Randomized Trial

The Associations Between Cognitive Dysfunction, Stress Biomarkers, and Administered Anesthesia Type in Total Knee Arthroplasties: Prospective, Randomized Trial

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Background: Postoperative cognitive dysfunction (POCD) is a serious complication associated with total knee arthroplasty (TKA) and has been shown to increase the length of hospital stay, cause functional impairment, and morbidity.

Objectives: We aimed to determine whether POCD is associated with the use of general or regional anesthesia in patients undergoing TKA. Our hypothesis was that POCD would be reduced in the group that received regional analgesia without any sedations. Our secondary hypothesis was POCD would be associated with biomarkers of surgical stress.

Study Design: Randomized controlled study between general and spinal anesthesia.

Setting: Single-centered, university hospital, from January to October 2017.

Methods: A total of 112 patients were assessed for eligibility, and a total of 57 patients completed the study. We divided the patients into general and regional anesthesia groups. Blood samples were obtained preoperatively at the first intraoperative, the third and the 24th postoperative hour. C-reactive protein (CRP), cortisol, insulin, and blood glucose levels were tested. We used 4 neurocognitive tests that were administered 1 day before operation, 7 days and 30 days after operation. Main outcome measures were neurocognitive tests scores for regional anesthesia without sedation and general anesthesia groups. Cortisol, glucose, insulin, and CRP levels.

Results: Patients who received regional anesthesia showed significantly higher Mini-Mental State Examination (MMSE) scored compared with the general anesthesia at the seventh day ($P = 0.037$). In the general anesthesia group, patients showed significantly higher variations for the Stroop number difference. There were negative correlations between MMSE scores measured at postoperative day 7 and the 1-hour intraoperative cortisol measurements ($r = –0.302$; $P = 0.022$) and 3-hour postoperative cortisol measurements ($r = –0.295$; $P = 0.026$).

Limitations: A limitation was the small number of patients.

Conclusions: We demonstrate that regional anesthesia results in better neurocognitive test scores than general anesthesia in patients undergoing TKA. Patients who received regional anesthesia showed lower cortisol, higher insulin, and lower glucose levels. We recommend that patients who undergo arthroplasty surgeries should receive regional anesthesia to avoid POCD at the early stages of the postoperative period.

Key words: Cognitive dysfunction, stress biomarkers, acute pain, regional anesthesia, spinal anesthesia

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The risk of total knee arthroplasty (TKA) increases with age, and the number of TKAs performed each year has increased considerably (1). TKA is a very effective surgery for patients and has been shown to result in favorable surgical outcomes, including noticeably lessened pain and enhanced physical function (1,2). However, like all operations, TKA can result in complications, including thromboembolism, bone-cement syndrome, anemia, cardiac arrhythmia, fat emboli syndrome, pneumonia, pain, delirium, and postoperative cognitive dysfunction (POCD) (3). POCD is one of the most serious complications associated with TKA and has been shown to increase the length of hospital stays and to cause functional impairment, morbidity, and diminished quality of life (4-7). The exact pathophysiology of POCD is uncertain. POCD has been shown to disturb a variety of cognitive function including memory, attention, orientation, and concentration (4,8). Further, complications arising from TKA have been shown to be associated with the use of general and regional anesthesia, and there are conflicting results about whether regional analgesia is protective for POCD (9). In the literature, there are few studies comparing general anesthesia patients with no-sedation regional anesthesia patients. We think that the sedation levels used for regional anesthesia may affect POCD levels.

In this study, we aimed to determine whether the incidence of POCD is associated with the use of general or regional anesthesia in patients undergoing TKA. Our hypothesis was that POCD would be reduced in the group that received regional analgesia without any sedations. Our secondary hypothesis was POCD would be associated with biomarkers of surgical stress (C-reactive protein [CRP], insulin, cortisol, and glucose).

Methods

We carried out this prospective randomized trial at our university hospital between January and October 2017. Our study was approved by the Ahi Evran University ethical committee (reference number: 2017-01/01; approval date: January 03, 2017). Trial registration: ISRCTN Registry (ISRCTN67177877).

A computer software program for block randomization was used to randomly divide the patients into general and regional anesthesia groups Inclusion criteria were: (1) elective case; (2) age < 90 years; (3) body mass index < 40; (4) Mini-Mental State Examination (MMSE) score of > 15; and (5) a unilateral case. We excluded patients with emergent trauma cases, patients with prior psychiatric or neurologic disorders, patients using steroid medications, chronic nonsteroidal anti-inflammatory drug (NSAID) usage, or patients with uncontrolled diabetes. After the randomization of the patients, we excluded anyone who showed a contraindication for the anesthesia type that they were assigned to. We defined any known prior difficult intubation anamnesis as a contraindication for general anesthesia. We defined any bleeding disorder, infection in the intervention site, and intracranial pathologies as being contraindications for regional anesthesia.

Routine general anesthesia for TKA involved using 100% oxygen followed by induction with propofol (2 mg/kg^{-1}) and rocuronium (0.6 mg/kg^{-1}). Anesthesia was maintained with sevoflurane (2%) and a mix of 50% O2 and 50% nitrous oxide. Routine regional anesthesia administration involved a single shot of 2.8 mL hyperbaric bupivacaine (0.5%) into the subarachnoid space of the L3-L4 intervertebral space. We did not use any sedation for patients in the regional anesthesia group during the operation. All patients received the same pain treatment of morphine patient-controlled analgesia, and rescue pain treatment was provided with tramadol and additional morphine when necessary. We did not use NSAIDs for pain therapy. Blood samples were obtained from each patient 15 minutes before anesthesia induction for base results, at the first intraoperative hour, the third postoperative hour, and the 24th postoperative hour. CRP (mg/L^{-1}), cortisol ($\mu g/dL^{-1}$), insulin ($\mu U/mL^{-1}$), and plasma glucose levels (mg/dL^{-1}) were tested. Plasma glucose levels were tested using the autoanalyzer hexokinase method, insulin and CRP levels with the high sensitivity enzyme-linked immunosorbent assay method, and cortisol levels with the chemiluminescence immunoassay method.

Neurocognitive Analysis

Neurocognitive tests were administered by one of our anesthesiology consultants under the supervision of a psychiatrist. The MMSE, the Cognitive Failure Questionnaire (CFQ), the Auditory Verbal Learning Test (AVLT), and the Stroop interference test were each administered by an anesthetist 1 day before operation (preoperative), 7 days after operation, and 30 days after operation. For the AVLT, we used 7 scores to reflect most of the verbal memory processes including learning, interference, retention, and retrieval. Similar to previous studies, we used word lists and trials to test the memory at different timepoints (10).

We used the Golden Stroop test in the current study, and patients were asked to name as many items as possible in 45 seconds. Our outcome variable was the number of items finished correctly. The Stroop test also allowed us to determine the testing word score (W), color (C), and color–word (CW) scores. We calculated the difference between the C and CW scores as the difference score (ID). We defined the ID number accordingly: ID number = C-CW. A lesser difference score indicates less interference (11). We defined POCD as any statistically significant changes of neurocognitive test scores from the preoperative levels for each group.

Statistical Analysis

Number Cruncher Statistical System 2007 software (NCSS, Kaysville, UT, USA) was used for statistical analysis. Work data descriptive statistics (mean, standard deviation, median, frequency, rate, minimum, maximum) were calculated for all variables, and normally distributed variables were compared using the Student t test. For nonparametric data, the Mann–Whitney U test was used for group comparisons. To evaluate the follow-up variables that were normally distributed, we employed a repeated measures test with a Bonferroni correction for the binary comparisons. We evaluated the follow-up variables using the Wilcoxon signed-rank test with the Friedman test for binary comparisons. Pearson correlation analysis and Spearman correlation analysis were used to evaluate the interrelationships between variables. P values < 0.05 were considered significant.

Results

A total of 80 patients met the inclusion criteria for the current study, but 23 of these patients were not included because they met the exclusion criteria. Thus a total of 57 patients were included in the current study (Fig. 1). Thirty-one (54.4%) of the patients received re-

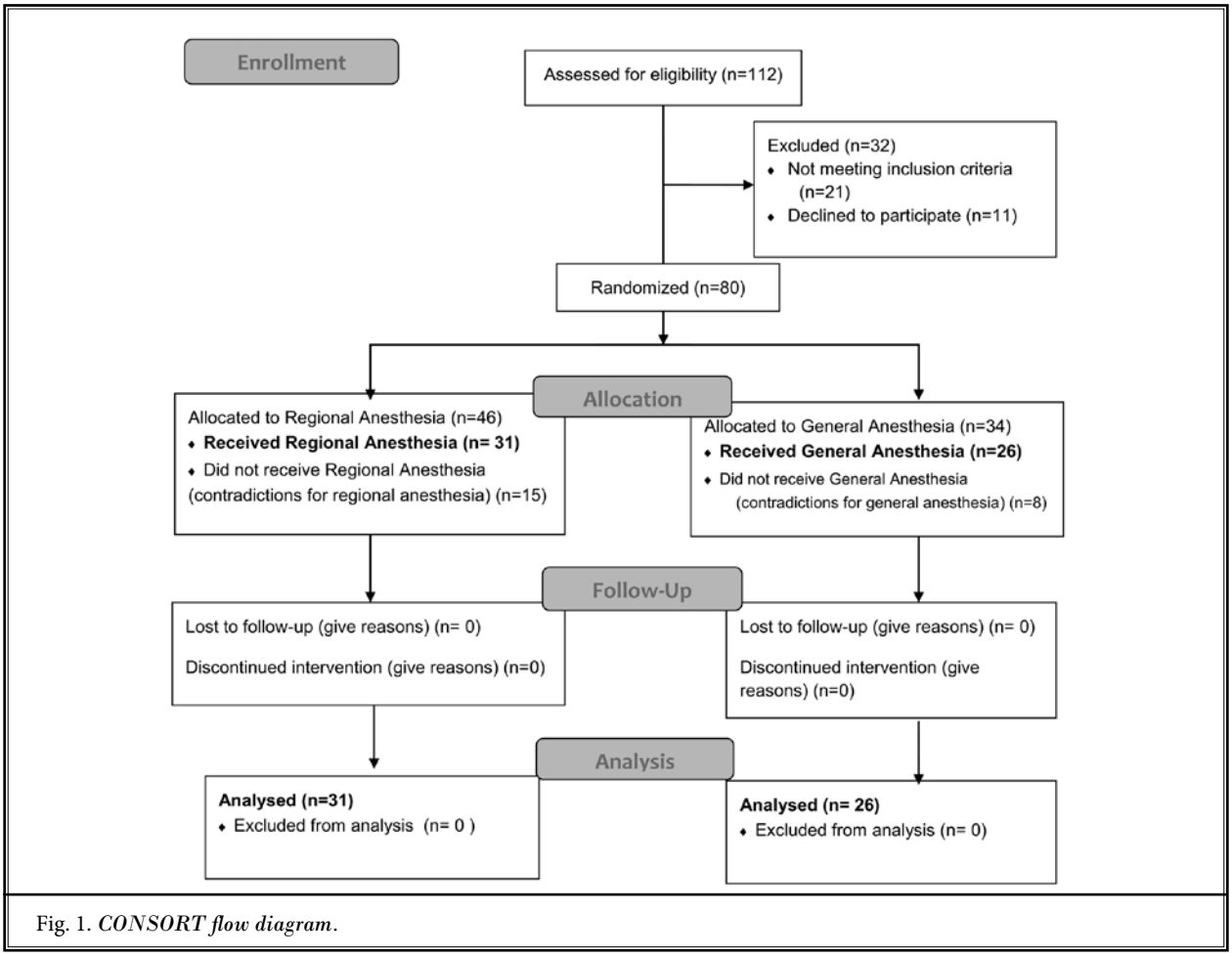

Fig. 1. *CONSORT flow diagram.*

gional anesthesia for the operation. Demographic data are presented in Table 1.

For the AVLT, we did not detect any differences between the 2 anesthesia types at any timepoint or for any of the comparisons ($P > 0.05$). As shown in Table 2, we observed a significantly higher MMSE score for the spinal anesthesia group compared with the general anesthesia group ($P = 0.037$) at the seventh postoperative day. The general anesthesia group showed significantly different MMSE scores at each timepoint ($P = 0.002$). The binary comparisons in the general anesthesia group showed a significantly greater change in MMSE score than the regional anesthesia group between the preoperative evaluation and postoperative day 7 ($P = 0.004$), and between postoperative day 7 and postoperative day 30 ($P = 0.01$), which we define as POCD.

As shown in Table 3, we did not detect any statistical association between CFQ scores and anesthesia type at any point in time (all $P > 0.05$). For the Stroop test results (Table 4), we found a significant difference in the general anesthesia group among all 3 evaluation timepoints ($P = 0.019$). The binary comparisons showed that between the preoperative evaluation and postoperative day 7, the mean score decreased significantly ($P = 0.003$), and that between postoperative days 7 and 30 the mean score increased significantly ($P = 0.047$). We found that the general anesthesia group showed significantly greater changes than the regional anesthesia group between the preoperative evaluation and postoperative day 7 ($P = 0.002$).

As shown in Table 5, the general anesthesia group did show higher cortisol levels than the regional anes-

Table 1. *Demographic data.*

	Anesthesia Type		
	General Anesthesia	**Spinal Anesthesia**	***P***
Age (years) mean ± SD	68.77 ± 4.94	69.84 ± 4.36	0.767
Body mass index (kg/m^2) mean ± SD	31.54 ± 3.20	32.29 ± 3.42	0.352
Number of patients (%)	26 (45.6)	31 (54.4)	

*P < 0.05.
Abbreviation: SD, standard deviation

Table 2. *MMSE test results by anesthesia type.*

MMSE			**Anesthesia Type**						‡***P***
			Total (n = 57)		**General Anesthesia (n = 26)**		**Spinal Anesthesia (n = 31)**		
Preoperative	mean ± SD		22.58 ± 2.79		22.62 ± 2.99		22.55 ± 2.66		***0.922***
7 day	mean ± SD		21.53 ± 4.08		20.27 ± 5.08		22.58 ± 2.64		***0.037****
30 day	mean ± SD		22.84 ± 4.06		22.31 ± 3.45		23.29 ± 4.52		***0.279***
	§***P***		***0.020****		***0.002***†		***0.783***		
Variations									
Preoperative 7 day		ΙΦ***P***	–9 to 3 (0) –1.05 ± 2.58	***0.009***†	–9 to 2 (–1) –2.35 ± 3.20	***0.002***†	–2 to 3 (0) 0.03 ± 1.11	***0.968***	***0.004***†
Preoperative 30 day		Ι***P***	–3 to 17 (0) 0.26 ± 2.60	***0.825***	–3 to 3 (–0.5) –0.31 ± 1.19	***0.141***	–2 to 17 (0) 0.74 ± 3.31	***0.345***	***0.121***
7 day to 30 day		Ι***P***	–3 to 17 (1) 1.32 ± 3.12	***0.001***†	–3 to 9 (1) 2.04 ± 2.99	***0.003***†	–1 to 17 (0) 0.71 ± 3.15	***0.216***	***0.010****

*P < 0.05. †P < 0.01. ‡Mann–Whitney U test. §Friedman test. ΦWilcoxon signed-rank test.
Abbreviation: SD, standard deviation.

Table 3. *Evaluation of the CFQ by anesthesia type.*

CFQ			Anesthesia Type						*P
			Total (n = 57)		General Anesthesia (n = 26)		Spinal Anesthesia (n = 31)		
Preoperative	mean ± SD		33.82 ± 14.30		31.15 ± 13.87		36.06 ± 14.49		0.199
7 day	mean ± SD		34.98 ± 13.72		31.81 ± 14.52		37.65 ± 12.63		0.110
30 day	mean ± SD		33.98 ± 12.91		31.15 ± 12.81		36.35 ± 12.72		0.131
	†P		0.203		0.717		0.268		
Variations									
Preoperative 7 day		‡P	–12 to 10 (1)	0.209	–12 to 8 (1)	1.000	–10 to 10 (1)	0.270	§0.579
			1.16 ± 4.72		0.65 ± 4.38		1.58 ± 5.03		
Preoperative 30 day		‡P	–21 to 8 (1)	1.000	–13 to 8 (2)	1.000	–21 to 8 (1)	1.000	§0.772
			0.16 ± 5.51		0 ± 4.85		0.29 ± 6.09		
7 day to 30 day		‡P	–19 to 8 (0)	0.528	–18 to 8 (0)	1.000	–19 to 7 (0)	1.000	§0.929
			–1.00 ± 5.51		–0.65 ± 5.03		–1.29 ± 5.95		

*Student t test. †Repeated measures test. ‡Bonferroni test. §Mann–Whitney U test.
Abbreviation: SD, standard deviation.

Table 4. *Evaluation of Stroop test results by anesthesia type.*

Stroop Test ID number			Anesthesia Type						*P
			Total (n = 57)		General Anesthesia (n = 26)		Spinal Anesthesia (n = 31)		
Preoperative	mean ± SD		11.74± 15.43		16.75± 20.06		7.55 ± 8.34		0.099
7 day	mean ± SD		9.35± 9.73		10.96 ± 11.49		8.00 ± 7.92		0.670
30 day	mean ± SD		10.98 ± 13.20		14.92 ± 17.08		7.68 ± 7.59		0.748
	†P		0.227		0.019		0.406		
Variations									
Preoperative 7 day		ϕP	–43 to 7 (0)	0.147	–43 to 3 (-2)	0.003	–13 to 7 (0)	0.231	0.002†
			-2.39 ± 8.65		-5.77 ± 11.44		0.45 ± 3.52		
Preoperative 30 day		ϕP	–25 to 11 (0)	0.955	–16 to 8 (-0.5)	0.144	–25 to 11 (1)	0.148	0.060
			0.75 ± 5.81		-1.81 ± 5.76		0.13 ± 5.80		
7 day to 30 day		ϕP	–14 to 34 (0)	0.121	–6 to 34 (0)	0.047†	–14 to 8 (0)	0.769	0.307
			–1.63 ± 7.22		3.69 ± 9.11		–0.32 ± 4.42		

*P < 0.05. †P < 0.01. ‡Mann–Whitney U test. §Friedman test. ϕWilcoxon signed-rank test.
ID number = C-CW the number of items has been scored.
Abbreviation: SD, standard deviation.

thesia group at the first hour (*P* = 0.044). The binary comparisons showed a significant elevation in cortisol levels from the preoperative evaluation to 1 hour intraoperatively (*P* = 0.001) and to 3 hours postoperatively (*P* = 0.001). Also, there were significant elevations in cortisol levels from 1 hour intraoperatively to 3 hours postoperatively (*P* = 0.048). We observed a significant decline in cortisol levels from 3 hours postoperatively to 24 hours postoperatively (*P* = 0.001). For the regional anesthesia group, cortisol measurements were significantly different between the measurement timepoints (*P* = 0.001). Binary comparisons revealed a decline in cortisol levels in the regional anesthesia group between the preoperative evaluation and 1 hour intraoperatively (*P* = 0.022), and a significant increase between 1 hour intraoperatively and 24 hours postoperatively (*P* = 0.013).

The results of the insulin tests are shown in Table 6. We observed that the spinal anesthesia group showed significantly higher insulin levels at 1 hour intraopera-

Table 5. *Cortisol measurement results by anesthesia type.*

Cortisol Measurements			Anesthesia Type						‡*P*
			Total (n = 57)		General Anesthesia (n = 26)		Spinal Anesthesia (n = 31)		
Preoperative	mean ± SD		13.77 ± 5.46		14.62 ± 4.39		13.05 ± 6.20		0.122
1 hour	mean ± SD		16.87 ± 8.68		24.24 ± 5.72		10.69 ± 5.18		0.044*
3 hour	mean ± SD		19.98 ± 10.82		27.65 ± 7.11		13.55 ± 9.10		0.542
24 hour	mean ± SD		14.99 ± 8.20		14.02 ± 7.59		15.80 ± 8.72		0.080
	§P		0.001†		0.001†		0.001†		
%Variation									
Preoperative 1 hour		ϕP	−53.9 to 344.2 (16.4)	0.024*	−5.8 to 344.2 (55.8)	0.001†	−53.9 to 105.2 (−19.4)	0.022*	¶0.001†
			29.53 ± 72.65		80.95 ± 73.11		−13.60 ± 34.4		
Preoperative 3 hour		ϕP	−81.6 to 488.5 (44.5)	0.001†	−12 to 400 (97.1)	0.001†	−81.6 to 488.5 (−16.6)	1.000	¶0.001†
			62.44 ± 109.84		109.09 ± 90.85		23.32 ± 110.34		
Preoperative 24 hour		ϕP	−66.5 to 299.5 (0.5)	1.000	−66.5 to 191.5 (−14.7)	1.000	−64.8 to 299.5 (22.8)	0.478	¶0.047*
			27.11 ± 85.61		3.60 ± 63.79		46.82 ± 97.01		
1 hour to 3 hour		ϕP	−67.9 to 630.1 (12.2)	0.008†	−38.6 to 121.6 (12.3)	0.048*	−67.9 to 630.1 (7.5)	0.279	¶0.810
			33.53 ± 101.85		16.90 ± 29.78		47.48 ± 134.85		
1 hour to 24 hour		ϕP	−80 to 384.6 (−10.9)	1.000	−80 to 114.6 (−49.5)	0.001†	−55.6 to 384.6 (44)	0.013*	¶0.001†
			32.11 ± 121.57		−36.87 ± 43.47		89.96 ± 135.77		
3 hour to 24 hour		ϕP	−82.1 to 902.2 (−38.1)	0.061	−82.1 to 43 (−54.5)	0.001†	−78.7 to 902.2 (24.7)	1.000	¶0.001†
			45.59 ± 198.85		−46.56 ± 31.85		122.89 ± 243.79		

*P < 0.05. †P < 0.01. ‡Student t test. §Repeated measures test. ϕBonferroni test. ¶Mann–Whitney U test.
Abbreviation: SD, standard deviation.

tively than the general anesthesia group (*P* = 0.019). In the general anesthesia group, insulin measurement variations were also significantly different among the measurement timepoints (*P* = 0.001). The binary comparisons showed a significant decline in insulin levels between the preoperative evaluation and 1 hour intraoperatively, but a significant increase between the preoperative evaluation and 24 hours postoperatively (both *P* < 0.001). For the regional anesthesia group, insulin measurement variations were found to be statistically significant between the measured timepoints (P < 0.001). The binary comparisons were similar to those in the general anesthesia group (all *P* < 0.001).

The results of the glucose analysis are shown in Table 7. We observed that the general anesthesia group showed significantly higher glucose levels compared with the regional anesthesia group at 1 hour intraoperatively (*P* = 0.001) and 3 hours postoperatively (*P* = 0.001). Similarly, the general anesthesia group also showed significant glucose measurement variations among the measured timepoints (*P* = 0.001). The binary analyses showed significant increases between the preoperative evaluation and all 3 measured timepoints (all *P* < 0.001), as well as a significant increase between 1 hour intraoperatively and 3 hours postoperatively (*P* = 0.001) and a significant decline between 3 hours and 24 hours postoperatively (*P* = 0.003). In the regional anesthesia group, glucose measurement variations were found to be statistically significant between the measured timepoints (*P* = 0.001). The binary comparisons showed an incline between all measured timepoints, respectively.

Results related to CRP levels are presented in Table 8. For the regional anesthesia group, the CRP measurements varied significantly by measurement point (*P*

Table 6. *Insulin measurements results by anesthesia type.*

Insulin Measurements		Anesthesia Type						‡P
		Total (n = 57)		General Anesthesia (n = 26)		Spinal Anesthesia (n = 31)		
Preoperative	mean ± SD	9.13 ± 5.14		7.98 ± 4.47		10.10 ± 5.52		0.168
1 hour	mean ± SD	5.42 ± 4.93		3.99 ± 3.54		6.62 ± 5.63		0.019*
3 hour	mean ± SD	11.27 ± 7.38		10.61 ± 6.93		11.82 ± 7.81		0.677
24 hour	mean ± SD	26.86 ± 15.64		22.90 ± 14.52		30.18 ± 16.00		0.061
	§P	0.001†		0.001†		0.001†		
% Variations								
Preoperative 1 hour	‖P	−95.4 to 2,010 (−45.7)	0.001†	−95.4 to 45.9 (−50.5)	0.001†	−88.2 to 2,010 (−42.5)	0.001†	0.124
		−6.96 ± 274.06		−48.16 ± 37.76		−27.60 ± 369.2		
Preoperative 3 hour	‖P	−73.1 to 3,293.5 (23.4)	0.065	−72.9 to 642.6 (24.7)	0.064	−73.1 to 3,293.5 (2.6)	0.347	0.442
		160.04 ± 604.70		71.11 ± 150.87		234.62 ± 806.85		
Preoperative 24 hour	‖P	−61.5 to 20,685 (220.4)	0.001†	−61.5 to 573.3 (258.3)	0.001†	−14 to 20,685 (188.1)	0.001†	0.541
		680.88 ± 2,759.50		244.95 ± 175.58		1,046.49 ± 3,726.38		
1 hour to 3 hour	‖P	−69 to 5,160 (107.9)	0.001†	−69 to 3,751.9 (294.9)	0.001†	−63.7 to 5,160 (69.6)	0.001†	0.102
		477.63 ± 954.58		634.82 ± 952.91		345.79 ± 951.24		
1 hour to 24 hour	‖P	−16.7 to 9,690 (424.1)	0.001†	−0.2 to 9,690 (657.4)	0.001†	−16.7 to 6,125 (384)	0.001†	0.242
		1,229.63 ± 1,927.28		1,497.28 ± 2,197.93		1,005.15 ± 1,671.42		
3 hour to 24 hour	‖P	−70 to 1,155.4 (105)	0.001†	−70 to 862.1 (91.8)	0.001†	−43.5 to 1,155.4 (185.4)	0.001†	0.423
		237.78 ± 283.50		195.88 ± 250.78		272.93 ± 307.93		

*P < 0.05. †P < 0.01. ‡Mann–Whitney U test. §Friedman test. ‖Wilcoxon signed-rank test.
Abbreviation: SD, standard deviation.

= 0.001). The binary comparisons showed significant declines between the preoperative evaluation and the 1-hour intraoperative and 3-hour postoperative evaluations (both $P = 0.001$). In the general anesthesia group, CRP measurement variations were significantly different among the timepoints ($P = 0.001$). There were significant increases for both groups at 24 hours postoperatively ($P = 0.001$).

As shown in Table 9, CFQ measurements and cortisol measurements were not significantly correlated ($P > 0.05$). However, there were negative correlations between MMSE scores measured at postoperative day 7 and the 1-hour intraoperative cortisol measurements (r = –0.302; $P = 0.022$), as well as the 3-hour postoperative cortisol measurements (r = –0.295; $P = 0.026$).

The correlations between the Stroop test results and cortisol, insulin, and glucose measurements are shown in Table 10. There was a positive correlation between the Stroop preoperative number difference scores and the 3-hour postoperative cortisol measurements (r = 0.235; $P = 0.048$). There were also significant and positive correlations between the preoperative Stroop number difference scores and the 1-hour intraoperative and 3-hour postoperative glucose measurements (r = 0.264 and 0.354, respectively; both $P < 0.05$). Finally, there were positive and significant correlations between the postoperative day 7 Stroop number difference scores and the 1-hour intraoperative and 3-hour postoperative glucose measurements (r = 0.261 and 0.273, respectively; both $P < 0.05$). We did not detect any significant correlations between CRP levels and MMSE, CFQ, Stroop, or AVLT results (all $P > 0.05$).

Table 7. *Glucose measurement results by anesthesia type*

Glucose Measurements		Anesthesia Type						‡*P*
		Total (n = 57)		General Anesthesia (n = 26)		Spinal Anesthesia (n = 31)		
Preoperative	mean ± SD	99.82 ± 21.63		104.29 ± 22.52		96.07 ± 20.47		0.134
1 hour	mean ± SD	112.50 ± 30.18		129.96 ± 26.58		97.86 ± 25.02		0.001†
3 hour	mean ± SD	130.55 ± 37.90		151.67 ± 39.47		112.84 ± 25.91		0.001†
24 hour	mean ± SD	134.63 ± 28.43		136.54 ± 26.06		133.03 ± 30.61		0.387
	§P	0.001†		0.001†		0.001†		
% Variations								
Preoperative 1 hour	ϕP	−17.8 to 109.7 (3.4)	0.001†	−4.7 to 52.4 (25.3)	0.001†	−17.8 to 109.7 (−2.3)	0.170	0.001†
		13.44 ± 23.36		25.68 ± 15.97		3.17 ± 23.81		
Preoperative 3 hour	ϕP	−19.7 to 133.3 (24.7)	0.001†	3.7-109.5 (44.1)	0.001†	−19.7 to 133.3 (14.4)	0.002†	0.001†
		32.50 ± 33.47		46.56 ± 28.54		20.70 ± 33.12		
Preoperative 24 hour	ϕP	0.9-131.3 (29.2)	0.001†	5.4-77.3 (28.4)	0.001†	0.9-131.3 (30.4)	0.001†	0.414
		37.24 ± 27.04		32.72 ± 20.47		41.03 ± 31.35		
1 hour to 3 hour	ϕP	−36 to 94.1 (17.1)	0.001†	−14.3 to 56 (13.4)	0.001†	−36 to 94.1 (20.7)	0.002†	0.923
		17.98 ± 24.59		16.88 ± 18.11		18.90 ± 29.21		
1 hour to 24 hour	ϕP	−40.3 to 136 (18.6)	0.001†	−22.1 to 40 (7.5)	0.124	−40.3 to 136 (37.5)	0.001†	0.001†
		24.67 ± 30.35		6.55 ± 16.47		39.86 ± 31.15		
3 hour to 24 hour	ϕP	−37.7 to 87.5 (0.8)	0.409	−37.7 to 11.8 (−6.3)	0.003†	−20.9 to 87.5 (21.9)	0.001†	0.001†
		7.46 ± 24.94		−8.08 ± 12.03		20.50 ± 25.61		

*P < 0.05. †P < 0.01. ‡Mann–Whitney U test. §Friedman test. ϕWilcoxon signed-rank test.
Abbreviation: SD, standard deviation

Discussion

In the current study, we aimed to determine the relationship between anesthesia type and postoperative cognitive function, and between anesthesia type and biomarkers of surgical stress (CRP, insulin, cortisol, and glucose) in patients undergoing TKA. We report that patients who received regional anesthesia showed significantly higher MMSE scores and better Stroop scores than patients who received general anesthesia. Also, we found that patients who received regional anesthesia showed lower cortisol and glucose levels and higher insulin levels. We did not detect any differences in either CFQ or AVLT results by anesthesia type. However, we did observe significantly higher MMSE scores at the seventh postoperative day in patients who received regional anesthesia compared with those who received general anesthesia. Further, the patients who received general anesthesia showed significantly more variation in their MMSE scores between measurement timepoints than the patients who received regional anesthesia. We also administered a Stroop test to each of our patient groups and report that the general anesthesia group showed a statistically significant variation in number differences. We observed that in the general anesthesia group, patients showed significantly higher preoperative and 7-day variation Stroop number differences, indicating that their test scores declined from the preoperative level and recovered by postoperative day 30.

Similar to our findings, Zywiel et al (12) reported a review of the literature suggesting that the use of general anesthesia, rather than regional anesthesia,

Table 8. *CRP measurement results by anesthesia type.*

CRP Measurements		Anesthesia Type						‡P
		Total (n = 57)		General Anesthesia (n = 26)		Spinal Anesthesia (n = 31)		
Preoperative	mean ± SD	0.50 ± 0.63		0.36 ± 0.28		0.61 ± 0.80		0.191
1 hour	mean ± SD	0.42 ± 0.50		0.32 ± 0.22		0.50 ± 0.64		0.279
3 hour	mean ± SD	0.40 ± 0.53		0.31 ± 0.24		0.48 ± 0.68		0.418
24 hour	mean ± SD	10.08 ± 3.64		10.08 ± 3.17		10.08 ± 4.05		0.737
	§P	0.001†		0.001†		0.001†		
% Variations								
Preoperative 1 hour	ϕP	−100 to 250 (−10.7)	0.001†	−100 to 250 (−10)	0.001†	−82.2 to 66.7 (−12.5)	0.001†	0.066
		−6.64 ± 42.24		−3.08 ± 57.22		−9.63 ± 24.13		
Preoperative 3 hour	ϕP	−87.3 to 180 (−14.3)	0.001†	−84.9 to 180 (−10.6)	0.001†	−87.3 to 157.1 (−20)	0.001†	0.075
		−9.55 ± 41.64		−7.45 ± 41.53		−11.32 ± 42.33		
Preoperative 24 hour	ϕP	59.4-12,442.9 (3,084.4)	0.001†	524.4-12,442.9 (4,002.8)	0.001†	59.4-8,741.7 (2,825.7)	0.001†	0.200
		3,788.16 ± 2,679.28		4,247.53 ± 2,725.43		3,402.87 ± 2,621.76		
1 hour to 3 hour	ϕP	−77.8 to 211.1 (−6.3)	0.012*	−77.8 to 211.1 (−2.9)	0.190	−76.5 to 157.1 (−9.1)	0.034*	0.287
		−0.97 ± 40.48		1.70 ± 46.68		−3.13 ± 35.34		
1 hour to 24 hour	ϕP	114-10,875 (3,194.4)	0.001†	863-10,875 (4,126.3)	0.001†	114-10,004.8 (2,648.9)	0.001†	0.288
		3,968.94 ± 2,609.19		4,282.18 ± 2,460.79		3,716.32 ± 2,736.61		
3 hour to 24 hour	ϕP	90.7-14,533.3 (3,381.1)	0.001†	828.6-14,533.3 (4,194.4)	0.001†	90.7-11,068.4 (3,071.8)	0.001†	0.236
		4,384.11 ± 3,093.97		4,951.06 ± 3,385.98		3,908.60 ± 2,793.33		

*P < 0.05. †P < 0.01. ‡Mann–Whitney U test. §Friedman test. ϕWilcoxon signed-rank test.
Abbreviation: SD, standard deviation

Table 9. *The association between cortisol measurements and CFQ/MMSE scores.*

		Cortisol Measurements							
		Preoperative		1 hour		3 hour		24 hour	
		r	P	r	P	r	P	r	P
CFQ	Preoperative	−0.085†	0.531	−0.123†	0.360	−0.130†	0.335	0.206†	0.124
	7 day	−0.098†	0.470	−0.151†	0.263	−0.158†	0.240	0.230†	0.086
	30 day	−0.105†	0.436	−0.129†	0.340	−0.156†	0.248	0.204†	0.128
MMSE	Preoperative	0.035	0.796	−0.069	0.611	−0.110	0.416	−0.056	0.679
	7 day	−0.106	0.433	−0.302	0.022*	−0.295	0.026*	−0.129	0.341
	30 day	0.042	0.759	−0.096	0.477	−0.134	0.319	−0.109	0.418

r: Spearman correlation analysis. *P < 0.05. †r: Pearson correlation analysis.

Table 10. *The association between Stroop results and stress biomarker measurements.*

		Cortisol Measurements							
		Preoperative		**1 hour**		**3 hour**		**24 hour**	
		r	**P**	**r**	**P**	**r**	**P**	**r**	**P**
Number Difference	Preoperative	0.262	0.057	0.227	0.090	0.235	0.048*	0.018	0.895
	7 day	0.099	0.463	0.079	0.557	0.046	0.734	–0.092	0.497
	30 day	0.218	0.104	0.044	0.743	–0.009	0.945	–0.006	0.962
		Insulin Measurements							
		Preoperative		1 hour		3 hour		24 hour	
		r	P	r	P	r	P	r	P
Number Difference	Preoperative	–0.082	0.542	–0.070	0.605	–0.030	0.826	–0.073	0.590
	7 day	–0.074	0.584	0.033	0.805	–0.054	0.689	–0.050	0.712
	30 day	0.037	0.785	0.145	0.282	–0.014	0.920	0.089	0.511
		Glucose Measurements							
		Preoperative		1 hour		3 hour		24 hour	
		r	P	r	P	r	P	R	P
Number Difference	Preoperative	0.071	0.602	0.264	0.047*	0.354	0.007†	0.076	0.572
	7 day	0.126	0.352	0.261	0.048*	0.273	0.040*	0.108	0.422
	30 day	0.078	0.564	0.119	0.379	0.145	0.281	–0.009	0.945

r: Spearman correlation analysis. *P < 0.05. †P < 0.01.

may be associated with a lowered risk of early POCD. They also suggested that this difference could not be detected until after postoperative day 7 and recommended optimizing the depth of anesthesia as well as intraoperative cerebral monitoring when general anesthesia was used. One study investigated POCD following major noncardiac surgery using neuropsychological tests to evaluate patients preoperatively and at 7 days and 3 months after surgery (13). This study reported that the incidence of POCD was significantly higher for the general anesthesia group at postoperative day 7. These results were similar to our findings that the regional anesthesia group in the current study showed better POCD results. In a recent study, Shi et al (14) used MMSE scores to investigate the incidence and mechanism of POCD following regional and general anesthesia in elderly hip replacement patients, and found that the incidence of POCD was significantly lower for the epidural anesthesia group when compared with the general anesthesia group. In support of this previous result, we also observed diminished MMSE scores in our general anesthesia group compared with our regional anesthesia group.

In our study, we report that the cortisol levels in the general anesthesia group were significantly higher than in the spinal anesthesia group at 1 hour intraoperatively. There was a significant rise for the general anesthesia group in terms of cortisol levels at both 1 hour intraoperatively and 3 hours postoperatively. At 1 hour intraoperatively, patients with regional anesthesia showed lower cortisol levels than those who received general anesthesia. However, the cortisol levels were equalized by 24 hours after surgery in both groups. Surgical stress may cause many changes throughout the human body. Elevated adrenocorticotropic hormone causes increased cortisol release, which in turn can lead to insulin resistance and hyperglycemia (15). Elevated glucose levels can increase the risk of postoperative wound infection (15). Surgical stress can also cause immunologic and metabolic changes, such as diminished natural killer cell toxicity, reduced T-cell function, and elevated proteolysis leading to muscle loss (15). A recent study reported that spinal anesthesia results in lower postoperative pain and blood loss when compared to general anesthesia in patients undergoing lower limb surgery (16). This report also suggested that cortisol

and albumin levels, but not CRP levels, were decreased in the spinal anesthesia group. These results are concurrent with our results that cortisol levels were lower in the regional anesthesia group, but that CRP levels were not significantly different between the groups.

The association between anesthesia and endocrine response is related to the concept of stress, which is characterized by fight-or-flight reaction. Surgery leads to a release of catecholamines and pituitary hormones, which are catabolic hormones, and inhibits insulin and other anabolic hormones (17). After major surgery, surgical pain stress and tissue damage can cause complex immune responses that can lead to postoperative infections. Anesthesia can affect patients by impacting the neurohormonal stress response. Previous studies indicate that regional anesthesia diminishes the stress response and the related consequences regarding cellular and humoral immunity (17,18).

In contrast to the results of the current study, a study by Rasmussen et al (19) reported no significant differences in cortisol levels between general and regional anesthesia groups. However, these results may differ from those of the current study because the previous study used saliva samples to measure cortisol levels, whereas we used blood samples. Furthermore, Silbert et al (20) investigated the incidence of POCD in extracorporeal shockwave lithotripsy patients and found no difference in POCD symptoms between general and regional anesthesia patients. The disparity between these results and those of the current study may be due to differences in the nature of the surgeries being studied as well as the pain levels involved.

Previous studies indicate that anesthetic drugs can have neurologic effects that may continue beyond the time of surgery. For example, studies in animal models have suggested that volatile anesthetics lead to changes that are consistent with dementia-like elevated oligomerization, diminished clearance of Aβ, and phosphorylation of tau (21-23). There is also evidence from animal studies that hypothermia caused by both intravenous and inhalation anesthetics can lead to hyperphosphorylation of tau (21). These results suggest that it might be preferable to avoid general anesthesia to reduce the incidence of POCD (21). As reported by Sieber et al (24), studies that do not report any differences in POCD by anesthesia type should be interpreted with caution because in most of these the patients who had regional anesthesia were sedated to an unknown depth. In our study, we did not administer any sedation to the regional anesthesia group, and this may have contributed to the lowered POCD symptoms among these patients. The drugs used for sedation can be a serious contributing factor for POCD themselves. Benzodiazepines, meperidine, and other opioids are drugs known to increase POCD. This difference in sedative use may explain the conflicts between studies with regards to POCD and regional anesthesia.

We did not find any statistical differences in CRP between the general and regional anesthesia groups in the current study, but both groups showed gradually increasing CRP levels at each timepoint. These levels peaked at similar levels at 24 hours postoperatively. In support of our findings, similar nonsignificant increases in CRP levels have been previously reported (25). The evidence for the relationship between CRP levels and POCD is contradictory, and one POCD study reported heightened levels of CRP in POCD patients (26). Similar to McDonagh et al (25), we did not find any association between POCD and CRP levels. We did, however, observe elevated levels of cortisol in patients with POCD. In a recent review, Androsova et al (27) reported that there were authors who detected elevated cortisol levels in cases of both postoperative delirium and POCD (28).

It has been shown that insulin receptors in the hippocampus and insulin signalling may have a crucial role in cognitive function, and the development of peripheral insulin resistance, even in nondiabetic patients, following major surgery has been well established (29-32). In a recent animal study, Kawano et al (29) suggested that surgery can damage central insulin signalling, thereby leading to increased hippocampal neuroinflammation and cognitive dysfunction. In our study, we showed that the regional anesthesia group showed significantly higher levels of insulin than the general anesthesia group 1 hour intraoperatively (P = 0.019). For all groups, patient had higher levels of insulin at 24 hours postoperatively, reflecting a gradual rise after the 1-hour intraoperative mark. In a recent study, Tang et al (33) investigated the association between postoperative insulin resistance and POCD in a group of 131 patients who underwent cardiac surgery and reported that insulin resistance was associated with both POCD and elevated levels of inflammatory factors.

Our study also revealed that patients in the general anesthesia group showed higher glucose levels than those in the regional anesthesia group at 1 hour intraoperatively and 3 hours postoperatively (both P = 0.001). For both groups, the intraoperative and postoperative glucose levels were higher than the preopera-

tive glucose levels. Similar to our findings, Smeets et al (34) showed that the addition of epidural anesthesia to general anesthesia diminishes cortisol and urine adrenaline levels. Further, authors reported that hyperglycemia could be prevented by epidural analgesia but that inhaled anesthetics did not affect glucose levels (15,35). Inhaled anesthetics have also been shown to have diverse effects on cytokines, depending on the agent used, and general anesthesia may weaken platelet aggregation (15,36,37).

In our study, cognitive differences between the 2 groups were mostly significant up to 7 days. We think that there were a couple of factors affecting our results. There are studies suggesting that POCD occurs frequently in adults with an incidence as high as 26% persisting 7 days after noncardiac surgery and decreases to lower levels after 30 days (38). We think that probable direct effects of surgery and anesthesia and outcomes due to postoperative delirium might have affected both groups at 30 days (38). Davis et al (38) investigated 16 studies and reported that at the time of the review there were no conclusive comparative data demonstrating that either general anesthesia or regional anesthesia are associated with a reduced risk for the development of POCD.

We also analyzed the presence of any significant correlations between neurocognitive tests and biomarkers. We found that 1-hour intraoperative cortisol levels were negatively correlated with MMSE scores at postoperative day 7 ($r = –0.302$; $P = 0.022$). We detected a significant positive correlation between the preoperative Stroop number differences score and the 3-hour postoperative cortisol levels ($r = 0.235$; $P = 0.048$). We further observed significant positive correlations between glucose levels and the Stroop test number difference results between postoperative day 7 and both 1-hour intraoperative and 3-hour postoperative glucose measurements ($r = 0.261$ and 0.273, respectively; $P < 0.05$). These results may suggest that higher cortisol, lower insulin, and higher glucose levels are associated with poor neurocognition after surgery. This may also explain why lower POCD incidence were observed in our regional anesthesia group.

The primary limitation to the current study is the small number of patients. In the future, a larger study will be needed to verify our results. Another limitation to our study is we investigated one group of surgery, and different surgeries may be associated with different pain scores and different POCD incidences.

Conclusions

We demonstrate that regional anesthesia without sedation results in better neurocognitive test scores than general anesthesia in patients undergoing TKA. We also demonstrated that patients who received regional anesthesia showed lower cortisol, higher insulin, and lower glucose levels. This suggests that lower levels of blood stress markers may be associated with the lower rate of POCD in patients who receive regional anesthesia. We recommend that patients who undergo arthroplasty surgeries should receive regional anesthesia to avoid POCD at the early stages of the postoperative period.

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