The stress response and anesthetic potency of unilateral spinal anesthesia for total Hip Replacement in geriatric patients

Li Zhu, Chun Tian, Min Li*, Ming-qing Peng, Kun-Long Ma, Zhong-lin Wang, Jia-hui Ding and Yi Cai

Department of Anesthesiology of Yongchuan Hospital of Chongqing Medical University, Chongqing,

Abstract: Recently, some scholars suggested that it is important to keep a stablehemodynamic state and prevent the stress responses in geriatric patients undergoing total hip replacement (THR). We conducted this randomized prospective study to observe anesthetic potency of unilateral spinal anesthesia and stress response to it in geriatric patients during THR. We compared the effect of unilateral spinal and bilateral spinal on inhibition of stress response through measuring Norepinephrine (NE), epinephrine (E) and cortisol (CORT). Plasma concentrations of NE, E and CORT were determined in blood samples using ELISA (enzyme-linked immunosorbent assays) at three time points: To (prior to anesthesia) T1 (at the time point of skin closure), T2 (twenty-four hours after the operation). Sixty patients were randomly divided into two groups: group A (unilateral spinal anesthesia) and group B (conventional bilateral spinal anesthesia). 7.5tymg of hypobaric bupivacaine were injected into subarachnoid cavity at group A and 12mg hypobaric bupivacaine were given at group B. The onset time of sensory and motor block, loss of pinprick sensation, degree of motor block, regression of sensory and motor blocks and hemodynamic changes were also recorded. These data were used to evaluate anesthetic potency of spinal anesthesia. The results of this experiment show that unilateral spinal anesthesia can provide restriction of sensory and motor block, minimize the incidence of hypotension and prevent the stress responses undergoing THR. It is optimal anesthesia procedure for geriatric patients by rapid subarachnoid injection of small doses of bupivacaine.

Keywords: Unilateral spinal anesthesia; conventional bilateral spinal anaesthesia; total hip replacement; stress response; geriatric patients.

INTRODUCTION

Total hip replacement (THR) is an appropriate and effective technique for safe pain relief and loss of function, caused by necrosis of femoral head and femoral neck fracture. Perioperative disturbances associated with the procedure are bone cement effect, thromboembolic complications and cardiovascular complications. In fact, most patients enrolled in THR are elderly, who are commonly coexisting with medical problems, such as heart disease or hypertension. They are particularly sensitive to the stress of surgery and anesthesia. As the concept of a “stress-free” perioperative period was developed in recent years, some scholars have proposed that it is important to perform optimal anesthesia procedure in order to reduce stress, improve operative outcomes and minimize perioperative complications in geriatric patients undergoing THR (Douglas 2002 and Kanonidou *et al*., 2007).

In the past few decades, continuous epidural block, conventional bilateral spinal anaesthesia or general anesthesia were normally used for geriatric patients. But there is no consensus about the most appropriate anesthetic technique to use in geriatric patients. The use of general anesthesia in elderly patients may be associated with delays in clinical recovery, when they were disoriented perioperatively. Regional anesthesia affects the coagulation system by preventing postoperative inhibition of fibrinolysis. Furthermore, it decreases the incidence of deep vein thrombosis after THR (Kanonidou *et al*., 2007and Tripkovic 2012). However, epidural block and conventional spinal anaesthesia might result in a more cephalic spread. Small doses of bupivacaine have been used to limiting the block at the operative side for knee arthroscopy and inguinal hernia repair (Kuusniemi *et al*., 1997 and Casati *et al*., 2004). Positive findings have been reported for unilateral spinal anesthesia in terms of cardiovascular stability, while limiting the extent of spinal block to those dermatomes mainly involved in the surgery (Borghi *et al*., 2010 and Casati A *et al*., 2001 and A Esmaoglu *et al*., 2004). Previous studies have not found the ideal dose to achieve perfect unilateral spinal block in geriatric patients undergoing THR. Therefore, our purpose was to assess the anesthetic potency of unilateral spinal block through evaluation of maximum sensory and motor block during THR in geriatric patients and its effect on hemodynamics. The addition of the spinal block has an advantage over the use of general anaesthesia alone; reducing the neuroendocrine response surgery (Bar-Yose *et al*., 2001). Since the eect of unilateral spinal anesthesia on stress response to THR has also not been investigated before in geriatric patients, we designed this study to compare the eects of unilateral or bilateral spinal anaesthesia on levels of NE, E and cortisol in geriatric patients undergoing THR.

**Corresponding author:* e-mail: li_min_yongchuan@126.com

PATIENTS AND METHODS

Subjects and grouping Between July 2012 and April 2014, total of 60 geriatric patients of American Society of Anesthesiology (ASA)β status admitted for THR were recruited with approval of the local ethics committee. Written informed consent was obtained from all participants or from their relatives if they were incapable of consent. Patients with contraindications to regional anesthesia and peripheral neuropathy were excluded. The patients were divided into two groups with 30 in each. Group A received unilateral spinal anesthesia and Group B received conventional bilateral spinal anaesthesia.

Anaesthetic methods. After the patients arrived in the induction room, 10 min elapsed before baseline haemodynamic data were obtained. All patients received premedication with midazolam (0.03mg/kg) and fentanyl (0.5-1μg/kg) before block placement, followed by 7ml/kg infusion of colloid to enlarge the blood capacity. Patients were placed in the lateral position with the operation side uppermost. Spinal anesthesia was administered through a 22 or 25-gauge spinal needle in the midline of the L3-4. Patients were randomized using a coded envelope technique to receive one of the two anesthesia technologies. In a patient of unilateral spinal anesthesia (n=30), Once a free flow of cerebrospinal fluid (CSF) was obtained, the needle orifice was turned toward the operated side and 3ml of hypobaric 0.25% bupivacaine (7.5mg) in sterile water (0.75% bupivacaine 1ml diluted with sterile water up to 3ml) was injected rapidly in 10 seconds (Kuusniemi *et al*., 2000 and Nair GS *et al*., 2009). The lateral decubitis position was maintained for at least 20 min 20 min after intrathecal injection. In a patient of bilateral spinal anaesthesia (n=30), after ensuring free flow of CSF, the needle orifice was turned facing cephalad and spinal anaesthesia was administered with 2.4ml hypobaric bupivacaine 0.5% at a rate of approximately 0.2ml· sec 1. Then, patients were immediately turned onto the supine position. and kept horizontal for at least 15min to fix the level of block.

Clinical efficacy. To date, sensory block was evaluated through the pinprick test and motor blockade was assessed through a modified Bromage score. If sympathetic block was incomplete, the regimen would carry out general anesthesia. From intrathecal injection to perfect sympathetic block, an unblinded observer estimate sensory and motor block bilaterally every five minutes.

We define perfect sympathetic block as a loss of pinprick sensation at T10 on the operated side accompanied with a modified Bromage score ≥2. The unblinded observer also recorded the interval time between intrathecal injection and perfect sympathetic block. Then, we transferred the patients to the operating table and surgeon started the surgery. Blinded observer continued to assess spinal block every 15 min until sensory level of the operated side was observed at T12, and then every 30min until complete regression of sympathetic block.

Hemodynamics. The numbers of control due to severe hemodynamic fluctuation and bradycardia were recorded. When the contractive pressure decreased to <90 mmHg, or mean arterial pressure (MAP) was <60 mmHg for >1 min, ephedrine at 5mg was administered. When the heart rate (HR) fell to <50 bpm for>1 min, atropine between 0.25 and 0.5mg was administered. When the contractive pressure rosed to >160mmHg, diastolic pressure to >100 mmHg, or HR to >120 bpm for >1 min, 0.5-1μg/kg fentanil, 4 mg/kg/h infusion of propofol, 5 mg urapidil, or 25 mg esmolol was intravenously injected accordingly. During the operative period, patients received infusion with a 2:1 crystal/colloid ratio (6-8ml/kg/h). Those with blood loss >20% were excluded from this study. Patients in the two groups breathed spontaneously during the operation period. SpO2 was closely monitored. When SpO2 decreased to <90%, oxygen was supplied using a mask.

Enzyme-linked immunosorbent assay (ELISA). Venous blood was extracted from all the selected patients from each group at T0 (prior to anesthesia), T1 (the time point of skin closure), and T2 (twenty-four hours after the operation). The blood samples were placed into pre-chilled heparin tubes and then centrifuged for plasma isolation. The obtained plasma samples were cryopreserved for determination of plasma concentrations of catecholamines (NE and E) and cortisol using ELISA (the kit was supplied by Shanghai Senxiong Biotech Industry Co., Ltd., Shanghai, China).

Postoperative evaluation. The blinded observer questioned volunteers daily for 72h about the presence of postoperative pain, nausea and vomiting, neurologic injury, subarachnoid haemorrhage, headache, backache, or other residual symptoms. Postoperative pain relief was adequate in all studied patients using PCEA (patient controlled epidural analgesia). Patients were evaluated every day by blinded observer until patients were judged ready for home discharge. Patients were discharged when their vital signs had been stable, when they were able to ambulate and pain controlled with oral medication, such as ibuprofen capsules.

STATISTICAL ANALYSIS

Statistical analyses of the data were performed using SPSS version 17.0 statistical software (SPSS Inc, Chicago, IL, USA). The Student's t test was used for statistical analysis of age, weight and height of patients, duration of surgery, times readiness to surgery and block resolution. The Mann-Whitney u test was used to compare complication, motor and sensory block. Hip fracture pattern, haemodynamic stability and hormones were analyzed by Pearson's chi-square test. The level of statistic significance was set at $P < 0.05$.

Table 1: The demographic characteristics of the patients

		Unilateral (n=28)	Bilateral (n=28)	P
Mean Age (year, SD)		78.50±5.15	79.36±5.41	0.546[a]
Height (cm, SD)		170.07±2.85	171.18±2.79	0.148[a]
Weight (kg SD)		67.50±3.40	68.32±3.37	0.368[a]
Hip fracture pattern		13(46.4)	12(42.9)	0.788[b]
Femoral head necrosis (n,%)				
Femoral neck fracture (n,%)		15 (53.6)	16 (57.1)	0.788[b]
Duration of surgery (min, SD)		92.18±10.30	92.43±9.77	0.926[a]
Perioperative complication (n,%)	Emphysema	7 (25.0)	6 (21.4)	0.947[c]
	Hypertension	5 (17.9)	6 (21.4)	
	Coronary heart disease	6 (21.4)	7 (25.0)	
	Hypertension and coronary heart disease	4 (14.2)	3 (10.7)	
	Emphysema and hypertension	3 (10.7)	2 (7.1)	
	Emphysema and coronary heart disease	3 (10.7)	4 (14.3)	

[a]The Student's t. [b]Pearson's chi-square test.[c] Mann–Whitney tests.

Table 2: The time of onset, during of block and hemodynamics Changes

	Unilateral (n=28)	Bitlateral (n=28)	P
The onset time (min, SD)	21.68±3.28	13.68±4.51	<0.05[a]
Time for regression of spinal Block (min, SD)	169.57±41.58	204.46±54.52	0.009[a]
Numbers of patients needing ephedrine (n,%)	2(7.1)	12(42.9)	0.002[b]
Numbers of patients needing atropine (n,%)	2(7.1)	3(10.7)	0.639[b]

[a]The Student's t. [b]Pearson's chi-square test.

Table 3: The sensory level on operative and nonoperative side after 30 minutes of block respectively n (%).

Group		T5	T6	T7	T8	T9	T10	L5	S1	S2
Unilateral Δn=28	Operative side*	0	0	2(7.1)	10(35.7)	8(28.6)	8(28.6)	0	0	0
	Nonoperative side	0	0	0	0	0	0	14(0.5)	11(39.3)	3(10.7)
Bilateral n=28	Operative side	1(3.6)	1(3.6)	3(10.7)	8(28.6)	8(28.6)	7(25)	0	0	0
	Nonoperative side	1(3.6)	1(3.6)	3(10.7)	8(28.6)	8(28.6)	7(25)	0	0	0

* No statistically significant difference versus operative side among groups (Mann-Whitney U: 355.000, P=0.528) ΔStatistically significant difference between operative and nonoperative side in unilateral group（ Mann-Whitney U: 0.000, P=0.000.

Table 4: The modified Bromage score on operative and nonoperative side after 30 minutes of block respectively n (%).

Group		0	1	2	3
Unilateral (n=28)	Operative side	0	1(3.6)	4(14.3)	23(82.1)
	Nonoperative side*	6(21.4)	22(26)	0	0
Bilateral (n=28)	Operative side	0	1(3.6)	4(14.3)	23(82.1)
	Nonoperative side	0	1(3.6)	6(21.4)	24(85.7)

*Statistically significant difference versus nonoperative side in bilateral group (Mann-Whitney U ：11.000，P<0.05).

Table 5: Comparisons of plasma NE, E and cortisol among the two groups at different time points (n=28, mean ± SD).

		Unilateral (n=28)	Bilateral (n=28)	P[a]
NE	T0	316.54±11.81*	320.18±13.21*	0.282
	T1	370.88±13.33	392.91±15.51	0.000
	T2	322.97±13.27	337.13±13.33	<0.05
N	T0	215.50±7.72*	215.11±6.82*	0.841
	T1	265.08±9.43	281.50±9.18	<0.05
	T2	225.75±8.40	248.89±8.94	<0.05
cortisol	T0	222.85±6.60*	221.45±9.05*	0.510
	T1	266.82±48.17	298.91±11.37	0.001
	T2	238.14±6.74	258.52±6.16	<0.05

[a] Pearson's chi-square test *Statistically significant difference in different time point reading of the same hormone and group (P<0.05).

RESULTS

60 geriatric patients were enrolled. Preoperative data from the 2 groups were compared, and the study showed no significant differences in all measured preoperative variables between 2 groups (table 1). Data from 4 patients were excluded: since the maximum sensory level on the operated side was less than T10 after intrathecal injection, 2 patients in each group (6.7%) were switched to general anesthesia to perform surgery. The other 56 patients are all received reliable anesthesia and there were no postoperative complications in 2 group. During the surgery, none of the patients required fentanyl or propofol. We improve postoperative analgesia in all scheduled patients. Time to discharge from the hospital in 2 group were average 10 days, having no directly related to the anesthetic technique.

Table 2 shows the onset time, the time for regression of sensory/motor blocks, numbers of patients needing rescue ephedrine or atropine requirements. In general, the median time required to achieve readiness to surgery was obviously delayed (22min; range, 17-30) in the group A, compared with that in the group B (13 min; range, 10-25 min). In group A, the time required for regression of sensory and motor blocks was noticeably shorter (169± 41.58 min; range, 100-258 min) than that of the group B (204 ± 54.52 min; range, 120-310 min).

Ephedrine to treat clinical hypotension was required in 2 patients (7.1%) of group A and 12 patients (42.9%) of the group B. We demonstrated that the incidence of hypotension in group A decreased obviously in comparison with that in group B. Atropine to treat bradycardia was reported in 2 patients (7.1%) and 3 patients (10.72%) in group A and group B, respectively. We concluded that there were no differences in bradycardia between the 2 groups.

Table 3 and table4 show the evolution of sensory and motor blocks on both the operative and nonoperative sides in all patients, respectively. In group A, the maximal level of sensory block on the operative side was significantly higher (T9; rang, T10-T7) in comparision with those on the non-operative side (S2; rang, S2-L5). But the maximal level of sensory block of the operative side was similar to that of the non-operative side in group B (T8; rang, T10-T5). Thus, no statistically significant differences in the maximal level of sensory block were observed in 2 groups on the operative sides. In group A, bromage score of the non-operative side was obviously lower (1; rang,0-1), compared with those of operative side (3; rang,1-3). However, there was no significant difference in terms of motor block between operative side and the non-operative side in group B (3; rang, 1-3). Therefore, the group A have the same bromage score of the operative side as group B.

Table 5 shows the concentrations of NE, N and cortisol at T0, T1 and T2.

There were no significant differences associated with the concentrations of NE, N and cortisol between the 2 groups prior to anesthesia (T0). In group A, the concentration of plasma NE, N and cortisol increased noticeably to 370.88±13.33, pg/ml, 265.08±9.43pg/ml, 266.82±48.17 pg/ml respectively at the time point of skin closure (T1); Twenty-four hours after the operation, the concentration of these hormones fell below the baseline respectively (322.97±13.27 pg/ml, 225.75±8.40pg/ml, 238.14±6.74pg/ml). In group B, the concentration of plasma NE, N and cortisol increased noticeably to 392.91 ±15.51pg/ml, 281.50±9.18pg/ml, 298.91±11.37 pg/ml respectively at skin closure (T1), which were also significantly higher than those in group A. Twenty-four hours after the operation, the concentrations of catecholamine and cortisol tended to decrease significantly (337.13±13.33 pg/ml, 248.89±8.94 pg/ml, 258.52±6.16 pg/ml). However, these hormones were still noticeably higher than those in group A at T2.

DISCUSSION

Aging is characterized by organ medical problems like heart disease or organ dysfunction, while the limitation of physiological reserve is evident during times of stress such as the perioperative period. In general, geriatric patients are more sensitive to anesthetic agents during surgery. So it is important to explore optimal anesthetic technique for old patients during THR.

Although practicality of restriction effect of unilateral spinal anesthesia has been investigated extensively, the results of such studies are conflicting. However, some scholars have concluded that the use of this technique can limit spinal block at the operative side and demonstrated that it could stabilize perioperative hemodynamics. Results of our study demonstrated that 7.5mg of hypobaric bupivacaine injected rapidly at 10 seconds produce a more restricted and efficient spinal anesthesia in THR. It seems that results similar to ours can be obtained with comparable doses of hyperbaric bupivacaine. HM Atef *et al*. reported that doses of bupivacaine as low as 5mg or 7.5mg can produce high success rate of unilateral spinal block in knee arthroscopy (Atef *et al.,* 2010). These scholars also suggested that higher doses (e.g., 10 or 15mg) of bupivacaine caused significantly prolonged recovery and might also cause higher levels of spinal block (Nair *et al.,* 2009). Moreover, Other scholars (Kuusniemi KS; Enk D etal) showed that high incidence of unilateral spinal block is also depended on intrathecal injection flow and faster injections produce a greater spread with plain solution (Kuusniemi *et al.,* 2000 and Enk *et al.,* 2001). For these reasons, we administered 7.5mg bupivacaine in 10 seconds in our study. The unilateral spinal block produced

a obvious delay in onset of surgical block; Kristiina S *et al*. have proved that the longer time provided better uniteral sensory and motor block and at least 20 minutes should be used in the lateral position (Kuusniemi *et al.,* 2000). The onset time of sensory and motor blocks in our study was 22 min. No significant difference associated with maximal level of sensory block and motor blockade were observed on the operative side between two groups. Our results are consistent with previous research results (Esmaoglu *et al.,* 2004). However, we find that time for complete regression of spinal anesthesia on the operated side are a bit shorter in the unilateral spinal anesthesia than those in bilateral spinal anesthesia. The results of our study owing to the lower dose of bupivacaine (Atef *et al.,* 2010). The unilateral spinal block results in reduction in the incidence of hypotension as compared with conventional bilateral spinal block, so it produced a more stable cardiovascular profile (Casati *et al.,* 2001and Esmaoglu *et al.,* 2004). Because the magnitude of cardiovascular reaction to spinal block was determined by the scale of sympathetic denervation, with some suggestions that the higher rate of unilateral sympathetic block, the lower would be the change in cardio-circulatory parameters (Yılmaz *et al.,* 2011).

In the last decades, considerable advances have been made in anesthetic knowledge and anesthetic techniques, some scholars suggested that reduction of stress in surgical patients may improve postoperative outcome [1, 15,16]. As the elderly are associated with cardiovascular disease, respiratory problems or diabetes mellitus, surgical stress might have profound effects on physiologic responses and neuroendocrine response (Atanassoff 1996 and Rodrigues *et al.,* 2009). So it is important to explore optimal anesthetic technique for geriatric patient to attenuate the surgical stress and reduce perioperative physiologic responses to surgical stress in THR. Early investigation of general anesthesia showed a significant increase in the incidence of myocardial infarction, atelectasis, hypoxemia and pneumonia compared with regional anesthesia (Meyers *et al.,* 1975 and Craig 1981 and Melinda *et al.,* 1995). Latterly Modig J *et al*. published investigations that the incidence of deep venous thrombosis (DVT) and pulmonary embolism was significantly decreased following regional anesthesia, as compared with general anesthesia for patients undergoing THR in 1983 (Modig *et al.,* 1983). Numerous studies have also shown that effective regional anaesthesia delivered peripherally or centrally can block the stress responses, which caused by somatic pain, not caused by visceral pain in adults (Stang *et al.,* 1988 and Dupont *et al.,* 1987). But Peter G proved that surgical stress can be totally suppressed while dermatome levels above T10 during spinal and epidural anesthesia in 1996 (Atanassoff 1996). To sum up, we concluded that regional anesthesia is appropriate for geriatric patients during THR. However, other scholars reported that epidural anesthesia might not complete blockade of afferent input in surgical procedures and incomplete nature of local blockade might result in pain or aggravate stress response (Kouraklis *et al.,* 2000). But spinal anesthesia can avoid this disadvantage.

As part of stress response to surgery, surgical stress have an effect on the neuroendocrine hormones and increases secretion of catabolic hormones, such as cortisol, catecholamines and glucagon, as well as cytokines (Atanassoff 1996). Some researchers have proved that spinal anesthesia prevents an increase of catecholamine release, by inhibiting cyclic aminomonophosphate (CAMP) during surgery (Pflug *et al.,* 1981). While NE activity is immediately increased in response to threatening stimuli, cortisol modulates the long-term neuronal changes associated with stress (Patrick *et al.,* 2000). In our study, we compared the effect of unilateral spinal and bilateral spinal on inhibition of stress response through measuring plasma levels of epinephrine (Epi) and norepinephrine (NE), as well as cortisol. Patients displayed an increase in concentrations of cortisol and catecholamines at the time point of skin closure in both group. But the plasma concentrations of cortisol and catecholamines were significantly higher in unilateral spinal anesthesia than those in bilateral spinal anesthesia. Twenty-four hours after the operation, both anesthetic technology caused a significant suppression of plasma cortisol and catecholamines. But patients given unilateral spinal anesthesia displayed no significantly increase in cortisol and catecholamines compared with concentrations of baseline. So our study has found that unilateral spinal anesthesia can attenuate stress response as evidenced by the change in cortisol and catecholamines.

In conclusion, unilateral spinal anesthesia can restrict the block by using small doses of hypobaric bupivacaine, rapid regain of motor function and minimize the incidence of cardiovascular adverse effects (Casati *et al.,* 2001and Atef *et al.,* 2010 and Yılmaz *et al.,* 2011). It also can decrease the stress response to surgery, while stress reduction has contributed to improve operative outcomes, reduce complications, and greatly shorten length of convalescent. Unilateral spinal requires a bit longer preparation time than that of bilateral spinal, but it is still a optimal anesthetic technique for geriatric patients in THR. Nevertheless, the exact extent of these beneficial results has not yet been clearly defined. Future prospective randomized, controlled trials are needed to confirm our findings.

REFERENCES

Atanassoff PG (1996). Effects of regional anesthesia on perioperative outcome. *J. Clin. Anesth.,* **8**(6): 446-455.

Atef H, El-Kasaby A and Omera M (2010). Optimal dose

of hyperbaric bupivacaine 0.5% for unilateral spinal anesthesia during diagnostic knee arthroscopy. *Local Reg Anest.,* **3**: 85-91.

Bar-Yosef S, Melamed R, Page GG, Shakhar G and Shakhar K *et al*. (2001). Attenuation of the tumor-promoting eect of surgery by spinal blockade in rats. *Anesthesiology,* **94**(6): 1066-1073.

Borghi B and Wulf H (2010). Advantages of unilateral spinal anaesthesia. *AINS,* **45**(3): 182-187.

Casati A and Moizo Elena (2004). A prospective, Randomized, Double-blind comparison of unilateral spinal anesthesia with hyperbaric bupivacaine, Ropivacaine, or levobupivacaine for Inguinal Herniorrhaphy. *Anesthesia & Analgesia,* **99**(5): 1387-1394.

Casati A and Fanelli G (2001). Unilateral spinal anesthesia. State of the art. *Minerva Anestesiol,* **67**(12): 855-862.

Craig DB (1981). Postoperative recovery of pulmonary function. *Anesthesia & Analgesia,* **60**: 46-52.

Douglas W (2002). From cuthbertson to Fast-track surgery: 70 years of progress in reducing stress in surgical patients. *Annals of Surgery,* **236**(5): 643-648.

Dupont D, Velin P and Cabour F (1987). Influence de l'anesthésie caudale sur la sécrétion des catécholamines chez l'enfant. *Annales Françaises d'Anesthésie et de Réanimation,* **6**(3):156-158.

Enk D, Prien T and Van Aken H (2001). Success rate of unilateral spinal anesthesia is dependent on injection flow. *Reg. Anesth Pain Med.,* **26**(5): 420-427.

Esmaoglu A, Karaoglu S and Mizrak A (2004). Bilateral vs. unilateral spinal anesthesia for outpatient knee arthroscopies. *Knee Surg. Sports Traumatol. Arthrosc.,* **12**(2): 155-158.

Kanonidou Z and Karystianou G (2007). Anesthesia for the elderly. *Hippokratia,* **11**(4): 175-177.

Kouraklis G, Glinavou A and Raftopoulos L (2000). Epidural analgesia attenuates the systemic stress response to upper abdominal surgery: A randomized trial. *Int. Surg.,* **85**: 353-357.

Kuusniemi, Kristiina S, Kalevi K, Pihlajamäki and Kalevi K (1997). A Low-dose hypobaric bupivacaine spinal anesthesia for knee arthroscopies. *Regional Anesthesia & Pain Medicine,* **22**(6): 534-538.

Kuusniemi, Kristiina S, Kalevi K, Pihlajamäki and Kalevi K *et al* (2000). A low dose of plain or hyperbaric bupivacaine for unilateral spinal. *Anesthesia Regional Anesthesia,* **25**(6): 605-610.

Melinda L Mingus (1995). Recovery advantages of regional anesthesia compared with general anesthesia: Adult patients. *Journal of Clinical Anesthesia,* **7**: 628-633.

Meyers JR, Lembeck L and O'Kane H (1975). Changes in functional residual capacity of the lung after operation. *Arch. Surg.,* **110**: 576-583.

Modig J, Borg T and Karlstrom G (1983). Hromboembolism after total hip replacement: Role of epidural and general anesthesia. *Anesthesia & Analgesia,* **62**(2): 174-180.

Nair GS, Abrishami A and Lermitte J (2009). Systematic review of spinal anaesthesia using bupivacaine for ambulatory knee arthroscopy. *Br. J. Anaesth,* **102**(3): 307-315.

Patrick D, Skosnik, Robert T, Chatterton Jr and Tara Swisher (2000). Modulation of attentional inhibition by norepinephrine and cortisol after psychological stress. *Int. J. Psychophysiol.,* **36**: 59-68.

Pflug EA and Halter JB (1981). Effect of spinal anesthesia on adrenergictone and the neuroendocrine responses to surgical stress in humans. *Anesthesiology,* **55**: 120-126.

Rodrigues SM, LeDoux JE and Sapolsky RM (2009). The influence of stress hormones on fear circuitry. *Annu. Rev. Neurosci.,* **32**: 289-313.

Stang HJ, Gunnar MR and Snellman L (1988). Local anesthesia for neonatal circumcision: Effect on distressand cortisol responses. *Journal of the American Medical association,* **259**(10): 1507-1508.

Tripkovic B (2012). Anesthesia for hip replacement surgery. *Medicinski. Glasnik.,* **9**(1): 143-151.

Wolf AR (1998). Stress response in orthopaedics and trauma in paediatrics: General versus regional anaesthesia. *Aesthesia,* **53**(2): 76-80.

Yılmaz Apaydın, Gulcan Erk and Ozlem Sacan (2011). Characteristics of unilateral spinal anesthesia at different speeds of intrathecal injection. *J. Anesth.,* **25**: 380-385.