POSTOPERATIVE COGNITIVE DYSFUNCTION IN ADULT AND ELDERLY PATIENTS

- General Anesthesia vs Subarachnoid or Epidural Analgesia

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Abstract

This study compared the effect of general anesthesia or regional vertebral analgesia (subarachnoid or epidural) on postoperative cognitive function in 60 young adult (group A) and 60 elderly (group E) patients undergoing orthopedic and urologic surgery. Wechsler Adult Intelligence Scale-Revised for cognitive functions assessment was done preoperatively, and postoperatively; one day and three days after surgery. Variations in heart rate, blood pressure, arterial oxygen and carbon dioxide tensions, and pH as well as serum bicarbonate, sodium and potassium levels, were assessed at the same time intervals. They did not show any significant change from the preoperative levels. Cognitive functions, one and three days after surgery, did not change significantly in young adult patients after either general or regional vertebral nor in elderly patients who received regional regional vertebral, as compared with the preoperative levels. Only elderly patients who received general anesthesia had significant decline in cognitive function one day after surgery. It significantly improved on the third postoperative day but still was significantly less than the preoperative level. Moreover, significantly better WAIS-R Scores were found in the elderly group one and three days after spinal anesthesia than after general anesthesia. The results indicate

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that general anesthesia poses a significant risk for the occurrence of early postoperative cognitive dysfunction in elderly patients that can persist for 3 day after surgery. Regional vertebral analgesia is advantageous over general anesthesia for elderly patients in terms of a better postoperative neuropsychological functioning.

Introduction

Elderly surgical patients present some specific challenges to anesthetists. Their number is increasing and they suffer more frequent major morbidity and mortality than younger counterparts undergoing comparable surgeries[1].

In recent years, attention has focused on the cognitive dysfunction that affects elderly patients after anesthesia and surgery[2,3]. This condition may occur following surgeries that were considered uncomplicated, or even after minor procedures. This even may not be apparent until the patient is discharged from hospital and tries to resume normal activities. The patient may then discover problems with recalling recent events and may tend to forget appointments, phone numbers. and names. For those who have not retired yet this deterioration can have serious consequences on their ability to work.

This condition is called Postoperative Cognitive Dysfunction (POCD). Unlike delirium, it is not associated with changes in level of consciousness and it does not fluctuate over the course of the day. Due to the subtle nature of POCD, the problem may be recognized only by the patient's relatives and a neuropsychological testing is necessary for its detection. It covers a large range of neuropsychological modifications ranging from concentration impairment to delirium, and affecting the full range of cognitive functions, including visual and auditory attention, primary and secondary memory, implicit memory and visiospatial functioning.

It has been recognized that there is no postoperative complication more frequent and of longer duration than postoperative cognitive dysfunction (POCD) in the elderly[4]. It can result in increased morbidity, delayed functional recovery, prolonged hospital stay, delay in rehabilitation, adverse social consequences with reduced quality of life and a concern of inducing some elderly patients prematurely into dependency. Indeed, the recognition of this situation must be incorporated into service provision.

Too many mechanisms and predisposing factors have been incriminated in the occurrence of POCD[5]. Increasing age, duration of anesthesia, episodes of hypoxemia, lack of education, a second operation, postoperative infections and respiratory complications, were identified as risk factors. Correlation with these factors however, has been inconsistent. Is the problem related to anesthesia, the impact of hospitalization, drugs unrelated to anesthesia, disease processes or is a consequence of the surgical problem? These are still unanswered questions. Attempts to reduce the severity of POCD have been hampered by lack of a definite etiology.

This study was undertaken to evaluate the influence of age and the type of anesthesia (general or regional vertebral) on the incidence of POCD following anesthesia and surgery.

Patients and Methods

The University of Alexandria Medical Institutional Review Board approved the study protocol. Following a written informed consent, 120 ASA I & II patients admitted for elective surgery in the orthopedic and in the urology surgical departments in Alexandria University Hospitals, were recruited to the study. Patients were selected of nearly matched ages; half of them over 60 years (elderly or group E), and the other 60 patients aged between 20 and 30 years (younger adults or group A). Patients in each group were randomly allocated to receive either standard general anesthetic (subgroups E_G and A_G) or regional vertebral (subarachnoid or epidural) analgesia (subgroups E_S and A_S). Patients were excluded if they had a history of any psychiatric or neurologic problems, or if they were subjected to gross hemodynamic or ventilatory fluctuations during the operation.

Patients who received general anesthesia (30 patients in group E and 30 patients in group A) had midazolam 0.1 mg/kg I.M. as a premedication 30 min before the operation. Anesthesia was induced with thiopentone 4-6 mg/kg and maintained with halothane 1-2% in 60% nitrous oxide in oxygen. Atracurium 0.5 mg/kg was used to facilitate tracheal intubation and to achieve muscular relaxation. At the end of the procedure, neuromuscular blockade was reversed with 2.5 mg neostigmine and 1 mg atropine.

Patients who received regional vertebral analgesia consisted of 30 patient of group E (17 subarachnoid and 13 epidural), and 30 patients of group A (11 subarachnoid and 19 epidural anesthesia). Heavy bupivacaine 0.5% (2-4 ml) was used for subarachnoid analgesia, and plain lidocaine 1.5% (15-20 ml) was used for lumbar epidural analgesia. Patients breathed oxygen-enriched air through nasal prongs. Midazolam 0.1 mg/kg I.V. was used for sedation during the operation with a 10% decrease in the dose for each 10 years over the age of 50. Crystalloids were used for I.V. infusion and blood loss of ≥15% of estimated blood volume was replaced with packed cells. Postoperative care was administered according to the usual routine in the recovery area and later on in the ward.

One day before surgery, all patients were examined and base line data were obtained; pulse rate mean arterial blood pressure using the pace-tect multichannel monitor, arterial blood gas analysis for arterial oxygen and carbon dioxide tensions, blood pH and serum bicarbonate levels using ABL II apparatus, and serum sodium and potassium levels using CIBA CORNING 614 apparatus. Also, the preoperative cognitive function was evaluated using Wechsler Adult Intelligence Scale-Revised (WAIS-R)[6]. This is an individually administered series of standardized test used to evaluate cognitive abilities and intellectual functions. It consists of 11 subsets; 6 verbal and 5 nonverbal performance tests and includes information, digit span, vocabulary, arithmetic, comprehension, similarities, picture completion, picture arrangement, block design, object assembly, and digit symbol. The scales have a mean, or average, standard score of 100 and a standard deviation of 10 (Table 1). It measures a broad spectrum of mental abilities with a very high degree of reliability. All the previously mentioned data were re-measured 1 and 3 days after recovery.

Table 1
Mental ability scoring by the WAIS-R [From the Diagnostic and Statistical Manual of Mental Disorders, version IV (DSM-IV)][7].

Classification	Scale range
Profound mental retardation	< 25
Severe mental retardation	25-40
Moderate mental retardation	40-55
Mild mental retardation	55-70
Border line	70-80
Dull normal	80-90
Normal	90-110
Bright normal	110-120
Superior	120-130
Very superior	> 130

Variables were identified as nonparametric when analyzed by Kolmogorov-Smirnov and Shapiro-Wilk tests for normality. Statistical analysis of Inter-subgroup differences in demographics consisted of Chi-quare test for sex distribution, Kruskal Willis test for the duration of surgery and Man-Whitney U test for age differences between the two subgroups within each group. Repeated-measures analysis of variance on ranks (Friedman's test) was used for analyzing changes within each subgroup. Significant results were further analyzed with Wilcoxon Signed Ranks test to identify the area of significance. Between subgroups the differences were tested with Mann-Whitney U test. Statistical significance was defined as a two-sided p-value of less than 0.05 and the results are presented as medians with 25th and 75th percentiles.

Results

Of the 120 patients included in our study, 102 underwent orthopedic surgery and 18 underwent urosurgical procedures, all were classified as moderate to major surgery, with a duration ranging from 30-110 minutes with a mean of 59.99 ± 23.51 (62.82 ± 26.2 in group E, and 57.17 ± 19.45 in group A). Patients were allocated into four subgroups (E_G, E_S, A_G and A_S), 30 patients each, according to age and to the type of anesthesia used.

The four subgroups were comparable as regards; sex (P=0.24) and duration of surgery (P=0.29), and each of the groups had its two subgroups comparable as regards the age of the patients (P=0.26 and P=0.08 for groups E and A respectively) (Table II).

Table II
Sex (male/female ratio), Age and duration of surgery (expressed as medians with 25th and 75th percentiles) of the tested subgroups.

	Group E		Group A	
	General	Reg. vertebral	General	Reg. vertebral
Sex (M/F)	19/11	17/13	18/12	24/6
Age (yr)	62.0 (61.0-64.3)	61.0 (60.0-63.3)	27.0 (25.0-29.0)	28.0 (26.8-30.0)
Duration of surgery (min)	67.5 (35.0-91.3)	57.5 (40.0-80.0)	50.0 (33.8-70.0)	55.0 (45.0-80.0)

No significant changes were found in the mean arterial pressure, heart rate and blood pH, nor in the serum levels of sodium, potassium and bicarbonate in the four subgroups, one and three days after the operation as compared to the preoperative values (Table III).

Table III

Hemodynamic (B.P. and H.R), Arterial blood gas tensions (PaO_2 and $PaCO_2$), blood PH and Serum bicarbonate, Sodium and Potassium levels in the four subgroups preoperatively, one day and three days after the operation. The values expressed are medians with 25th and 75th percentiles.

	Group E						Group A					
	General			Reg. vertebral			General			Reg. vertebral		
B.P.	preop	1d	3d	preop	1d	3d	preop	1d	3d	preop	1d	3d
	96.5 (90.0-100.3)	96.5 (92.0-100.0)	96.5 (93.0-100.3)	99.5 (95.3-102.5)	98.5 (95.0-101.3)	98.5 (94.0-100.0)	100.0 (92.0-102.3)	100.0 (91.0-102.0)	99.0 (95.0-102.0)	102.0 (98.5-104.3)	100.0 (99.0-103.5)	100.0 (98.8-103.5)
P	**0.063**			**0.389**			**0.305**			**0.692**		
H.R.	72.0 (70.0-74.3)	71.5 (70.0-75.3)	71.0 (69.0-74.0)	85.0 (82.0-88.5)	85.5 (80.8-89.0)	85.5 (81.0-89.3)	74.5 (69.8-78.3)	73.0 (71.0-79.3)	74.5 (71.0-79.5)	80.0 (79.0-82.0)	81.0 (80.0-83.0)	80.0 (79.0-83.0)
P	**0.436**			**0.885**			**0.097**			**0.122**		
P_aO_2	96.0 (94.0-97.0)	95.0 (94.0-96.3)	95.0 (93.0-97.0)	95.0 (93.8-96.0)	95.0 (94.0-96.0)	95.0 (94.0-96.0)	96.0 (95.8-97.0)	96.0 (96.0-98.0)	96.0 (95.0-98.0)	93.0 (91.8-95.3)	95.0 (90.0-97.0)	95.0 (90.0-97.0)
P	**0.744**			**0.102**			**0.736**			**0.719**		
P_aCO_2	41.0 (39.8-43.0)	41.0 (40.0-42.0)	40.5 (40.0-42.0)	42.0 (40.0-45.3)	42.0 (41.0-44.3)	42.0 (41.0-45.0)	39.5 (38.8-40.0)	39.5 (38.8-41.0)	39.5 (38.0-41.0)	39.5 (38.8-40.0)	39.0 (37.0-40.3)	40.0 (38.0-40.0)
P	**0.881**			**0.098**			**0.575**			**0.733**		
HCO_3	22.0 (21.0-24.0)	22.0 (20.8-24.0)	22.5 (20.8-24.0)	22.0 (21.0-24.0)	22.5 (20.8-24.0)	22.5 (21.0-24.0)	23.0 (22.0-24.0)	23.0 (22.0-24.0)	23.0 (21.8-24.0)	24.0 (22.8-25.0)	23.5 (22.0-24.3)	23.0 (22.0-25.0)
P	**0.388**			**0.498**			**0.424**			**0.254**		
PH	7.39 (7.35-7.40)	7.40 (7.32-7.40)	7.395 (7.32-7.40)	7.40 (7.37-7.40)	7.40 (7.34-7.41)	7.40 (7.38-7.43)	7.40 (7.38-7.40)	7.40 (7.35-7.40)	7.39 (7.38-7.40)	7.395 (7.38-7.40)	7.395 (7.38-7.40)	7.40 (7.38-7.41)
P	**0.648**			**0.085**			**0.816**			**0.485**		
S. Na	139.0 (137.0-143.0)	139.0 (136.0-140.0)	140.0 (137.0-140.3)	140.0 (136.8-144.3)	140.0 (137.5-140.5)	139.5 (137.0-140.0)	144.5 (140.0-149.3)	143.0 (140.0-147.0)	146.0 (137.0-149.0!	141.0 (139.0-143.3)	142.0 (140.0-147.3)	145.0 (140.0-148.0)
P	**0.340**			**0.337**			**0.101**			**0.390**		
S. K	4.50 (4.10-4.90)	4.60 (428-4.73)	4.30 (4.18-4.73)	4.45 (4.08-4.90)	4.40 (4.00-4.80)	4.30 (4.10-4.90)	4.25 (4.98-4.63)	4.35 (4.10-4.60)	4.75 (4.10-4.90)	4.05 (4.00-4.53)	4.50 (3.98-4.80)	4.05 (4.00-4.53)
P	**0.580**			**0.426**			**0.168**			**0.570**		

The preoperative WAIS-R scores were in the normal category (90-110) in all the tested subgroups. The scores however, decreased significantly in the elderly subgroup who received general anesthesia (subgroup E_G), when measured one day after surgery to the borderline level (70-80). Three days after surgery, the measured scores in this subgroup were significantly improved to 85.17 + 5.3 (dull normal level) but were still significantly lower than the preoperative value. Also, the scores one and three days after surgery were significantly better in elderly patients who received regional vertebral than general anesthesia. There was no significant deterioration in the measured WAIS scores in the rest of the tested subgroups (E_S, A_G and A_S), neither at one day nor at three days after the operation as compared to the preoperative levels (Table IV, Fig. 1).

Table IV

Weschsler Adult Intelligence Scores-Revised (WAIS-R) for the four subgroups, preoperatively, one day and three days after the operation. Medians with 25th and 75th percentiles are shown.

Patient group		Group E			Group A		
		General	Reg. vertebral	P^{Φ}	General	Reg. vertebral	P^{Φ}
WAIS-R Score	Preop	90.0 (87.8-94.0)	93.5 (89.0-96.0)	0.079	100.0 (95.0-107.3)	103.5 (97.0-110.0)	0.623
	1 day	73.0* (70.0-74.0)	93.0 (88.8-95.0)	<0.001	100.0 (94.8-107.3)	103.5 (96.5-110.0)	0.552
	3 days	87.0*‡ (80.0-90.0)	93.0 (90.0-95.3)	<0.001	102.5 (94.0-106.3)	103.5 (96.5-110.0)	0.504
P^{Ω}		<0.0001	0.094		0.445	0.068	

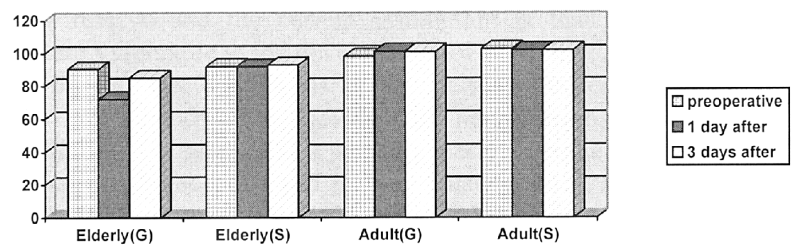
*: Significant difference with preoperative value (P<0.001). (Wilcoxon Signed Rank test).

‡: Significant difference with one-day value (P<0.001). (Wilcoxon Signed Rank test).

Φ: Mann-Whitney test.

Ω: Friedman test.

Fig. 1
Mean Weschsler Adult Intelligence Scores (WAIS) for the four subgroups, preoperatively, one day and three days after the operation.



Discussion

Our study confirmed the occurrence of short-term postoperative cognitive deficit in a significant number of elderly patients after non-cardiac surgery performed under general anesthesia. Although there is consensus on its existence, attempts to reduce its severity have been hampered by lack of a definite etiology, which is likely to be multifactorial.

In this study we investigated the influence of age and the type of anesthesia (general or regional vertebral), on the occurrence of POCD. While avoiding a number of potential confounding factors, this excludes the possibility of examining interaction effects. For example a history of preoperative neurologic disease has been demonstrated to increase the rate of POCD[8]. Therefore, we had excluded patients with pre-existing cognitive, psychiatric or central nervous system disorders. In addition, the effects of other factors[9] such as blood loss, hypoxemia and hypercarbia had been minimized by excluding patients who were subjected to gross hemodyanmic or ventilatory fluctuations during the operation. Also, all the hemodynamic, ventilatory and the metabolic parameters that could be impeached in the occurrence of POCD were carefully monitored during the whole study and did not show any significant change from the preoperative levels. Ultimately, the impact of age and anesthetic technique on the occurrence of POCD had been focused.

Age frequently has been reported as a risk factor for cognitive alteration after anesthesia[2,3]. This was quite evident in our results and is probably related to the important changes in both physiology and pharmacokinetics occurring with ageing and the possible interaction of anesthetic drugs with current medication in the elderly[10,11].

Actually, little is known about the effects of anesthetics on the aged brain. The age-associated structural and functional changes in the CNS have reduced functional reserve and the current assumption is that this makes the elderly more vulnerable to the development of POCD[11]. The mechanism is unknown but one hypothesis is that it may be related to further decreases in already low levels of neurotransmitters such as acetylcholine[12]. Drugs used as a part of general anesthesia interact with central cholinergic receptors and may modulate cognitive functions[10,13]. Propofol at high doses and volatile anesthetics are potent inhibitors of nicotinic acetyl choline receptors while atracurium and its metabolite laudanosine activate them, and some other anesthetics may cause block of the central muscarenic acetyl choline receptors. The effects of these drugs and their multiple interaction sites with different affinities could explain POCD[11]. However, several old studies[14,15,16] failed to validate this relationship. This had been attributed to the rough psychological evaluation used in these studies that could not detect more subtle defects[3,16]. We chose the Wechsler Adult Intelligence Scale-Revised for its applicability to wide differences in level of functioning, sensitivity to small changes in function and extensive psychometric data documenting the instrument's reliability and validity[17]. Also, to guarantee more accuracy and validity the test was performed by the researcher and by a specialized psychiatric technician, well trained in performing and interpreting the test results. Most recent studies[2,4,18,19] agreed with our results in approving old age as a major risk factor in the occurrence of POCD.

The evidence to date suggests that although cognitive deficits may occur postoperatively, no particular anesthetic technique appears to be implicated[20]. There is presently no scientific basis for recommending (or avoiding) a specific anesthetic agent or technique for anesthesia in this regard. Although still in controversy, recent studies did not show that anticholinergic drugs, barbiturate premedication or benzodiazepines are implicated in the development of postoperative delirium[20,21,22]. The anesthetic technique used in our study was standardized to the customary work in our operating room because the objective of this study was to detect alterations in cognitive function that could be found after either general or neuroaxial regional anesthesia under conditions generalisable to the real-life situation of a busy operating room, rather than to compare the effects of different anesthetic agents. The choice between subarachnoid and epidural blocks in the regional anesthesia group was left to the anesthesiologist responsible for the patient because the physiologic effects of both techniques are almost the same and there is no reason to expect different behavioral sequelae[23]. All the patients receiving regional vertebral analgesia received midazolam sedation. This may have served to negate any differences between the groups[16].

Our data support the recent trends[24] towards increased use of neuroaxial blockade to reduce major complications in the elderly. POCD significantly occurred in elderly patients who received general anesthesia but did not in those who received regional vertebral analgesia with sedation. This demonstrates that exposure to general anesthesia also should constitute a major risk factor that can lead to POCD in the elderly. Several studies have looked at general versus regional anesthesia, since general anesthesia may lead to changes in cerebral blood flow and cerebral metabolic oxygen consumption[10]. It also could provoke persistent alterations in specific cognitive domains in the elderly where ageing-related neuronal changes may exacerbate pharmacotoxic effects[11,12]. Neuraxial blockade on the other hand has several physiological effects that provide a rationale for expecting to improve outcome[22,24]. In addition to avoidance of adverse effects of general anesthesia and minimizing the number of medications used, its use may carry the benefit of reducing several major postoperative complications in a wide range of elderly patients. Neuraxial blockade with epidural or subarachnoid analgesia reduces the incidence of deep vein thrombosis, pulmonary embolism, transfusion requirements, pneumonia, respiratory depression, myocardial infarction, and renal failure[24]. All these complications can predisopose to the development of POCD[8,9,20]. Furthermore, the induced surgical stress response that could also contribute to the occurrence of POCD is substantially altered by neuraxial blockade but not by general anesthesia[8,20,24].

Nevertheless, the issue of whether neuroaxial analgesia offers advantages over general anesthesia for elderly patients in terms of neurophychological functioning and the ability to perform activities of daily living, had remained controversial. Riis[25], Berggren[26], Ghoneim[23] and Williams-Russo[27] could not find differences in the postoperative mental abilities between patients who received general and regional vertebral anesthesia. On the other hand, significant cognitive impairment in elderly patients after general anesthesia and not after subarachnoid or epidural analgesia, had been detected by Hole[28] and by Chung[29] during the early postoperative days. Rasmussen[30] also found that the incidence of POCD was significantly greater one week after general anesthesia than after regional analgesia and Campbell[31] noted that his elderly patients who received general anesthesia tended to perform less well in some aspects of cognitive function than those who received local analgesia at 24 hours after cataract surgery. Finally, Tzabar[32] reported a highly significant greater incidence of cognitive failures after general anesthesia compared with local analgesia for 3 days after day case surgery, and Bigler[15] noted a shorter time of ambulation as an advantage for subarachnoid analgesia over general anesthesia for acute hip surgery in elderly patients despite his observation of the absence of persistent mental function impairment after either of the techniques.

The variability of the results of various studies could largely be attributed to the absence of a standard POCD definition, the heterogeneity of procedures to measure cognitive deficits and the methods used for statistical analysis, but could also be related to the disparity in targeted population[3,33]. In addition, the complex interaction of diverse etiological factors can make it difficult to isolate the influence of anesthesia itself[33,34].

Looking for changes in mental status is an important part in the postoperative care in the geriatric patient. The condition can be silent, and unnoticed, or misdiagnosed as depression. However, the effects are evident in increased morbidity, delayed functional recovery, prolonged hospital stay, delay in rehabilitation and may jeopardize return to independence[4,20,35]. Substantial additional costs accrue after discharge from the hospital, because of the increased need for institutionalization, rehabilitation, and home care. In order to avoid delays in the postanesthesia care unit (PACU) and in the time to discharge after outpatient anesthesia, fast and predictable recovery of cognitive function is of major importance. Nevertheless, the importance of perioperative cognitive decline has long been debated[35]. Descriptions such as “subtle”, “transient”, and “subclinical” have been used to minimize the importance of these changes to clinicians, patients, and their families. Fortunately, POCD is a reversible condition in the majority of elderly surgical patients. However, a significant correlation between perioperative cognitive decline and long-term cognitive dysfunction had recently been demonstrated[36]. This linkage between perioperative injury and long-term cognitive function suggests that perioperative dysfunction may serve either as a marker of brain injury, increased susceptibility to brain injury, decreased reserve capacity, or inability to recover or tolerate similar injury (plasticity)[35]. The clinical importance of cognitive dysfunction further emphasize the need for aggressive strategies to monitor and improve both the neurocognitive function in elderly surgical patients.

Understanding the risk factors and etiologic mechanisms and trying to eliminate or reduce them in addition to better psychologic care preoperatively and postoperatively when indicated must have contributed to better outcome[37]. This can improve our understanding of the problems affecting older patients and lead to development of improved strategies for diagnosis, care, research, and medical education in this area. Concern that the elderly brain “takes a hit” during general anesthesia and surgery is better justified and guidelines for the anesthesiological management of at risk patients are mandatory.

References

1. DEL GUERCIO LRM, COHN JD: Monitoring operative risk in the elderly. *JAMA*; 243(13), 1350-5, 1980.
2. MOLLER JT, CLUITMANS P, RASMUSSEN LS, HOUX P, RASMUSSEN H, CANET J, ET AL: Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. *Lancet*; 351(9106), 857-61, 1998.
3. RASMUSSEN LS: Postoperative Cognitive Dysfunction in Older Adults. *Geriatric & Aging*; 6(10), 36-8, 2003.
4. DODDS C, ALLISON J: Postoperative cognitive dysfunction in the elderly surgical patient. *Br J Anaesth*; 81, 449-62, 1998.
5. PARIKH SS, CHUNG F: Postoperative delirium in the elderly. *Anesth Analg*; 80, 1223-32, 1995.
6. WECHSLER D: *Wechsler Adult Intelligence Scale-Revised*: Manual. New York, Psychological Corporation 1981.
7. *American Psychiatric Association: Diagnostic and Statistical manual of mental disorders*, fourth edition (DSM-IV). International version. Washington DC: American Psychiatric Association, 1995.
8. LIU LL, LEUNG JM: Predicting adverse postoperative outcomes in patients aged 80 years or older. *J Am Geriatr Soc*; 48, 405-12, 2000.
9. MARCANTONIO ER, GOLDMAN L, ORAV EJ, COOK EF, LEE TH: The association of intraoperative factors with the development of postoperative delirium. *Am J Med*; 105(5), 380-4, 1998.
10. ANCELIN ML, DE ROQUEFEUIL G, LEDESERT B, RITCHIE K, BONNEL F, CHEMINAL JC: Expposure to anaesthetic agents, cognitive functioning and depressive symptomatology in the elderly. *Br J Psychiatry*; 178, 360-6, 2001.
11. CULLEY DJ, BAXTER M, YUKHANANOV R, CROSBY G: The Memory Effects of General Anesthesia Persist for Weeks in Young and Aged Rats. *Anesth Analg*; 96, 1004-9, 2003.
12. FODALE V, SANTAMARIA LB: The inhibition of central nicotinic nAch receptors is the possible cause of prolonged cognitive impairment after anesthesia. *Anesth Analg*; 97, 1207, 2003.
13. FODALE V, SANTAMARIA LB: Drugs of anesthesia, central nicotinic receptors and post-operative cognitive dysfunction. *Acta Anaesthesiol Scand*; 47, 1180, 2003.
14. SIMPSON BR, WILLIAMS M, SCOTT JF, SMITH AC: The effects of anaesthesia and elective surgery on old people. *Lancet*; 6, 297-303, 1967. 2, 884-93, 1961.
15. BIGLER D, ADELHOJ B, PETRING OU, PEDERSON NO, BUSCH P, KALHKE P: Mental function and morbidity after acute hip surgery during spinal and general anaesthesia. *Anaesthesia*; 40(7), 672-6, 1985.
16. NIELSON WR, GELB AW, CASEY JE, PENNY FJ, MERCHANT RN, MANNINEN PH: Long-term cognitive and social sequelae of general versus regional anesthesia during arthroplasty in the elderly. *Anesthesiology*; 73, 1103-9, 1990.
17. CZUBAJ, CAMILLA ANNE: *The Wechsler Adult Intelligence Scale-Revised*, Revisited. Education; 117(3), 271-3, 1997.
18. CANET J, RAEDER J, RASMUSSEN LS, ENLUND M, KUIPERS HM, HANNING CD, JOLLES J, KORTTILA K, SIERSMA VD, DODDS C, ABILDSTROM H, SNEYD JR, VILA P, JOHNSON T, MUNOZ CORSINI L, SILVERSTEIN JH, NIELSEN IK, MOLLER JT: Cognitive dysfunction after minor surgery in the elderly. *Acta Anaesthesiol Scand 2003*; 47(10), 1204-10.

19. RITCHIE K, POLGE C, DE ROQUEFEUIL G, DJAKOVIC M, LEDESERT B: Impact of anesthesia on the cognitive functioning of the elderly. *Int Psychogeriatr*; 9(3), 309-26, 1997.
20. JIN F, CHUNG F: Minimizing perioperative adverse events in the elderly. *British Journal of Anaesthesia*; 87(4), 608-24, 2001.
21. RASMUSSEN LS, STEENTOFT A, RASMUSSEN H, KRISTENSEN PA, MOLLER JT: Benzodiazepines and postoperative cognitive dysfunction in the elderly. ISPOCD Group. International Study of Postoperative Cognitive Dysfunction. *Br J Anaesth*; 83, 585-9, 1999.
22. BALLANTYNE JC: Editorial II: Does epidural analgesia improve surgical outcome? *Br J Anaesth*; 92(1), 4 – 6, January 1, 2004.
23. GHONEIM MM, HINRICHS JV, O'HARA MW, MEHTA MP, PATHAK D, KUMAR V, CLARK CR: Comparison of psychologic and cognitive functions after general or regional anaesthesia. *Anesthesiology*; 69, 507-15, 1988.
24. RODGERS A, WALKER N, SCHUB S, MCKEE A, KEHLET H, VAN ZUNDERT A, SAGE D, FUTTER M, SAVILLE G, CLARK T, MACMAHON S: Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomized trials. *BMJ*; 321, 1439, 2000.
25. RIIS J, LOMHOLT B, HAXHOLDT O, KEHLET H, VALENTIN N, DANIELSEN U, ET AL: Immediate and long-term mental recovery from general versus epidural anesthesia in elderly patients. *Acta Anaesthesiol Scand*; 27, 44-9, 1983.
26. BERGGREN D, GUSTAFSON Y, ERIKSSON B, BUCHT G, HANSSON LI, REIZ S, WINBLAD B: Postoperative confusion after anaesthesia in elderly patients with femoral fractures. *Anesth Analg*; 66(6), 497-504, 1987.
27. WILLIAMS-RUSSO P, SHARROCK NE, MATTIS S, SZATROWSKI TP, CHARLSON ME: Cognitive effects after epidural vs general anesthesia in older adults. A randomized trial. *JAMA*; 274(1), 44-50, 1995.
28. HOLE A, TERJESEN T, BREIVIK H: Epidural versus general anaesthesia for total hip arthroplasty in elderly patients. *Acta Anaesthesiol Scand*; 24(4), 279-87, 1980.
29. CHUNG F, MEIER R, LAUTENSCHLAEGER E, CARMICHAEL FJ, CHUNG A: General or spinal anaesthesia: wich is better in the elderly? *Anesthesiology*; 67, 422-7, 1987.
30. RASMUSSEN LS, JOHNSON T, H, KUIPERS HM, KRISTENSEN D, SIERSMA VD, VILA P, JOLLES J, PAPAIOANNOU A, ABILDSTROM H, SILVERSTEIN JH, BONAL JA, RAEDER J, NIELSEN IK, KORTTILA K, MUNOZ L, DODDS C, HANNING CD, MOLLER JT: Does anaesthesia cause postoperative cognitive dysfunction? A randomized study of regional versus general anaesthesia in 438 elderly patients. *Acta Anaesthesiologica Scandinavica*; 47(3), 260-6, 2003.
31. CAMPBELL DNC, LIM M, KERR MUIR M, O'SULLIVAN G, FALCON M, FISON P, WOODS R: A prospective randomized study of local versus general anaesthesia for cataract surgery. *Anaesthesia*; 48, 422-8, 1993.
32. TZABAR Y, ASBURY AJ, MILLAR K: Cognitive failures after general anaesthesia for day-case surgery. *Br J Anaesth*; 76(2), 194-7, 1996.
33. ANCELIN ML, DE ROQUEFEUIL G, RITCHIE K: Anesthesia and postoperative cognitive dysfunction in the elderly: a review of clinical and epidemiological observations. Rev *Epidemiol Sante Publique*; 48(5), 459-72, 2000.
34. SELWOOD A, ORRELL M: Long term cognitive dysfunction in older people after non-cardiac surgery. Ouctomes from various studies differ, and no definite conclusion is possible. *BMJ*; 328, 120-121, 2004.
35. NEWMAN MF, GROCOTT HP, MATHEW JP, WHITE WD, LANDOLFO K, REVES JG, LASKOWITZ DT, MARK DB, BLUMENTHAL JA: Report of the Substudy Assessing the Impact of neurocognitive

Function on Quality of Life 5 Years After Cardiac Surgery. *Stroke*; 32, 2874, 2001.

36. ZAKRIYA K, SIEBER FE, CHRISTAMS C, WENZ JF, FRANCKOWIAK S: Brief Postoperative Delirium in Hip Fracture Patients Affects Functional Outcome at Three Months. *Anesth Analg*; 98, 1798-802, 2004.
37. INOUYE SK, BOGARDUS ST, CHARPENTIER PA, LEO-SUMMERS L, ACAMPORA D, HOLFORD TR, COONEY LM: A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients. *N Engl J Med*; 340(9), 669-76.