Int J Clin Exp Med 2017;10(11):15453-15458
www.ijcem.com /ISSN:1940-5901/IJCEM0057159

Original Article

Protective effect of combined general and regional anesthesia on postoperative cognitive function in older arthroplasty patients

Chen Chen[1], Min Li[1], Kejie Wang[3], Jiang Shen[1], Linyi Yang[1], Xiaoxuan Bu[1], Gongming Gao[2]

Departments of [1]Anesthesiology, [3]Orthopedics, The First People's Hospital of Changzhou, Changzhou, Jiangsu Province, P.R. China; [2]Department of Orthopedics, The Second People's Hospital of Changzhou, Nanjing Medical University, Changzhou, Jiangsu Province, P.R. China

Received March 23, 2017; Accepted September 22, 2017; Epub November 15, 2017; Published November 30, 2017

Abstract: Purpose: Postoperative cognitive dysfunction (POCD) occurs frequently in elderly people especially for those after major surgeries. Arthroplasty improves quality of life in elderly patients but is associated with high incidence of POCD. The problem that whether the different anesthesia methods have effects on POCD has long been a controversy. The objective of this study was to observe whether combined general and regional anesthesia affected perioperative cognitive trajectory in elderly patients with arthroplasty. Methods: Ninety patients with knee and hip arthroplasty aged between 60 yr and 79 yr were randomly allocated to general anesthesia group or combined general and regional anesthesia groups. Mini-mental state examination (MMSE) was performed to assess cognitive function changes before and at one week after surgery. Results: The postoperative MMSE was significantly higher in the combined anesthesia group than in the general anesthesia group (p=0.005). The postoperative MMSE score was significantly improved compared with preoperative MMSE score in both groups ($p < 0.05$). Conclusions: Our study demonstrated that combined general and regional anesthesia protected perioperative cognitive trajectory, providing evidence supporting use of regional anesthesia along with general anesthesia in elderly orthopedic patients who are vulnerable to postoperative cognitive decline.

Keywords: General regional combined anesthesia, postoperative cognitive dysfunction, arthroplasty

Introduction

Postoperative cognitive dysfunction (POCD) is defined as a disorder in thought process, which affects cognition including memory, comprehension and attention [1]. POCD occursin patients of different ages after noncardiac surgery with longer-term POCD at 3 months in adults older than 60 yr (10% to 13%) [2, 3]. POCD increases morbidity and mortality of the elderly after surgeries and dramatically worsen their quality of life [4]. Research into POCD is still preliminary as the etiology of POCD, which has yet to be unraveled [5].

To the best of our knowledge, the effects of combined general and regional anesthesia on perioperative cognitive trajectory have yet to be reported. Anesthesia methods are significant elements in perioperative management which have effect on postoperative recovery especially in such major surgery as arthroplasty [6-8]. Increasing evidence has indicated that quality of perioperative management plays an important role in the postoperative cognitive trajectory [9, 10].

This study was aimed to compare early postoperative cognitive function after combined general and regional anesthesia or general anesthesia alone to determine the protective effects of combined anesthesia in cognitive function. Meanwhile, difference in time of emergence, occurrence of delirium, VAS score, time in PACU and times of giving analgesics in ward were also compared in the two groups.

Materials and methods

After approval of the ethics committee of the Third Affiliated Hospital of Soochow University and written informed consent of all the patients,

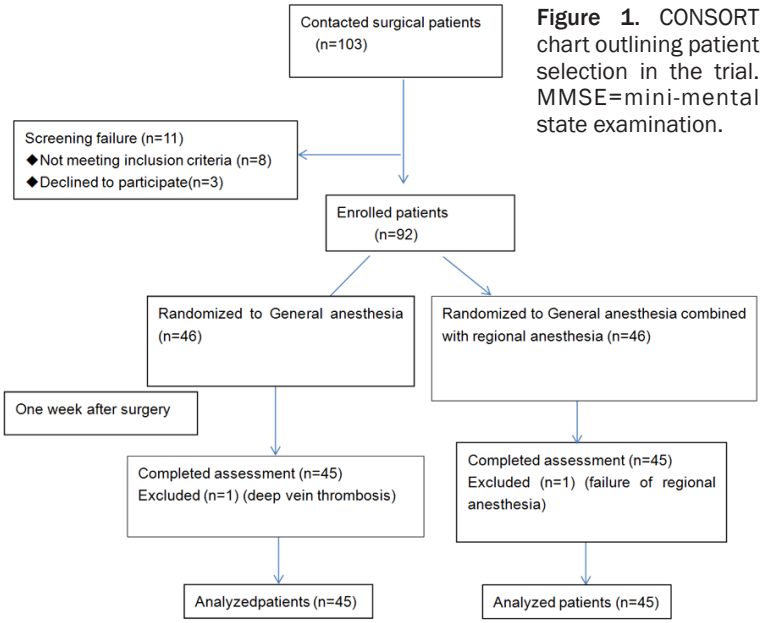

Figure 1. CONSORT chart outlining patient selection in the trial. MMSE=mini-mental state examination.

92 orthopedic patients were consecutively enrolled in our study from March 2014 to June 2015. Inclusion criteria were as follows: patients aged between 60 yr and 79 yr; scheduled for elective unilateral arthroplasty (total knee arthroplasty [TKA] or total hip arthroplasty [THA]) for the first time. Exclusion criteria were as follows: with the American Society of Anesthesiologists risk classification > III; with a history of symptomatic cerebrovascular disease (e.g. stroke with a residual deficit), psychiatric illness; with alcoholism (> 2 drinks/day); with inability to read or listen and thus unable to complete cognitive testing; score < 23 on a baseline MMSE; abnormal coagulation; infection in the puncture site or contraindication for anesthesia or surgery. Eligible patients were randomized into two groups including the general anesthesia group, and combined general and regional anesthesia group. A table of random numbers was used to generate random numbers, which were recorded in serially numbered, opaque, sealed envelopes. These envelopes were retained by a member of the study other than the attending anesthetist who practiced the anesthesia. The protocol for this clinical trial was registered at www.chictr.org.cn (ChiCTR-IOR-15005828).

Regional anesthesia was performed in the combined anesthesia group by an experienced attending doctor under ultrasound guidance (Sonosite, Sonosite Inc., USA) and nerve stimulator (Multi Stim VARIO, PAJUNK, Germany). Femoral nerve and sciatic nerve block were conducted in TKA while lumbar plexus and sciatic nerve block were conducted in THA. The local anesthetic was 0.5% of Ropivacaine. After confirming regional anesthesia, general anesthesia was induced in both groups with 0.3 μg/kg sulfentanyl and 2-2.5 mg/kg propofol. Laryngeal mask (I-gel, Intersurgicval Ltd., UK) was laid after loss of consciousness. Anesthesia with propofol and remifentanil was used to maintain BIS 50-60 (BIS, Aspect A-2000 monitoring system, Aspect medical system, MA, USA). Standard monitoring variables such as heart rate, pulse oxygen saturation and mean arterial pressure were recorded every 5 min. When the patients had spontaneous breathing and BIS was higher than 85, laryngeal mask was removed and the patients were transferred to postoperative care unit (PACU) where an anesthesia nurse recorded time to emergence, delirium, visual analogue scale (VAS) 10 min after emergence and time to discharge. A nurse performed the bedside VAS evaluation every 6 h in the ward, recorded analgesic intake times 24 h after surgery and observed delirium.

MMSE is often performed for measuring cognitive changes over time in clinical and research settings. Repeated MMSE testing is used to determine cognitive decline or improvement. It tests neurocognitive functions, such as orientation, attention, calculation, recall, executive capacity and language [11]. The maximal score of MMSE is 30 points and MMSE ≤ 23 is considered as abnormal. A research assistant who was unaware of the anesthesia methods performed MMSE before surgery as the baseline and seven days after surgery.

We used a 60% change of SD in the MMSE score to detect the anesthetic effect. On the basis of two-sided type I error 0.05 and a power of 80%, we expected to enroll 45 participants in each group for the investigation.

Table 1. Patient profile

	GA (N=45)	GR (N=45)	Evaluation
Age (yr)	71 (64 to 75)	70 (65 to 73)	P=0.52
Males/Females	21/24	20/25	P=0.83
ASA (I/II)	23/22	21/24	P=0.67
Education (< 12 y/≥ 12 y)	39/6	42/3	P=0.29
Occupation (retired/work)	43/2	40/5	P=0.23
Region to live (native/foreign)	43/2	44/1	P=0.55
Annual income ($)	1548 (980 to 3769)	1735 (1256 to 4027)	P=0.49
Duration of surgery (min)	105 (85 to 125)	100 (80 to 120)	P=0.47
preMMSE	26 (24 to 28)	26 (25 to 27)	P=0.16

Data represent median (IQR). preMMSE=preoperative mini-mental state examination; GA=general anesthesia; GR=combined general and regional anesthesia.

Table 2. MMSE results

	GA (n=45)	GR (n=45)	*P* value
Preop.	24±4	25±3	0.16
Postop.	26±4	28±2	0.005
p value	0.003	< 0.0001	

Data represent mean ± SD. PREOP.=preoperation; POSTOP.=postoperation; GA=general anesthesia; GR=combined general and regional anesthesia; MMSE=mini-mental state examination.

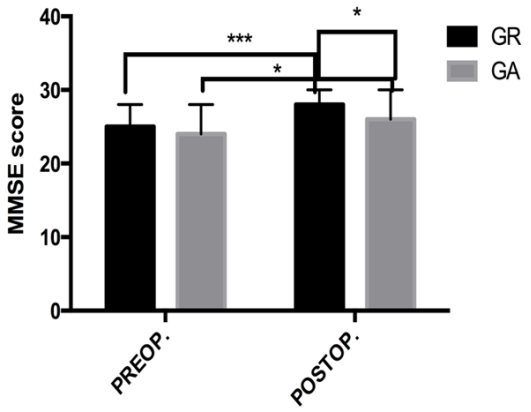

Figure 2. Comparison of perioperative MMSE scores in different anesthesia groups. GA=general anesthesia; GR=combined general and regional anesthesia; MMSE=mini-mental state examination; preop.=preoperation; postop.=postoperation; *p < 0.05; ***p < 0.001.

Data were analyzed using SPSS v20.0 (SPSS, Chicago, IL, USA). The baseline characteristics of the two groups (e.g., age, gender, ASA grade, duration of surgery, preoperative MMSE score, types of surgery), the primary outcome (perioperative MMSE score) and the secondary outcomes (e.g. incidence of delirium, time to emergence, time to leave PACU, VAS score) were analyzed using ANOVA and chi-square test as appropriate. A *p*-value < 0.05 was considered as statistically significant.

Results

A total of 92 patients were enrolled from March 2014 to June 2015 in the Third Affiliated Hospital of Suchoo University, Changzhou, Jiangsu, China. Forty-five patients were randomized to each group. Two patients were excluded for various reasons. Data of 90 patients were analyzed. No surgical site infection or deep vein thrombosis was observed in these patients after surgery. Patient selection process is outlined in the CONSORT flowchart (**Figure 1**).

Baseline characteristics of these patients, including age, gender, ASA grade, preoperative MMSE score, duration of surgery and type of surgery, are listed in **Table 1**. There was no significant difference between the two groups.

As shown in **Table 2** and **Figure 2** and no significant differences in preoperative MMSE scores of the two groups were seen between groups (p=0.16). However, the postoperative MMSE in both groups was higher than in the preoperative period (p < 0.0001 in GR group; p=0.003 in GA group). The postoperative MMSE score in the general anesthesia group was significantly lower than in the combined anesthesia group (p=0.005). Patients undergoing different types of anesthesia maintained similar level of BIS 50-60 (p=0.55). There was no difference in requirements for propofol (p=0.06) and remifentanil (p=0.08). However, the dose of sulfentanyl was significantly lower in the combined anesthesia group than in the general anesthesia group (p < 0.001). The combined anesthesia patients recovered from anesthesia earlier (p=0.02) and stayed a shorter time (P=0.03) in PACU than the general anesthesia group. Further, VAS was significantly lower in the combined general and regional anesthesia group than in the general anesthesia group in PACU

Table 3. Patient profile during and after surgery

	GA (N=45)	GR (N=45)	*p* value
BIS	53 (40 to 60)	55 (40 to 60)	P=0.55
Propofol (mg)	790 (660 to 850)	640 (590 to 720)	P=0.06
Remifentanil (mg)	1.5 (1.0 to 3.0)	1.0 (0.5 to 2.0)	P=0.08
Sulfentanyl (μg)	50 (45 to 80)	40 (35 to 55)	P < 0.001
Time of Emergence (min)	25 (10 to 40)	15 (5 to 20)	P=0.02
Delirium	4	0	P=0.04
VAS	4 (3 to 5)	2 (0 to 3)	P=0.04
Time in PACU	55 (30 to 75)	35 (25 to 55)	P=0.03
Time of analgesics (24 h)	1 (1 to 2)	0 (0 to 1)	P=0.002

Data are presented as median (IQR). BIS=bispectralindex; VAS=visual analogue scale; PACU=postanesthesia care unit; GA=general anesthesia; GR=combined general and regional anesthesia.

10 min after extubation (p=0.04). Four patients in the general anesthesia group had delirium compared with none in the combined anesthesia group (p=0.04). In the postoperative 24 hours, the general anesthesia patients needed more analgesics (p=0.002) (**Table 3**).

Discussion

In this study, we found that combined general and regional anesthesia might protect perioperative cognitive trajectory when compared with general anesthesia. The results also highlighted anesthetic sparing of peripheral nerve blocks especially sparing of potent opioids during surgery and in the early postoperative period. Faster emergence and less delirium were also detected in the combined anesthesia group.

In our study, it is found that combined anesthesia technique might protect early postoperative cognitive function when compared with general anesthesia. First of all, regional analgesia provided better perioperative analgesia. Weber CF et al found that regional anesthesia in patients undergoing carotid endarterectomy (CEA) positively affected early postoperative neurocognitive outcomes [12]. Postoperative pain contributes to the development of memory deficits after anesthesia and surgery via up-regulation of hippocampal NMDA receptors. Animal experiments in aged rats suggested that postoperative pain management played an important role in the prevention of POCD in elderly patients [13]. Secondly, combined anesthesia results in anesthetic sparing. Opioids depressed cholinergic transmission which played a key role in cognitive function [14]. Thus, combined anesthesia reduces use of general anesthetics and at the same time lessens anxiety and pain. Efficient and effective regional anesthesia minimizes use of opioids during and after surgery, and at the same time provides quick emergence. Factors affecting POCD such as anxiety, depression and sleep deprivation can be diminished by combining general and regional anesthesia [15-18]. Delirium is associated with early POCD [19, 20]. The incidence of delirium was much lower in the combined anesthesia group (p=0.04) and provides a rationale for better MMSE in the combined anesthesia group.

However, according to a systematic review, the effect of regional anesthesia was not superior to general anesthesia on POCD [21]. There are several reasons for the results. Regional block is not a satisfactory anesthesia method, especially for elderly patients undergoing major surgery. Elderly patients are prone to anxiety in the perioperative period. Lee A found that regional anesthesia might cause cerebral desaturation, which is believed to correlate with the incidence of POCD [22].

The mechanism of POCD is still unknown. Martin F et al found that peripheral nerve block used for postoperative analgesia exerted a prolonged anti-inflammatory effect [23]. Hema Bagry et al also reported that continuous peripheral nerve block with Ropivacaine contributed to attenuation of postoperative inflammatory response [24]. We hypothesized that regional anesthesia may protect early postoperative cognitive function by inhibiting inflammatory response. Unfortunately, both studies found no changes in plasma cytokines.

The study limitation relates to the use of MMSE in the clinical study as a bedside tool to assess cognitive changes: it may not be sensitive totally. However, MMSE is an easy, valid and reliable bedside test clinically and is an established and reliable predictor of cognitive dysfunction in non-surgical subjects [25, 26]. Another limitation is the relatively small sample size that

precludes any generalization of our results. We need multicenter studies with a larger sample size and different types of surgery to compare the effects of combined anesthesia.

In conclusion, our study provided anevidence support for the use of combined general and regional anesthesia in elderly patients to protect postoperative cognitive function.

Address correspondence to: Gongming Gao, Department of Orthopedics, The Second People's Hospital of Changzhou, Nanjing Medical University, Changzhou 213000, Jiangsu Province, P.R. China. E-mail: ggm2005@sina.com

References

[1] Bryson GL and Wyand A. Evidence-based clinical update: general anesthesia and the risk of delirium and postoperative cognitive dysfunction. Can J Anaesth 2006; 53: 669-677.

[2] Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, Rabbitt P, Jolles J, Larsen K, Hanning CD, Langeron O, Johnson T, Lauven PM, Kristensen PA, Biedler A, van Beem H, Fraidakis O, Silverstein JH, Beneken JE and Gravenstein JS. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. Lancet 1998; 351: 857-861.

[3] Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM and Gravenstein JS. Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 2008; 108: 18-30.

[4] Steinmetz J, Christensen KB, Lund T, Lohse N and Rasmussen LS. Long-term consequences of postoperative cognitive dysfunction. Anesthesiology 2009; 110: 548-555.

[5] Deiner S and Silverstein JH. Postoperative delirium and cognitive dysfunction. Br J Anaesth 2009; 103 Suppl 1: i41-46.

[6] Lee A, Kim SH, Hong JY and Hwang JH. Effect of anesthetic methods on cerebral oxygen saturation in elderly surgical patients: prospective, randomized, observational study. World J Surg 2012; 36: 2328-2334.

[7] Barreveld A, Witte J, Chahal H, Durieux ME, Strichartz G. Preventive analgesia by local anesthetics: the reduction of postoperative pain by peripheral nerve blocks and intravenous drugs. Anesth Analg 2013; 116: 1141-1161.

[8] Silbert BS, Evered LA and Scott DA. Incidence of postoperative cognitive dysfunction after general or spinal anaesthesia for extracorporeal shock wave lithotripsy. Br J Anaesth 2014; 113: 784-791.

[9] Krenk L, Kehlet H, Bæk Hansen T, Solgaard S, Soballe K and Rasmussen LS. Cognitive dysfunction after fast-track hip and knee replacement. Anesth Analg 2014; 118: 1034-1040.

[10] Nadelson MR, Sanders RD and Avidan MS. Perioperative cognitive trajectory in adults. Br J Anaesth 2014; 112: 440-451.

[11] Folstein MF, Folstein SE and McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-198.

[12] Weber CF, Friedl H, Hueppe M, Hintereder G, Schmitz-Rixen T, Zwissler B and Meininger D. Impact of general versus local anesthesia on early postoperative cognitive dysfunction following carotid endarterectomy: GALA study subgroup analysis. World J Surg 2009; 33: 1526-1532.

[13] Chi H, Kawano T, Tamura T, Iwata H, Takahashi Y, Eguchi S, Yamazaki F, Kumagai N and Yokoyama M. Postoperative pain impairs subsequent performance on a spatial memory task via effects on N-methyl-D-aspartate receptor in aged rats. Life Sci 2013; 93: 986-993.

[14] Laalou FZ, De Vasconcelos AP, Oberling P, Jeltsch H, Cassel JC and Pain L. Involvement of the basal cholinergic forebrain in the mediation of general (propofol) anesthesia. Anesthesiology 2008; 108: 888-896.

[15] Voigt Hansen M, Rasmussen LS, Jespersgaard C, Rosenberg J and Gogenurl. There is no association between the circadian clock gene HPER3 and cognitive dysfunction after noncardiacsurgery. Anesth Analg 2012; 115: 379-385.

[16] Patron E, Messerotti Benvenuti S, Zanatta P, Polesel E, Palomba D. Preexisting depressive symptoms are associated with long-term cognitive decline in patients after cardiac surgery. Gen Hosp Psychiatry 2013; 35: 472-479.

[17] Laalou FZ, Jochum D and Pain L. Postoperative cognitive dysfunction (POCD): strategy of prevention, assessment and management. Ann Fr Anesth Reanim 2011; 30: 49-53.

[18] Hansen MV, Madsen MT, Andersen LT, Hageman I, Rasmussen LS, Bokmand S, Rosenberg J and Gögenur I. Effect of melatonin on cognitive function and sleep in relation to breast cancer surgery: a randomized, double-blind, placebo-controlled trial. Int J Breast Cancer 2014; 2014: 416531.

[19] Lynch EP, Lazor MA, Gellis JE, Orav J, Goldman L, Marcantonio ER. The impact of postoperative pain on the development of postoperative delirium. Anesth Analg 1998; 86: 781-785.

[20] Bickel H, Gradinger R, Kochs E and Forstl H. High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study. Dement Geriatr Cogn Disord 2008; 26: 26-31.

[21] Mason SE, Noel-Storr A and Ritchie CW. The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium: a systematic review with meta-analysis. J Alzheimers Dis 2010; 22: 67-79.

[22] Lee A, Kim SH, Hong JY and Hwang JH. Effect of anesthetic methods on cerebral oxygen saturation in elderly surgical patients: prospective, randomized, observational study. World J Surg 2012; 36: 2328-2334.

[23] Martin F, Martinez V, Mazoit JX, Bouhassira D, Cherif K, Gentili ME, Piriou P, Chauvin M and Fletcher D. Antiinflammatory effect of peripheral nerve blocks after knee surgery: clinical and biologic evaluation. Anesthesiology 2008; 109: 484-490.

[24] Bagry H, de la Cuadra Fontaine JC, Asenjo JF, Bracco D and Carli F. Effect of a continuous peripheral nerve block on the inflammatory response in knee arthroplasty. Reg Anesth Pain Med 2008; 33: 17-23.

[25] Guerrero-Berroa E, Luo X, Schmeidler J, Rapp MA, Dahlman K, Grossman HT, Haroutunian V and Beeri MS. The MMSE orientation for time domain is a strong predictor of subsequent cognitive decline in the elderly. Int J Geriatr Psychiatry 2009; 24: 1429-1437.

[26] Zhang N, Wei C, Du H, Shi FD and Cheng Y. The effect of memantine on cognitive function and behavioral and psychological symptoms in mild-to-moderate Alzheimer's disease patients. Dement Geriatr Cogn Disord 2015; 40: 85-93.