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The influence of dexamethasone administration in spinal anesthesia for femur fracture on postoperative cognitive dysfunction

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Abbreviations (in alphabetical order):
ASA = American Society of Anesthesiologists
CAM = Confusion Assessment Method
CI = Cognitive Impairment
DSA = Dexamethasone in Spinal Anesthesia
HPA = Hypothalamic -Pituitary- Adrenal
MCI = Mild Cognitive Impairment
POCD = Postoperative Cognitive Dysfunction
SA = Spinal Anesthesia
VAS = Visual Analog Scale

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Abstract

Background and Purpose: *Cognitive side-effects often complicate postoperative care especially in elderly and fragile patients.The aim of this research is to establish the influence of intrathecal dexamethasone administration in spinal anesthesia with levobupivacaine on postoperative pain, consciousness and values of cortisol levels for patients with femur fracture.*

Methods: *The study is planned as a prospective, interventional, randomized clinical trial. A total of 60 patients ASA2 and ASA3 status, scheduled for surgical procedures will be sorted into two groups and undergo surgery. One group will have spinal anesthesia with levobupivacaine, SA group, and the other study group will have spinal anesthesia with addition of dexamethasone, DSA group. The primary outcome measure is the occurrence of postoperative disturbance of consciousness and plasma cortisol levels. As a secondary outcome measure, we are following pain intensity, blood glucose levels and recovery. Cortisol and glucose are analysed in five measurements. Peripheral venous blood samples are collected before anesthesia, one hour after surgery, third, fifth and on the tenth day after surgery. Postoperative cognitive dysfunction is defined by using Confusion Assessment Method (CAM) criteria. Visual analog scale (VAS) is used to record pain severity among patients.*

Results: *We collected data for 28 patients so far. Preoperative cortisol levels were 713,25nmol/L,pain intensity(VASscore) 8,3. Postoperative cortisol plasma levels in 17 patients in DSA group were significantly lower 384(184-511) nmol/L in comparison to 11 patients in SA group with postoperative cotisol plasma levels 551(397-753) nmol/L. The duration of analgesia in DSA group was 428(350-510) minutes and in SA group 212(183-254) minutes. According to CAM criteria, postoperative cognitive disturbances were seen in 8 (72%) patients in SA group, and 3 (17%) patients in DSA group.*

Conclusion: *The addition of dexamethasone to the local anesthetic has proven so far that it significantly prolongs the duration of sensory block and, thus, decreases opioid requirements and postoperative cognitive disturbances.*

INTRODUCTION

Surgical stress is the systemic response to surgical injury and is characterized by activation of the sympathetic nervous system, endocrine responses as well as immunological and haematological changes *(1, 2,*

3). Spinal analgesia administered before the pain stimulus or surgical injury, prevents harmful central nervous system response and inflammation as an early consequence of operation as well *(4, 5, 6)*. Neuroinflammation is believed to have a role in the pathogenesis on postoperative delirium /confusion and postoperative cognitive dysfunction *(8)*.

Cognitive side-effects such as emergence agitation (EA), postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) are often complicating the postoperative care especially in elderly and fragile patients *(8)*.

The aim of this research is to establish the influence of intrathecal dexamethasone administration in spinal anesthesia with levobupivacaine on postoperative pain, consciousness and values of cortisol levels for elderly patients with femur fracture.

MATERIAL AND METHODS

The research was carried out in the double-blinded manner, with due approval from the institutional Ethics Committee and an informed consent from all study subjects. The study is planned as a prospective, interventional, randomized clinical trial. Inclusion criteria were patients with well-defined fracture femur for surgical procedure in spinal anaesthesia. Exclusion criteria were diabetes mellitus, autoimmune disease, corticosteroid and immunosupressive use. A total of 60 patients ASA2 and ASA3 status, scheduled for surgical procedures were sorted into two groups and undergo surgery in spinal anesthesia with 12,5mg of levobupivacaine, SA group, and with addition of 8mg of dexamethasone, DSA group. The primary outcome measure was the occurrence of postoperative disturbance of consciousness and plasma cortisol levels. As a secondary outcome measure, we followed pain intensity, blood glucose levels and recovery. Cortisol and glucose were analyzed in five measurements. Peripheral venous blood samples were collected before anesthesia, one hour after surgery, third, fifth and on the tenth day after surgery. Postoperative delirium was defined by using Confusion Assessment Method (CAM) criteria. Visual analogue scale (VAS) is used to record pain severity among patients.

RESULTS

We collected data for 28 patients with femur fracture undergoing surgery so far. In DSA group median age was 83 years (range 73-95), and SA group median age was 78 years (range 54-91), 6 patients were ASA 2, 22 were ASA 3. All patients completed the study; there was no statistical difference in patients' demographics.Preoperative cortisol plasma levels in 17 patients in DSA group and 11 patients in SA group were increased (Table 1).

Postoperative cortisol plasma levels in 17 patients in DSA group were significantly lower 384(range 184-511) nmol/L in comparison to 11 patients in SA group with postoperative cotisol plasma levels 551 (range 397-753) nmol/L. The duration of analgesia in DSA group was 428+72.57minutes and in SA group 212+34.76 minutes. A pain-free period in the DSA group was longer than that in the SA group(P<0.001). Receiving time to VAS >6 and the first analgesic dose prescription in the DSA group was significantly longer than that in the SA group (P<0.001) Table 2.

According to CAM criteria some kind of postoperative cognitive impairment was seen in 8(72%) patients in SA group of which we had 5 patients (45%) with moderate cognitive impairment (hyperalert, overly sensitive to environmental stimuli, startled easily) and 3 patients (27%) with mild cognitive impairment (disorganized thinking). In the DSA group we had 3 patients (17%) who developed

TABLE 1

Comparisons of patient's demographic and clinical data with hip fracture.

	Group DSA				Group SA			
	N	Median	Minimum	Maximum	N	Median	Minimum	Maximum
Age (yr)	17	83	73	95	11	78	54	91
Cortisol before block nmol/L	17	713,25	445,10	1020,64	11	639,50	301,15	887,56
VAS before block	17	8,2	5	10	11	8,3	6	10
Duration of surgery (min)	17	114,54	65,15	170,00	11	108,30	63	175

Data presented as median(min-max) measured variables. Age, Cortisol before block, VAS = visual analog scale, duration of analgesia P<0.05

TABLE 2

Comparisons of postoperative cortisol levels, pain level, analgesia duration and POCD.

	Group DSA				Group SA			
	N	Median	Minimum	Maximum	N	Median	Minimum	Maximum
Cortisol after block nmol/L	17	384,56	184,10	511,35	11	551,40	397,05	753,17
Total of analgesia	17	428	350	510	11	212	183	254
VAS 12h postop	17	0	0	0	11	0,60	0	3
VAS 1 postop day	17	1	1	6	11	3,87	1	6
VAS 2 postop.day	17	0,50	1	2	11	2,50	1	5
CAM POCD (%)	17	3	Mild CI 2 (11%)	Moderate CI 1 (5%)	11	8	Mild CI 3 (27%)	Moderate CI 5 (45%)

Data presented as median(min-max) measured variables. VAS postop = postoperative visual analog scale, TA = total analgesia; CAM=Confusion Assessment Method, POCD= Postoperative Cognitive Dysfunction, CI=Cognitive Impairment , P<0.05

mild or moderate cognitive impairment which was due to patients' preoperative cognitive status.

Hypotension was mild to moderate in both groups and was not different.

There was not postdural puncture headache detected. Other complications such as bradycardia, nausea, and vomiting were not different between the two groups and no neurologic deficit was observed in any patients.

DISCUSSION

Femur fracture is a common, mutilating and very expensive health problem. 10% of all fractures are femur fractures and these patients occupy more than 25% of beds in orthopedic hospitals. The mortality rate is very high, and only less than a half of injured people become mobile again after surgery *(1)*. In Croatia, there are about 6000 fractures per year.

These are mainly elderly patients. Approximately 70% of patients will be of ASA physicalstatus 3–4: 35% have one co-morbidity; 17% have two; and 7% have three or more. The most common comorbidities are cardiovascular disease (35%), respiratory disease (14%), cerebrovascular disease (13%), diabetes (9%), malignancy (8%) and treated renal disease (3%) *(9)*.

Approximately 25% of patients with hip fracture have moderate or severe cognitive impairment, and a further 15–25% have mild cognitive impairment. Approximately 25% of patients with hip fractures have at least moderate cognitive impairment (abbreviated mental test score < 7), 20% are institutionalised, and 50% require walking aids or are immobile *(10)*.

Mortality after hip fracture has remained relatively unchanged for the last two decades. Currently, 8.4% of patients die within 30 days of surgery. However, it has been suggested that up to half of postoperative deaths are potentially preventable. Thirty-day mortality is increased for older, sicker, male patients. Up to 15–30% of patients die within a year of surgery *(11, 12)*. The duration of the recovery of cognition after anesthesia and surgery is multifactorial and among other factors is dependent on the type of anesthesia used, the type of surgery and the patient. POCD is considered to be a subtle deterioration in cognitive function, lasting for weeks, months or longer. It can be considered to be a mild cognitive disorder characterized by impairment of memory, learning difficulties and reduced ability to concentrate. Patients are frequently anxious about the surgery they are about to undergo *(13)*.

Major surgery causes an endocrine response with release of hypothalamic-pituitary-adrenal (HPA) and sympathetic nervous system hormones. Cognitive impairment has been associated with high levels of glucocorticoids, as documented in a variety of experimental and clinical studies. Cortisol has been found to be toxic to cells in the hippocampus, and this structure plays a critical role in the consolidation of short-term into long-term explicit memory as well as descending control of the HPA axis. This gave rise to the hypothesis that repeated episodes of stress cause decreased hippocampal inhibition of the HPA axis and, thus, prolonged hyperactivation. It seems that cortisol secretion pattern is profoundly affected (i.e. flattened) by major surgery and this flattening is significantly related to the occurrence of early postoperative cognitive dysfunction *(14, 15, 16)*.

Our early results confirm corellation between increased plasma cortisol levels after fracture with VAS score and cognitive imapairment. Mild cognitive impair-

ment (MCI) is associated with a higher risk of postoperative delirium. Perioperative cortisol and inflammatory alterations observed in MCI may provide a physiological explanation for this increased risk *(13).* Spinal anaesthesia results in less immunosupression, i.e. maintains the number of Th1 cells, thus stimulating the cell immunity *(6).* Recent findings demonstrate a neuroprotective effect of local anaesthetics, leading to significant reduction in cognitive dysfunction after surgery *(4).* Elderly patients > 60 yr of age and undergoing major surgery subjected to general anaesthesia displayed more frequent cognitive impairment during the immediate postoperative period in comparison to those who received a regional technique *(12).* Daniels AH *et al.* showed that many elderly hip fracture patients had unrecognized CI before surgery, and cognitive impairment (CI) patients had significantly more pain than normal cognitive (NC) patients did. Appropriate identification of preoperative CI and treatment of pain are crucial in optimizing patient outcomes. Patients with PreCI have an increased incidence of POCD and cognitive decline. Preoperative CI is a good predictor of subsequent postoperative cognitive dysfunction (POCD) and cognitive decline after 12 months in this group of patients is low *(11).* Dexamethasone added to the local anesthetic and administered intrathecally relieves pain by reducing inflammation and blocking transmission of nociceptive C-fibers and by suppressing ectopic neural discharge *(17).* It has been shown that the duration of postoperative analgesia was prolonged when dexamethasone is given as an adjunct for peripheral nerve blocks *(18, 19).* Although dexamethasone has been used intrathecally for many years, it has not been evaluated when it was given in conjunction with bupivacaine intrathecally. Our investigation confirmed the effect of conjugation of dexamethasone with levobupivacaine the prolong duration time of spinal anesthesia and analgesia compared with spinal anesthesia with only levobupivacaine.

CONCLUSION

The addition of dexamethasone to the local anesthetic significantly prolongs the duration of sensory block and decreases opioid requirements and postoperative cognitive disturbances. There is a need to improve their knowledge around risk factors, prevention and management of postoperative cognitive dysfunction.

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