Original Article

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Postoperative Cognitive Dysfunction After General and Regional Anesthesia: A Prospective Randomized Controlled Trial

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Abstract

Background: Postoperative cognitive dysfunction (POCD) is a well recognized complication following various operative procedures. The role of anesthetic agent in etiopathogenesis is still controversial. The present study aims to describe and compare effects of general and regional anesthesia on post-operative cognitive functions among patients undergoing orthopedics surgery. *Methods:* A total of 80 patients aged 20-60 years, belonging to either sex, scheduled for <120 minutes duration orthopaedic surgery of lower limb, with good physical status, and with ±20% ideal weight were included. Patients unwilling for consent, past anesthetic use, cognitive impairment, sub-normal intelligence, substance use disorder, psychiatric disorder, and chronic medical condition were excluded. Patients were randomized to receive either general anesthesia (n=40) or regional anesthesia (n=40) during surgery. After routine preanesthetic examination and laboratory investigations, Hindi version of mini-mental status examination scale was applied prior to surgery and at 24h, 2weeks, and 6weeks postoperatively. *Results:* The prevalence of POCD at 24 h, 2 weeks, and 6 weeks after the surgery was higher among general anesthesia group (80%, 52.5%, and 27.5% respectively) compared with regional anesthesia group (57.5%, 27.5%, and 15% respectively). When compared with regional anesthesia group, the cognitive domains related to orientation to time, place, registration, recall, and copying at 24 h and recall at 2 weeks postoperatively were significantly affected in general anesthesia group. *Conclusion:* Although POCD has multifactorial etiopathogenesis, the role of general anesthesia cannot be completely refuted. Besides preoperative and intraoperative precautions, postoperative cognitive remediation techniques may be recommended. Further studies investigating effect of individual anesthetic agent in causing POCD is required.

Keywords: Anesthesia; Postoperative Complications; Cognitive Dysfunction.

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Introduction

Use of anesthesia during surgery often leads to post-operative cognitive dysfunction (POCD)[(1)], which is characterized by impairment in attention, memory, language comprehension, abstract thinking, and reaction time, with preserved level of consciousness. Nearly all patients have one or more cognitive dysfunction during post-operative period, of which 19-80% persist at 1 week and 6-60% at 3months following surgery [(1,2)]. POCD is associated with poor rehabilitation outcomes and higher surgical mortality [(1,2)]. Several hypothesis have been suggested in development of POCD[(1,6)]. However, role of type of anesthetic

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agents in developing POCD is still controversial[6]. A few studies have recommended use of regional anesthesia to prevent risk of POCD due to general anesthesia[3,4]. Whereas, others did not reported significant difference in POCD with general and regional anesthesia[5]. There is a relative lack of longitudinal studies from India evaluating POCD induced by general and regional anesthesia[7,8]. Such studies will help in rational treatment decisions in selecting appropriate anesthesia for high risk patients. The present study aims to describe and compare effects of general and regional anesthesia on post-operative cognitive functions among patients undergoing orthopedics surgery.

Methods

A total of 80 patients scheduled for orthopaedic surgery of lower limb, of lesser than 120 minutes duration, aged 20-60years, belonging to either sex, with physical status I to II (American Society of Anesthesiology), and with body weight being 20% above or below ideal weight, were recruited in the study. The patients after consent were randomly assigned to one of the 2 groups, group 1(n=40) received general anesthesia and group 2 (n=40) received regional anesthesia during the surgery. Patients not willing for consent or with history of prior use of anesthesia, cognitive impairment, sub-normal intelligence, substance use disorder, psychiatric disorder, chronic medical disorder such as neurological disorder (eg. cerebrovascular accident, seizures, unconsciousness), cardiac disease (eg. hypertension, ischemic heart disease), respiratory disease (eg. asthma, recurrent infections), endocrinal disorder (eg. diabetes mellitus, hypothyroidism) and malignancy, were excluded. All patients underwent routine pre-anesthetic checkup including sociodemographic details, past and present history of medical and surgical illness, drug history, general and systemic physical examination including airway, vitals, and glassgow coma scale, routine laboratory investigations including hemogram, blood counts, renal fuction test, liver function test, fasting blood sugar, electrocardiography, chest x-ray. Sedatives were avoided on night before surgery. Hindi version of mini-mental status examination (HMSE) scale was applied 1 day prior to surgery and 24 hours, 2 weeks, and 6 weeks after the surgery. All patients were informed about the type of anesthesia to be given, however the observer applying HMSE was blinded. Patient's vitals were maintained within 20% of pre-operative values, oxygen saturation was kept above 90%. Peri-operative events of hypoxia, hypotension, thromboembolic episodes, and respiratory distress were documented. Post-operative pain was managed using 15mg/kg body weight paracetamol given 15 minutes prior to stopping anesthesia. The study was started after approval from institute ethics committee.

Tools and Technique

The modified Hindi Version of Mini-Mental Status Examination [9]

The Mini-Mental Status Examination is the most frequently used method to assess the cognition in post-operative period[1].The modified hindi version of the Mini-Mental Status Examination, also known as Hindi Mental Status Examination (HMSE), is a validated 22 items questionnaire which can be used even among illiterate Indian population. It tests cognitive domains such as orientation to time and place, attention and concentration, recognition of objects, language function, both comprehensive and expressive speech, motor function, and praxis. The score of ≤23 is used to screen the major neurocognitive disorders, with 88% sensitivity and 82% specificity.

General Anesthesia (GA; Group 1)

All patients in Group 1 were intravenously injected 0.03mg/kg body weight midazolam, followed by 2μg/kg body weight fentanyl and 0.01mg/kg body weight ondansetron, followed by 2 mg/kg propofol. After pre-oxygenation with 3 minutes of 100% oxygen, tracheal intubation was facilitated with intravenous administration of 0.01mg/kg body weight vecuronium. Maintenance was done using 40% oxygen – 60% nitrous oxide – isoflurane with 1.2 MAC. After surgery neuromuscular blockade was reversed with intravenous neostigmine 50μg/kg with glycopyrrolate 10 μg/kg.

Regional Anesthesia (RA; Group 2)

All patients in Group 2 were injected 10-12mg of hyperbaric bupovacaine in subarachnoid space at level of L3-L4 inter-vertebral space.

Analysis

Data were analysed using IBM SPSS version 20 software. Sociodemographic variables were described. Frequencies and percentages were used to describe the data. Due to small sample size and

skewed distribution, nonparametric tests were used. Categorical data were analyzed using Chi-square analysis, whereas, continuous variables were analysed by using Mann-Whitney Test for comparison in HMSE score between the two groups (i.e. GA vs RA) and Wilcoxon Signed Ranks Test for comparison of HMSE score obtained at 24h, 2weeks, and 6weeks w.r.t. preoperative score (baseline). A statistical significance level of 5% was used (p = 0.05) for all the comparisons.

Results

Socio-demographic profile

A total of 40 cases and 40 controls were recruited, mean age for group 1(GA) was 33.53y±12.74, whereas, for group 2(RA) was 42.05y±14.35 (Z=2.67, p=0.01), majority comprised of males (72.5% vs 67.5%; X2 =0.24, p=0.63), and rural residence (57.5% vs 50%; X2=0.45, p=0.50). There was no significant difference in socio-economic status (High: 50% vs 32.5%; Low: 50% vs 67.5%; X2 =2.53, p=0.11) and educational status among the two groups (Illiterate: 5.0% vs 17.5%; Primary(1-5 standards): 2.5% vs 5%; Middle(6-8 standards): 7.5% vs 7.5%; Secondary(8-10 standards): 20.0% vs 17.5%; Higher Secondary(10-12 standards): 22.5% vs 20.0%; Graduate and above: 42.5% vs 32.5%; X2=3.77, p=0.58).

HMSE Score

The prevalence of postoperative cognitive decline at 24h, 2weeks, and 6weeks after the surgery among patients who received General Anesthesia was 80%, 52.5%, and 27.5% respectively, whereas, among patients who received Regional Anesthesia was 57.5%, 27.5%, and 15% respectively. The mean HMSE score among group 1 (General Anesthesia) and Group 2 (Regional Anesthesia) prior to surgery (31.00 ± 0.00 and 30.95 ± 0.22 respectively; Z=-1.42, p=0.16) did not differed significantly (Table 1). Whereas, at 24 h (28.82 ± 1.44 and 30.00 ± 1.08 respectively; Z=-3.57, p<0.01) and 2 weeks after the surgery (30.38 ± 0.70 and 30.70 ± 0.51 respectively; Z=-2.20, p=0.03) differed significantly (Table 2, 3). However, the scores at 6 weeks after the surgery (30.68 ± 0.57 and 30.82 ± 0.44 respectively; Z=-1.08, p=0.28) did not differed significantly (Table 4).

The Wilcoxon Signed Rank Test revealed that among group 1 who received general anesthesia during surgery had significant decline in HMSE score at 24 h (Z=-4.98; p<0.01), 2 weeks (Z=-4.24; p<0.01), and 6 weeks (Z=-3.13; p<0.01) postoperatively when compared with preoperative(baseline) HMSE score (Table 5), whereas, among group 2 who received regional anesthesia during surgery had significant decline in HMSE score at 24 h (Z=-4.28; p<0.01) and 2 weeks (Z=-2.28; p=0.01), however the decline was not significant at 6 weeks (Z=-1.90; p=0.06) postoperatively when compared with preoperative (baseline) HMSE score (Table 6).

The cognitive domains related to orientation to time (Z=-4.69; p<0.01), place (Z=-4.24; p<0.01), registration (Z=-2.45; p=0.01), recall (Z=-4.90; p<0.01), repetition (Z=-2.00; p=0.04), and copying (Z=-3.46; p<0.01) was found significantly lower among group 1(GA) after 24 h postoperatively when compared with preoperative score (baseline), whereas, only recall score was significantly declined at 2 weeks (Z=-4.03; p<0.01) and 6 weeks (Z=-2.89; p<0.01) postoperatively. Among group 2(RA), when compared with preoperative score (baseline), there was significant decline in 24 h postoperative score of orientation to time (Z=-3.46; p<0.01), place (Z=-2.82; p=0.01), recall (Z=-3.46; p<0.01), and repetition (Z=-2.24; p=0.03), whereas, only recall score was significantly declined at 2weeks (Z=-2.83; p=0.01) and 6 weeks (Z=-2.24; p=0.03). There was significant difference between the two groups in the domains related of orientation to time (Z=-2.25; p=0.02), place (Z=-2.37; p=0.02), registration (Z=-1.97; p<0.05), recall (Z=-2.67; p<0.01), and copying (Z=-3.73; p<0.01) at 24h, whereas, only recall score significantly differed (Z=-2.33; p=0.02) at 2 weeks postoperatively. None of the domains differed significantly among the two groups at 6 weeks postoperatively

Discussion

Findings of the present study reveled that the prevalence of postoperative cognitive decline at 24 h, 2 weeks, and 6 weeks after the surgery was higher among patients who received general anesthesia (80%, 52.5%, and 27.5% respectively) when compared with those who received regional anesthesia (57.5%, 27.5%, and 15% respectively). When compared with regional anesthesia group, patients who received general anesthesia (group 1) had significantly greater decline in overall cognition at 24 h and 2 weeks after the surgery, particularly in domains related to orientation to time, place,

Table 1: Comparison of preoperative HMSE score between two groups

HMSE Preoperative	Group 1 General Anesthesia	Group 2 Regional Anesthesia	Z	P
Orientation to time	5.00 ± 0.00	5.00 ± 0.00	0.00	1.00
Orientation to place	5.00 ± 0.00	5.00 ± 0.00	0.00	1.00
Registration	3.00 ± 0.00	3.00 ± 0.00	0.00	1.00
Attention	3.00 ± 0.00	3.00 ± 0.00	0.00	1.00
Recall	3.00 ± 0.00	2.98 ± 0.15	0.00	1.00
Naming	1.00 ± 0.00	1.00 ± 0.00	1.00	0.32
Repetition	3.00 ± 0.00	3.00 ± 0.00	0.00	1.00
Three step task	3.00 ± 0.00	3.00 ± 0.00	0.00	1.00
Visual command	1.00 ± 0.00	1.00 ± 0.00	0.00	1.00
Writing sentence	1.00 ± 0.00	1.00 ± 0.00	0.00	1.00
Copying a figure	3.00 ± 0.00	3.00 ± 0.00	0.00	1.00
Overall MMSE score	31.00 ± 0.00	30.95 ± 0.22	-1.42	0.16

Table 2: Comparison of 24 hour postoperative HMSE score between two groups

HMSE 24h Postoperative	Group 1 General Anesthesia	Group 2 Regional Anesthesia	Z	p
Orientation to time	4.45 ± 0.50	4.70 ± 0.46	-2.25	0.02
Orientation to place	4.55 ± 0.50	4.80 ± 0.40	-2.37	0.02
Registration	2.85 ± 0.36	2.95 ± 0.22	-1.97	<0.05
Attention	2.95 ± 0.22	2.90 ± 0.30	-0.84	0.40
Recall	2.38 ± 0.49	2.70 ± 0.46	-2.67	<0.01
Naming	1.00 ± 0.00	1.00 ± 0.00	-1.00	0.32
Repetition	2.90 ± 0.30	2.88 ± 0.33	-0.35	0.73
Three step task	2.98 ± 0.15	3.00 ± 0.00	-1.00	0.32
Visual command	1.00 ± 0.00	1.00 ± 0.00	0.00	1.00
Writing sentence	1.00 ± 0.00	1.00 ± 0.00	0.00	1.00
Copying a figure	2.70 ± 0.46	3.00 ± 0.00	-3.73	<0.01
Overall MMSE score	28.82 ± 1.44	30.00 ± 1.08	-3.57	<0.01

Table 3: Comparison of 2 weeks postoperative HMSE score between two groups

HMSE 2 wks Postoperative	Group 1 General Anesthesia	Group 2 Regional Anesthesia	Z	p
Orientation to time	5.00 ± 0.00	4.98 ± 0.15	-1.00	0.32
Orientation to place	5.00 ± 0.00	4.98 ± 0.15	-1.00	0.32
Registration	2.98 ± 0.15	3.00 ± 0.00	-1.00	0.32
Attention	3.00 ± 0.00	2.95 ± 0.22	-1.42	0.16
Recall	2.52 ± 0.50	2.78 ± 0.42	-2.33	0.02
Naming	1.00 ± 0.00	1.00 ± 0.00	0.00	1.00
Repetition	2.95 ± 0.15	2.92 ± 0.26	-0.46	0.65
Three step task	3.00 ± 0.00	3.00 ± 0.00	0.00	1.00
Visual command	1.00 ± 0.00	1.00 ± 0.00	0.00	1.00
Writing sentence	1.00 ± 0.00	1.00 ± 0.00	0.00	1.00
Copying a figure	2.92 ± 0.26	3.00 ± 0.00	-1.75	0.08
Overall MMSE score	30.38 ± 0.70	30.70 ± 0.51	-2.20	0.03

Table 4: Comparison of 6 weeks postoperative HMSE score between two groups

HMSE 6 wks Postoperative	Group 1 General Anesthesia	Group 2 Regional Anesthesia	Z	p
Orientation to time	5.00 ± 0.00	5.00 ± 0.00	0.00	1.00
Orientation to place	5.00 ± 0.00	5.00 ± 0.00	0.00	1.00
Registration	3.00 ± 0.00	3.00 ± 0.00	0.00	1.00
Attention	3.00 ± 0.00	2.98 ± 0.15	-1.00	0.32
Recall	2.72 ± 0.45	2.85 ± 0.36	-1.36	0.18
Naming	1.00 ± 0.00	1.00 ± 0.00	0.00	1.00
Repetition	2.98 ± 0.15	2.98 ± 0.15	0.00	1.00
Three step task	3.00 ± 0.00	2.90 ± 0.44	-1.00	0.32
Visual command	1.00 ± 0.00	1.00 ± 0.00	0.00	1.00
Writing sentence	1.00 ± 0.00	1.00 ± 0.00	0.00	1.00
Copying a figure	3.00 ± 0.00	3.00 ± 0.00	0.00	1.00
Overall MMSE score	30.68 ± 0.57	30.82 ± 0.44	-1.08	0.28

Table 5 : Comparison of HMSE score at postoperative 24 hour, 2weeks, and 6weeks w.r.t. preoperative (baseline) among patients who received general anesthesia (group 1).

HMSE Group 1: General Anesthesia	Postoperative 24h Preoperative		Postoperative 2 week Preoperative		Postoperative 6 week Preoperative	
	Z	P	Z	p	Z	P
Orientation to time	-4.69	0.00	0.00	1.00	0.00	1.00
Orientation to place	-4.24	0.00	0.00	1.00	0.00	1.00
Registration	-2.45	0.01	-1.00	0.32	0.00	1.00
Attention	-1.41	0.16	0.00	1.00	0.00	1.00
Recall	-4.90	0.00	-4.03	0.00	-2.89	0.00
Naming	0.00	1.00	-1.00	0.32	-1.00	0.32
Repetition	-2.00	0.04	-1.41	0.16	-1.00	0.32
Three step task	-1.00	0.32	0.00	1.00	0.00	1.00
Visual command	0.00	1.00	0.00	1.00	0.00	1.00
Writing sentence	0.00	1.00	0.00	1.00	0.00	1.00
Copying a figure	-3.46	0.00	-1.73	0.08	0.00	1.00
Overall MMSE score	-4.98	0.00	-4.24	0.00	-3.13	0.00

Table 6 : Comparison of HMSE score at postoperative 24h, 2weeks, and 6weeks w.r.t. preoperative (baseline) among patients who received regional anesthesia (group 2).

HMSE Group 2: Regional Anesthesia	Postoperative 24h Preoperative		Postoperative 2 week Preoperative		Postoperative 6 week Preoperative	
	Z	p	Z	p	Z	P
Orientation to time	-3.46	0.00	-1.00	0.32	0.00	1.00
Orientation to place	-2.82	0.01	-1.00	0.32	0.00	1.00
Registration	-1.00	0.32	0.00	1.00	0.00	1.00
Attention	-2.00	0.05	-1.41	0.16	-1.00	0.32
Recall	-3.46	0.00	-2.83	0.01	-2.24	0.03
Naming	0.00	1.00	0.00	1.00	0.00	1.00
Repetition	-2.24	0.03	-1.73	0.08	-1.00	0.32
Three step task	0.00	1.00	0.00	1.00	-1.00	0.32
Visual command	0.00	1.00	0.00	1.00	0.00	1.00
Writing sentence	0.00	1.00	0.00	1.00	0.00	1.00
Copying a figure	0.00	1.00	0.00	1.00	0.00	1.00
Overall MMSE score	-4.28	0.00	-2.84	0.01	-1.90	0.06

registration, recall, and copying at 24 h, and only recall at 2 weeks postoperatively. However, neither of the two groups had cognitive decline to the extent of major neurocognitive disorder (MMSE Score < 24). Findings of our study is supported by previous study among elderly which reported significantly greater prevalence of POCD after general anesthesia compared to regional anesthesia after 1week postoperatively [4,7], whereas insignificantly after 3months postoperatively [4]. Also studies have reported statistically significant impairment of cognitive function after three days following general anesthesia, but not after use of local anesthesia (10–12). Anwer and colleagues (2006) reported similar findings among elderly, but not among young adults [13]. Whereas, Machado and colleagues (2000) reported significant 24 h POCD after general balanced anesthesia, but not with total intravenous anesthesia and regional anesthesia [14]. Whereas, contrary to our findings, a few studies have reported insignificant difference in POCD after general and regional anesthesia postoperatively [5].

Findings of our study suggest direct effect of general anesthesia that might have played in greater decline in cognition in group 1 [6,15,16], in addition to indirect effects[1,6] such anticholinergic effect on cognition, intraoperative poor cerebral oxygenation and cerebral micro-emboli that might have played in decline in cognition after regional anesthesia (group 2). Whereas, a few studies have refuted the role of anticholinergic [17], poor cerebral oxygenation [18], and cerebral micro-emboli [19,20] in POCD.

The use of regional anesthesia to the control group and the use of well defined selection criteria have provided a methodological strength to the present study in minimizing several confounding bias observed by previous studies such as elderly age, low education, pre-existing medical illness eg. hypothyroidism and metabolic syndrome, cerebro-vascular accidents, neuropsychiatric illness eg. depression and cognitive dysfunction, type of surgery (cardiac and hip), longer duration of surgery, respiratory complications, infections, re-operation, post-operative pain and inflammation, and delirium [1,4,6,21].

Conclusion

To conclude the present study highlights the role of general anesthestic agent in causing postoperative cognitive decline. Although magnitude of this decline was small, however, it was observed in both the groups. When compared to regional anesthesia, cognitive decline after general anesthesia was significantly greater in domains related to orientation to time and place, registration, recall, and copying at 24 h, and only recall at 2 weeks postoperatively. Compared to previous studies on elderly population, present study extends findings over to young and middle aged adults. Hence, findings suggest besides preoperative and intraoperative precautions, postoperative cognitive remediation techniques such as reorienting, attention, recent memory, verbal fluency, and visuo-spatial task may be recommended during early postoperative period, whereas recent memory task may be continued till later. Future studies investigating the effect of individual anesthetic agent in causing POCD is required.

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