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A Comparative Study of Pregnant Patients with Cardiac Disease undergoing General Anesthesia Versus Regional Anesthesia in View of Post-operative Neurocognitive Dysfunction after Cesarean Section

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Abstract

Aim: Our aim was to comparatively evaluate the post-operative neurocognitive dysfunction following general and regional anesthesia in pregnant patients with cardiac disease undergoing elective cesarean section. *Materials and Methods:* Sixty pregnant patients with congenital or rheumatic heart disease undergoing elective cesarean section were divided into two groups, General anesthesia group (Group G, n = 30) and Regional Anesthesia Group (Group R, n = 30). Neuro-Cognitive Tests - Trail Making test A & B, Digit symbol substitution test, Benton visual retention test and Benton visual recognition test were performed one day prior to surgery and at 6h, on day 1 and day 3 post-operatively. *Results:* Neuro-cognitive tests when compared from their pre-operative values to 6h, day 1 and day 3 post-operatively, there was a significant increase (p <-0.001) in both Groups G and Group R. Whereas when compared between the Group G and Group R at pre-operative, 6h, day 1 and day 3 post-operatively there was no significant difference between them (p > 0.05). Cognitive dysfunction occurred in both the groups but it was short lasting in Group R. Post-operative cognitive dysfunction incidence in Group G was 23% as compared to 10% in Group R on day 3. *Conclusion:* Neurocognitive functions are affected in post-operative pregnant patients with cardiac disease irrespective of the technique of anesthesia. However, recovery is delayed in patients receiving general anesthesia.

Keywords: Cardiac disease; Epidural anesthesia; General anesthesia; Post-operative cognitive dysfunction.

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Introduction

Post-operative Cognitive Dysfunction (POCD) is impairment of cognitive function such as attention, perception, memory, concentration, information processing seen after anesthesia and surgery.[1] Patients undergoing cardiac surgeries, elderly patients above the age of *60 years* are at increased risk for cognitive decline though it can occur at any age or after any type of surgery.[2,3] Mechanism of cognitive impairment is not clear but it has been hypothesized that inflammatory response to surgery and anesthesia plays an important role.[4] Other factors such as alterations

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in blood pressure, cardiac output, degree of hypocarbia, use of vasopressors significantly affect the cerebral perfusion.[5,6] There is a marked difference in physiological effects of general anesthesia (GA) and regional anesthesia (RA) on cerebral metabolic rate, oxygen delivery and cerebral metabolism.

Literature shows that pregnancy affects cognitive function and has often been associated with cognitive deficits.[7,8] Heart diseases are more frequently seen in females and rheumatic heart disease often becomes apparent during pregnancy as there is increase in cardiac output secondary to rise in blood pressure and heart rate.[9] It has frequently been speculated that cognitive dysfunction might be avoided by performing appropriate surgery under RA. Majority of studies have concentrated on incidence of POCD between RA and GA in geriatric patients undergoing cardiac, ocular, abdominal, vascular, urologic and orthopedic surgeries and parturient undergoing lower segment cesarean section (LSCS).[10,-13] There is sparse literature available on incidence of POCD in pregnant patients with cardiac disease. There has been a controversy regarding distinctive advantage of a particular technique of anesthesia (GA *vs* RA) in prevention of POCD.[11]

Therefore, we conducted a prospective study in 60 pregnant patients with cardiac disease to comparatively evaluate the effect of GA and RA (epidural anesthesia) on POCD in the immediate post-operative period using various neuro-cognitive tests.

Materials and Methods

This study was carried out on 60 pregnant patients with cardiac disease, between *18* and *32 years* of age after obtaining informed valid consent and Ethics Committee approval over a period of *two years*. Patients were divided into two groups, Group G (n = 30) receiving general anesthesia and Group R (n = 30) receiving epidural anesthesia posted for LSCS. All patients were evaluated pre-operatively with thorough physical examination, Mini mental status examination (MMSE) and appropriate routine investigations. Pregnant patients with cardiac disease, with stable hemodynamic status, those who were able to read and write and with sound mental status were included in the study. Patients suffering from known neuropsychological dysfunction, seizure disorder, anti-psychotic medications, history of head injury or neuro surgery in the past, patients who were deaf, dumb or blind and MMSE score < 24 were excluded from the study.

Neurocognitive functions of obstetric patients were assessed using neuropsychological tests-Trail Making Test A (TMT-A), Trail Making Test B (TMT-B), Digit Symbol Substitution Test (DSS), Benton Visual Retention Test (BVRet) & Benton Visual Recognition Test (BVRoc) one day prior to surgery (pre-operative value). TMT-A, TMT-B and DSS measures visuomotor speed, conceptual tracking and attention, concentration respectively. In TMT-A and TMT-B, time taken to connect alphabets in ascending order and time taken to connect alphabets and numbers alternatively was noted respectively. In DSS time taken to substitute digit with symbol was recorded. BVRet and BVRec are in tandem to each other, which measures immediate visual recall memory and visual spatial ability. In these two tests, correctly recalled pictured objects were noted as True Positives else were termed as False Positives. Obstetric patients who were unable to complete these tests pre-operatively were subsequently excluded from the study and were replaced by other patients.

On the day of surgery, after clinical examination, 18G intravenous access secured. Electrocardiogram (ECG), Pulse-oximeter and non-invasive arterial pressure monitors were attached for monitoring pulse rate (PR), oxygen saturation (SpO_2), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) which were measured every *5 min* intra-operatively. Selection of patients in individual groups was random and patients satisfying selection criteria were studied.

General Anesthesia

After pre-oxygenation, rapid sequence induction was done with Inj. Thiopentone *3–5 mg/kg* and Inj. Succinylcholine *0.75 mg–1 mg/kg*, followed by orotracheal intubation maintaining cricoid pressure. Anesthesia was maintained with Inj. Vecuronium *0.05 mg/kg*, pentazocine *0.5 mg/kg*, midazolam *0.025 mg/kg*, 0.5 MAC Isoflurane and 50% O_2 + 50% Air with controlled ventilation. Neuromuscular blockade was reversed with Inj. Neostigmine *0.05 mg/kg* and Inj. Glycopyrrolate *0.08 mg/kg* at the end of surgery followed by extubation.

Regional Anesthesia

Epidural anesthesia was given using 16G Tuohy's needle in L_{3-4} interspace and epidural catheter was secured. Inj. Bupivacaine *0.5% 8–12 ml* was given after giving test dose to get desired level.

Intra-operative Monitoring

Intra-operatively in both the groups, patients were continuously monitored and vitals (PR, SBP, DBP, Pulse Pressure variation, Blood Pressure variation) were recorded every *5 min* interval. Soon after the delivery *20 units* of Oxytocin was administered slowly over *20 min* in both the groups. Intra-operative events such as hypoxia (SpO_2 < 95%), hypotension (SBP < 25% of the baseline value), bradycardia (PR < *50/min* or 25% from the baseline) or excess blood loss was noted and appropriately treated. Any other intra-operative complications when occurred, were noted and treated accordingly. Post-operative pain relief was provided with Inj. Diclofenac sodium *1 mg/kg* or Inj. Tramadol-HCL *1 mg/kg* to keep patient pain free or with tolerable mild pain.

Post-operative Cognitive Function Assessment

Post-operatively neurocognitive functions were again assessed after *6 h*, on *day 1* and on *day 3* post-operatively using same neuropsychological tests which were used pre-operatively. Each time different sets of test forms and picture cards were used to avoid learning by repetition.

Post-operative cognitive dysfunction

POCD was considered to be present when there was more than 25% increase in time taken or 25% decrease in value or score of at least two Neuropsychological tests, as compared to pre-operative time/score in a patient. Incidence of such cognitive dysfunction was noted.

*Stat**ist**ical analysis*

Normal distribution of data was tested using Kolmogorov Smirnov test. ANOVA test was used to compare within the groups if data is normally distributed. To compare between the groups, Student *t*-test was used for normally distributed data and Mann-Whitney *U* test was used for data which was not normally distributed. Data was expressed as Mean ± SD. A *p* value < 0.05 was considered as statistically significant difference.

Results

Sixty pregnant patients with cardiac disease who underwent LSCS after receiving GA or epidural anesthesia were included in the study. Demographic parameters with respect to age, duration of anesthesia, level of education and hemodynamic parameters *i.e.*, PR, SBP, DBP, pulse rate variation, blood pressure variation, SpO_2 < 95% were comparable between Group G and Group R. Shows in Table 1.

Time taken to complete TMT-A, TMT-B and DSS, when compared from pre-operative values to *6 h*, *day 1* and *day 3* post-operatively, there was statistically significant increase ($p < 0.001$) in both Groups G and Group R. Whereas when compared between the Group G and Group R at pre-operative, *6 h*, *day 1* and *day 3* post-operatively there was no statistical significant difference between them ($p > 0.05$) except in Group G which took longer duration to complete DSS at *6 h* as compared to Group R (50 ± 6.7 *vs* 44.5 ± 7.9 *secs*, $p < 0.05$) shows in Table 2 and Fig. 1). Number of mistakes done in Trail making test A and Trail making test B, within the groups when compared from pre-operative values to different time intervals, as well as when compared between the groups were also not significant ($p > 0.05$).

In BVRet shows in Table 3 True positives when compared from the pre-operative values to *6 h*, *day 1* and *day 3* post-operatively within the groups showed a significant decrease ($p < 0.001$) whereas False positives were significantly increased only in Group G at *6 h* ($p < 0.05$). When compared between the Groups G and Group R for True positives and false positives there was no significant difference ($p > 0.05$).

In BVRec shows in Table 3 it was observed that there was a significant decrease in True positives when compared from pre-operative values to *6 h* and *day 1* post-operative ($p < 0.001$) in both the groups. Whereas on post-operative *Day 3*, Group R had equal number of correctly identified objects (True positives) as compared to their pre-operative values (5.1 ± 0.7 *vs* 4.9 ± 0.7, $p > 0.05$) but in Group G there was a significant decrease in True positives (5.2 ± 0.7 *vs* 4.6 ± 0.7, $p < 0.001$). Similarly, identification of false objects (False positive) were more in Group G from pre-operative value to *6 h*, *day 1* and *day 3* post-operatively ($p < 0.01$). Whereas in Group R there was no significant false positives identified from pre-operative value to post-operative *day 1* and *day 3*. ($p > 0.05$). When compared between the groups on post-operative day 3, number of false positives were less in Group R ($p < 0.05$) which signifies that deterioration persisted in Group G for a longer time.

Incidence of cognitive dysfunction was more in Group G as compared to Group R (23% *vs* 10%) on post-operative *day 3* displays in Fig. 2. From the

above data even though clinically less deterioration was noted in Group R, it was not significant than Group G. Cognitive dysfunction occurred in both the Groups but in Group G it was long-lasting as there was significant increase in false positives compared to Group R. Also, in Group R incidence was less, as less than half of patients had cognitive dysfunction as compared to Group G (3 *vs* 7 patients) on post-operative day 3.

Table 1: Baseline Demographic, Hemodynamic Parameters

Parameters	Group G (n = 30)	Group R (n = 30)
Age (Mean ± SD)	24.7 ± 2.9 years	23.6 ± 3.7 years
Duration of Anesthesia	65.8 ± 9.5 min	71.7 ± 9.5 min
Pulse rate (per minute)	79.8 ± 5.0	80.5 ± 4.9
Systolic Blood Pressure (mm hg)	125.7 ± 16.8	124.7 ± 10.7
Diastolic Blood Pressure (mm hg)	76.1 ± 6.4	77.1 ± 5.6
Mini Mental Status Examination (MMSE) Score	27.6 ± 0.9	27.5 ± 1.0
Values are shown as Mean ± SD, $p > 0.05$		
Level of Education (No of Patients)		
I –< 5th standard	5	4
II –6th to 10th standard	11	12
III – 11th to 12th standard	7	9
IV – > 12th standard	7	5
Pulse Rate Variation > 25% from baseline)	2	2
BP Variation (> 25% from baseline)	2	1
SpO_2 < 95%	1	1

$p > 0.05$

Table 2: Neuropsychological tests–trail making test a, trail making test b, digit symbol substitution test.

Tests	Group G (n = 30) Time taken (seconds)	Group R (n = 30) Time taken (seconds)
Trail Making Test A		
Pre-operative	111.5 ± 25.7	104 ± 22.1
6 h	190.5 ± 42.5 ***	169.0 ± 39.6 ***
Day 1	168.5 ± 42.5 ***	148.8±34.2 ***
Day 3	138.4 ± 31.1***	125.3 ± 27.2 ***
Trail Making Test B		
Pre-operative	192.6 ± 36.7	181 ± 40.7
6 h	277.8 ± 45.6 ***	264.4 ± 53 ***
Day 1	252.9 ± 41.7 ***	242 ± 49.1 ***
Day 3	226.4 ± 35.5 ***	212.8 ± 42.8 ***
Digit Symbol Substitution Test		
Pre-operative	33.2 ± 4.6	32.9 ± 5.9
6 h	50 ± 6.7 ***	44.5 ± 7.9 ***,#
Day 1	44 ± 6 ***	40.5 ± 6.9 ***
Day 3	38.3 ± 5.7 ***	36.4 ± 6.9

*** $p < 0.001$ (Comparison between pre-operative values and post-operative 6 h, Day 1, Day 3 within the group respectively)

\# $p < 0.05$ (Comparison between Group G and Group R at 6 h)

Table 3: Neuropsychological Tests–benton Visual Retention Test, Benton Visual Recognition Test

Tests	Group G (n = 30)	Group R (n = 30)
Benton Visual Retention Test		
True Positives		
Pre-operative	10.8 ± 1.4	10.9 ± 1.4
6 h	7.9 ± 1.4 ***	8.3 ± 1.4 ***
Day 1	8.8 ± 1.1 ***	9.4 ± 1.3 ***
Day 3	9.6 ± 1.4 ***	10.2 ± 1.3 ***
False Positives		
Pre-operative	0.2 ± 0.6	0.3 ± 0.6
6 h	0.7 ± 1.2 *	0.7 ± 1.2
Day 1	0.5 ± 0.9	0.4 ± 0.7
Day 3	0.2 ± 0.6	0.3 ± 0.4
Benton Visual Recognition Test		
True Positives		
Pre-operative	5.2 ± 0.7	5.1 ± 0.7
6 h	3.6 ± 0.7 ***	4.0 ± 0.7 ***
Day 1	4.2 ± 0.6 ***	4.6 ± 0.6 ***
Day 3	4.6 ± 0.7 ***	4.9 ± 0.7
False Positives		
Pre-operative	0.4 ± 0.7	0.7 ± 0.8
6 h	1.4 ± 1.0 **	1.3 ± 1.0 **
Day 1	1.0 ± 0.9 **	1.0 ± 0.8
Day 3	1.0 ± 1.0 **	0.8 ± 0.7 #

*** $p < 0.001$ (Comparison between pre-operative values and postoperative 6 h, Day 1, Day 3 within the group respectively)

** $p < 0.01$ (Comparison between pre-operative values and postoperative 6 h, Day 1, Day 3 within the group respectively)

* $p < 0.05$ (Comparison between pre-operative values and postoperative 6 h, Day 1, Day 3 within the group respectively)

# $p < 0.05$ (Comparison between Group G and Group R at post-operative Day 3)

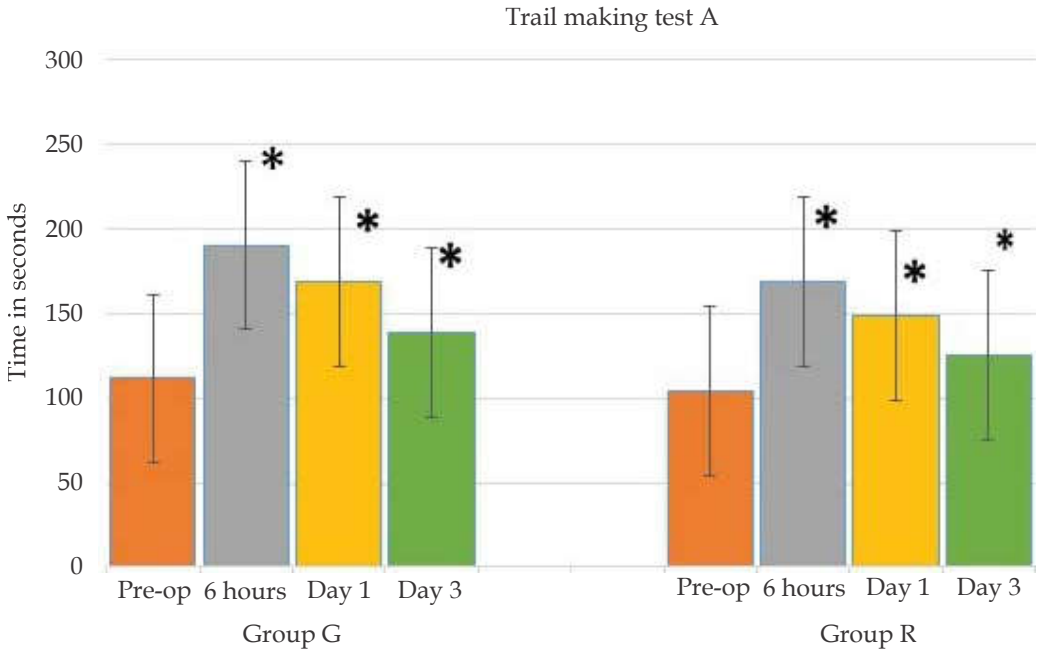

Fig. 1A

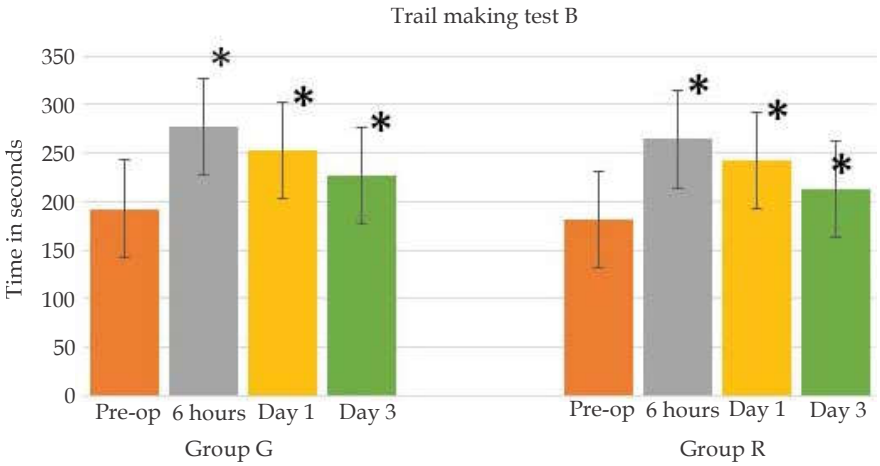

Fig. 1B

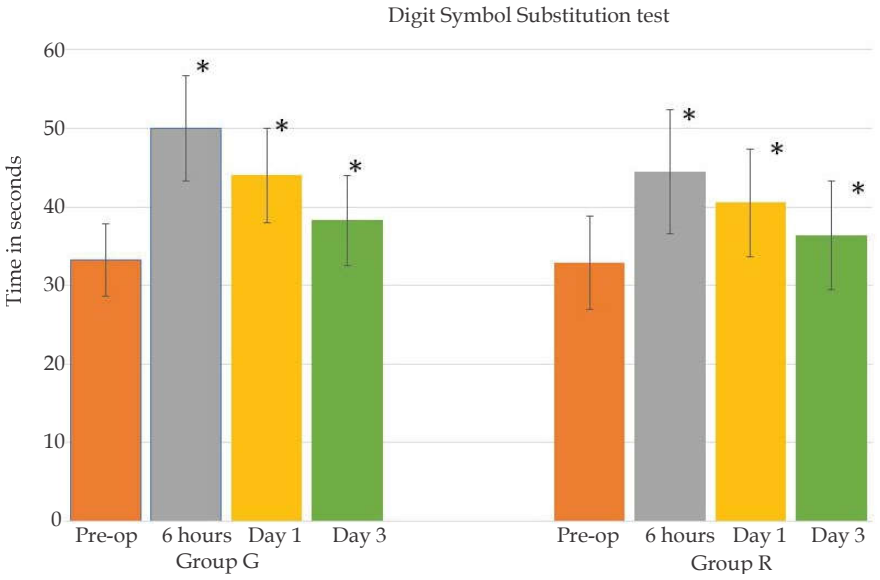

Fig. 1C

Fig. 1: Neuropsychological Tests: (A)-Trail Making Test A, (B)-Trail Making Test B, (C) - Digit Symbol Substitution Test (Mean ± SD) (* $p < 0.001$) (Pre-op – pre-operative, 6 hours – post-operative 6th hour, Day 1 – post-operative day 1, Day 3 – post-operative day 3)

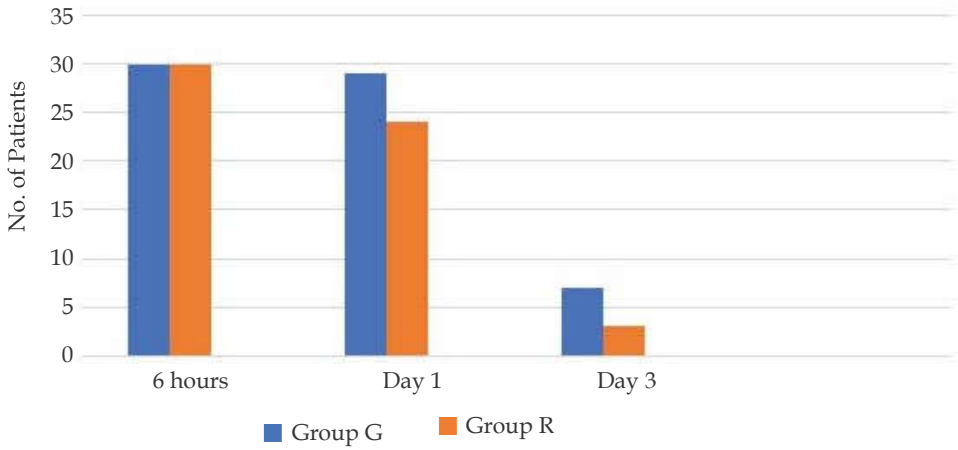

Fig. 2: Incidence of Cognitive Dysfunction.
(6 hours – post-operative 6th hour, Day 1 – post-operative day 1, Day 3 – post-operative day 3)

Discussion

Over the past four to five decades studies have been performed to assess the cognitive function after anesthesia and surgery but the proportion of patients affected remains unchanged. It is evident from the literature that elderly patients possess an increased risk of developing POCD. Inflammatory response and calcium dysregulation of the brain has been postulated as the mechanism of POCD, although mechanism is still not clearly understood.[14] Poor cognition is also noted in young individuals after ambulatory surgery. Chung *et al*.[15] reported serious accident in two patients who drove without an escort following a day care surgery. Cognitive decline in pregnancy is an established phenomenon which can last for *two years* post-pregnancy.[16] Pregnancy is shown to be associated with memory loss, increased forgetfulness, poor concentration, poor attention, disorientation, confusion and reading problems.[7] Neural imaging study done during pregnancy has revealed decreased grey matter volume in brain regions associated with social cognition.[16] Cardiovascular disease is another risk factor for developing neurocognitive decline. It has been linked with Alzheimer's disease. Also, long standing hypotension and low cardiac output is known for causing cognitive impairment.[5] Along with the surgical procedure during pregnancy, a compromised cardiac condition can further expand the chances of POCD.

Anesthetic drugs, analgesics, opioids, benzodiazepines have been studied to impair cognition and these effects extend into post-operative period. Numerous studies have focused on development of POCD between GA and RA but protective benefit of either of the two techniques is still not proven.[11]

In a systematic review article by Davis *et al*.[12] sixteen studies were eventually investigated wherein only three studies showed some difference in cognitive function favoring RA over GA and other thirteen studies concluded POCD was independent of type of anesthesia.

Anwer HM *et al*.[17] compared POCD between GA and RA in elderly patients undergoing urologic and orthopedic surgery using Wechsler Adult Intelligence Scale-Revised score on post-operative *day 1* and *day 3*, found an increased incidence on post-operative *day 3* in GA group. Similarly, Rasmussen *et al*.[18] studied 438 patients who underwent major non-cardiac surgery, used four neuropsychological tests and found that incidence of POCD was significantly higher after GA on 7th post-operative day, although no difference was found at the end of three months between GA and RA. Mason *et al*.[10] in their meta-analysis analyzed studies done majorly on orthopedic, urology, abdominal and vascular surgeries observed that GA may increase the incidence of POCD in the early post-operative period though no difference on long-term follow up was found. However, they recommended use of RA whenever possible in vulnerable patients. In the present study, w.r.t neuropsychological tests there was no statistically significant difference between the groups however, poor cognition persisted for longer duration in GA Group when compared by their pre-operative values, as well as more than half of the patients had cognitive dysfunction in Group G compared to Group R.

Alten *et al*.[13] compared effects of GA (Sevoflurane and Desflurane group) and spinal anesthesia on short-term (*pre-operatively*, post-operatively - *1h*, *3h* and *day 1*) post-operative cognitive function in ASA1 patients following cesarean section and concluded no effect on cognitive function. The probable reason being GA was titrated according to Bi-spectral index and neuromuscular monitoring. In the present study, cognitive dysfunction occurred in pregnant patients with cardiac disease in both the groups on post,operative *6 h*, *day 1* and *day 3*, however in Group R it was short-lasting.

In GA, opioids form an integral part of pain management along with benzodiazepines for achieving balanced effect. Both opioid and benzodiazepines have shown an increased risk of POCD whereas RA being local anesthetic based, use of above anesthetic drugs are minimal. Hence, RA can have a decreased incidence of POCD.[19] In the present study, only 10% of patients continued to have cognitive dysfunction as compared to 23% of patients in Group G. This incidence of POCD in Group G could have been further decreased with the use of cerebral monitors though the evidence is limited to one study.[20] The limitations of the present study included-1) only early post-operative period was studied and the study was not continued in the late post-operative period, 2) Cerebral monitors were not used to monitor the depth of anesthesia and hence further minimize the use of anesthetic drugs.

Conclusion

In conclusion, POCD development in post-operative pregnant patients with cardiac disease treated with general anesthesia and regional anesthesia were comparable. However, early post-operative

recovery was delayed in patients receiving general anesthesia and hence, it is preferable to use regional anesthesia in patients vulnerable to develop POCD.

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