6.45±3.80	8.20±3.15*
WMS-R Logical Memory (long-term free recall)	5.85±3.22	7.08±3.33	5.74±4.05	8.34±4.33**
Clock drawing test	6.70±3.52	7.74±3.24	6.68±3.55	6.80±3.46
WMS-R Digit span subtest (FS+BS)	8.55±2.47	8.20±2.39	7.95±2.54	7.82±2.03
Word list generation (#animals/min)	15.42±4.79	17.4±3.94	14.8±4.21	17.8±4.78**
Visuospatial function	8.08±2.05	8.40±1.68	7.27±2.90	8.48±1.77*

Quantitative data are presented as mean±standard deviation. MMSE: Mini-Mental State Examination; GI: General anesthesia; GII: General anesthesia with epidural analgesia. WMS-R: Wechsler Memory Scale-Revised; FS: Forward span; BS: Backward span. *GII significantly different compared to GI ($p<0.05$); **GII significantly different compared to GI ($p<0.01$). $^{\delta}$GI postoperative significantly different compared to GI preoperative ($p<0.05$).

alcoholism.[5] Age appears to be the critical factor with volume and thickness loss in the prefrontal cortex, reduced antioxidant capacity, decreased levels of neurotransmitters, and associated receptors.[21] Cardiac or orthopedic procedures are mostly associated with POCD.[2,22] In the perioperative period, anesthetics are also blamed for triggering POCD;[23] meanwhile, there is no robust data to demonstrate the superiority of regional or local technics in this issue. The well-known ISPOCD study affirmed that regional anesthesia (RA) (spinal or epidural) was associated with reduced incidence of POCD compared to GA in major non-cardiac surgery early in the course; significant difference disappeared at the third month between study groups.[3] Controversies exist in the literature announcing no difference between GA and RA concerning cognitive performance. Two meta-analyses investigated the effects of GA and RA on POCD.[23,24] The previous one reported the potential association between GA and POCD, and authors encouraged the use of RA in patients prone to cognitive impairment.[23] The following meta-analysis, four years later, including 16 RCTs, concluded that no definitive data were showing the superiority of RA to prevent POCD in a large variety of surgeries.[24] In fact, they have common studies; however, the results of the former are almost non-significant, with an odds ratio of 1.34. Major concerns are the heterogeneity of studies (such as diagnosis of POCD, types of RA) and different sedation protocols added to various types of RA, which means that that none of the groups was devoid of anesthetics.[24]

GA is indispensable in abdominal surgery, and combination with EA offers better pain control, reduced opioid use, and essentially modulation of the surgical stress response. Perioperative stress indispensable for recovery after surgery may substantially impair central nervous system homeostasis. Experimental and clinical studies revealed affected synaptic plasticity, dysregulation of the cholinergic system, altered microglial activation, or hippocampus dysfunction due to chaotic stress response.[25] The hippocampus, which was defined as crucial for memory function, appeared to be particularly vulnerable to neuroinflammation.[26] According to our literature search, two randomized studies were comparing EA and GA combination with GA, one historic trial in the early 1980s, and the second in abdominal surgery.[12,27] The recent study affirmed comparable cognitive decline with GA and combined technique.[27] The authors commented that other factors (lower education level and general surgery) would affect mainly postoperative decline. In this study, we aimed to focus on a relatively homogenous surgery group from the point of the stress response. All subjects underwent an abdominal procedure, with minimal risk of embolism lasting more than two hours, and an average length of stay.

In our study, not the incidence of POCD, but domains of cognitive decline were significantly different between groups. Memory function, verbal skills, and visuospatial function appeared to be better preserved in the combined group. The recent orthopedic trial reported similar results comparing GA with GA and peripheral block combination.[28] The authors explained the difference by the reduced opioid requirement in the combined group. During the early postoperative course, epidural analgesia provided reduced incidence of POCD compared to systemic opioids after hip fracture among octogenarians.[29] Pain control was successfully achieved in both groups. Regional techniques do not only offer adequate pain control (and decreased opioid need), but they also modulate cytokine response to surgery. Experimental studies ensued interesting results on postoperative pain and cognitive functions. The laparotomy model resulted specifically in spatial dysfunction, learning disability, or memory among rats presented as limited movement area or preference of corners.[30] However, improved analgesia prevented the development of memory deficits after laparotomy.[31] Increased pro-inflammatory cytokines accompany mostly the picture. The hippocampus known for vulnerability to inflammation coordinates learning and memory.[25,32] The effects of inflammation on the hippocampus have already been investigated in age-related cognitive decline.[32] We observed remarkably better pain scores in combined anesthesia with acceptable scores in the GA group, which might contribute to preserved memory

or visuospatial functions. As this study did not involve the measurement of the inflammatory response, we were concentrated on cognitive functions.

Postoperative complications were similar between study groups. Systemic complications were supposed to be associated with postoperative cognitive decline.[32] Respiratory complications and infections seemed to be related to POCD in a large study group.[33] However, investigators could not show statistical significance in multivariate analysis. The incidence of POCD was similar in patients with or without postoperative complications in this study. Larger trials should be designed to detect the effects of systemic complications.

This study has some limitations. The major limitation is the absence of long-term results as a variable rate of early cognitive decline may recover. However, the detection of the incidence of late POCD was not the aim of this study, but it was focused on the early POCD for comparing two different anesthesia methods. The second limitation may be the definition of POCD, which differs among studies. Initially, the calculation of a composite z score is proposed based on a control group not exposed to surgery.[1] Subsequently, a decrease of more than 1 SD, at least on two neuropsychological tests, is proposed as a diagnostic criterion.[22] In our previous studies, we also used the second definition in cardiac surgery patients.[34,35] The third point may be that our test battery cannot be considered as a conventional "comprehensive" test battery since it was specially designed to be practical for use by an anesthesiologist (G.O), who was supervised by a behavioral neurologist (H.G). However, we think that this was not a major flaw, as incidence rates of POCD were similar to previous studies.

In conclusion, GA and EA, combined with GA, resulted in similar POCD in elderly patients undergoing abdominal surgery. However, in combined anesthesia group memory, linguistic and visuospatial functions appeared to be better preserved. Effective pain control in this group might have benefits in preventing cognitive decline in some domains. We think that more extensive studies, utilizing a comprehensive neuropsychological battery and also having a longer-term follow-up time points may better document the advantages of effective pain control on the cognitive functions of the elderly people undergoing surgery, who are already at risk for age-related cognitive decline, such as Alzheimer's disease.

Ethics Committee Approval: The study was approved by the Institutional Review Board (approval number: 2007/2607), and signed consent was obtained from patients.

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ORİJİNAL ÇALIŞMA - *ÖZET*

İleri yaş grubu hastalarda genel ve epidural anestezi ile yalnızca genel anestezi uygulamalarının nörokognitif fonksiyonlara etkilerinin karşılaştırılması

Dr. Günseli Orhun,[1] Dr. Zerrin Sungur,[1] Dr. Kemalettin Koltka,[1] Dr. Meltem Savran Karadeniz,[1] Dr. Hacer Ayşen Yavru,[1] Dr. Hakan Gürvit,[2] Dr. Mert Şentürk[1]

[1]İstanbul Üniversitesi İstanbul Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, İstanbul
[2]İstanbul Üniversitesi İstanbul Tıp Fakültesi, Nöroloji Anabilim Dalı, Davranış Nörolojisi ve Hareket Bozuklukları Birimi, İstanbul

AMAÇ: Ameliyat sonrası erken dönemde kognitif bozukluk yaşlı popülâsyonda sık görülür. Anestezi yönetimi ameliyat sonrası kognitif düşüşü etkileyebilir. Etkin analjezi, erken derlenme ve stres yanıtın modülasyonu nöroaksiyel blokların avantajlarıdır. Bu çalışmanın amacı, genel anestezi ve epidural analjezi ile kombine edilen genel anestezinin postoperatif kognitif bozukluk (PKB) için etkisini karşılaştırmaktır. Hipotezimiz genel anestezi (GA) ile birlikte nöroaksiyel bloğun, PKB önlenmesinde olumlu bir etkisi olacağıydı.

GEREÇ VE YÖNTEM: Kalp cerrahisi dışında operasyona gelen 60 yaşın üstündeki hastalar bu ileriye yönelik randomize çalışmaya dâhil edildi ve hastalar iki gruba ayrıldı. Birinci gruptaki hastalara (GI) GA uygulandı; ikinci grupta (GII) ise epidural analjezi ile GA kombine edildi. Hastaların kognitif fonksiyonları, nöropsikolojik test bataryası kullanılarak ameliyattan bir hafta önce ve bir hafta sonra değerlendirildi. PKD, iki veya daha fazla testte bazal değerden bir standart sapma düşüş olarak tanımlandı.

BULGULAR: Çalışmayı toplam 116 hasta tamamladı. GI'de GII'den anlamlı olarak yüksek olan maksimum ağrı skorları hariç (sırasıyla, 4.9±2.8'e karşılık 1.7±1.7; p<0.001) demografik ve operatif veriler gruplar arasında benzerdi. PKD insidansında gruplar arasında fark saptanmadı (GI'de %26 ve GII'de %24). Bellek performansı, görsel mekânsal fonksiyonlar ve dil beceri testleri GII'de GI'e göre anlamlı olarak yüksek bulundu.

TARTIŞMA: Genel anestezi ve genel anestezi ile kombine epidural analjezi, abdominal cerrahi geçiren yaşlı hastalarda benzer PKD insidansı ile sonuçlandı. Bununla birlikte, kombine anestezi grubunda hafıza, dil becerileri ve görsel mekânsal fonksiyonların daha iyi korunduğu görüldü. Etkin ağrı kontrolü bazı alanlarda kognitif işlevlerin korunmasında katkı sağlayabilir durmaktadır.

Anahtar sözcükler: Ameliyat sonrası ağrı; ileri yaş, kognitif bozukluk, genel anestezi, epidural analjezi,

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