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# Spinal Dexamethasone Effect on Cognitive Disorders After Hip Surgery

Livija Sakic<sup>1,2,3</sup>, Dinko Tonkovic<sup>3,4</sup>, Zlatko Hrgovic<sup>5</sup>, Antonio Klasan<sup>6,7</sup>

<sup>1</sup>Department of Anesthesiology, Reanimatology and Intensive Medicine, University Hospital "Sveti Duh", Zagreb, Croatia

<sup>2</sup>Faculty of Dental Medicine and Health Osijek, Josip Juraj Strossmayer University of Osijek, Croatia

<sup>3</sup>School of Medicine, University of Zagreb, Zagreb, Croatia

<sup>4</sup>Department of Anesthesiology, Reanimatology and Intensive Medicine, University Hospital Center, Zagreb, Croatia

<sup>5</sup>Goethe University Clinic, Frankfurt am Main, Germany

<sup>6</sup>AUVA UKH Steiermark, Graz, Austria

<sup>7</sup>Johannes Kepler University, Linz, Austria

**Corresponding author:** Livija Sakic, Department of Anesthesiology, Reanimatology and Intensive Medicine, Josip Juraj Strossmayer University of Osijek, University Hospital "Sveti Duh", Zagreb, Croatia (e-mail: mitzilivilla@yahoo.com).

### ABSTRACT

**Background:** Proximal femoral fractures (PrFF) are one of the most common causes of emergency admission in the elderly population. The majority of patients have pre-existing conditions that get worsened by unplanned surgery. **Objective:** Purpose of this article was to evaluate if a single shot of dexamethasone with levobupivacaine administered intrathecally reduces postoperative pain and cognitive complications in patients with proximal femoral fractures. **Methods:** The study was performed at a level II trauma center which is a part of a teaching hospital with a catchment population of around 300,000 patients, the first author's affiliation. Around 500 PrFF are performed yearly in the center. All participants gave oral and written informed consent before randomization. **Results:** In total, 60 patients with a PrFF, ASA status 2 or 3 were randomized into two groups for spinal anaesthesia as DLSA study group (received 8 mg of dexamethasone and 12.5 mg of 0.5 % levobupivacaine) or LSA control group (received 12.5 mg of 0.5 % levobupivacaine). Post-operative cognitive disturbance was evaluated using simplified Confusion Assessment Method (CAM) scale, pain intensity was measured using Visual Analogue Scale (VAS) and blood samples for defining cortisol concentrations were taken before and after the surgical procedure. The primary outcomes were effects of intrathecal dexamethasone on plasma cortisol affecting cognitive disturbances. Secondary outcomes included pain scores and length of hospital stay. The DLSA group demonstrated a reduced incidence of postoperative cognitive dysfunction (POCD),  $p=0.043$ , longer analgesia duration,  $p<0.001$ , decreased cortisol levels and shorter hospitalization  $p=0.045$ . Intrathecal dexamethasone was the only significant predictor of postoperative delirium, OR 7.76,  $p=0.019$ . **Conclusion:** Single shot intrathecal administration of dexamethasone with levobupivacaine used in anaesthesia for proximal femoral fractures reduces the stress response by decreasing plasma cortisol concentrations prolonging analgesia. Complications such as delirium and POCD occurred with significantly lower frequency allowing better postoperative rehabilitation and shortening the hospitalization.

**Keywords:** proximal femoral fracture, spinal anesthesia, dexamethasone, delirium.

## 1. BACKGROUND

Proximal femoral fractures (PrFFs) are known for most painful stress injuries and in the elderly (1). This pain syndrome can change the cognitive functions, which can be reduced with prompt surgical treatment and punctual quality rehabilitation (2, 3). Postoperative cognitive dysfunction (POCD) is common after hip fracture and, unless systematic screening occurs, is likely to be underrecognized and have a difficult postoperative course (4). Achieving effective analgesia is particularly difficult because it is necessary to personalize the treatments and, at the same time, the ineffective analgesia may lead to serious complications such as patient's fear and anxiety, lead to aggressive behavior and disturbance of cognition, and has an unfavorable effect on physiological parameters. Significantly higher cortisol levels can last up to eight weeks after injury in elderly patients (5). Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis with higher cortisol levels is involved in the pathophysiology of delirium (6) similarly, association between higher plasma cortisol levels and POCD in aged patients following hip fracture surgery occurs (6, 7). Delirium refers to observable changes in consciousness and attention, whereas POCD may refer to a patient exhibiting significant declines from patient's own baseline level of performance in one or more neuropsychological domains (8). Dexamethasone can inhibit cortisol secretion by inhibiting the hypothalamo-pituitary-adrenal axis primarily at the pituitary

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level by transcription mechanism in the cells, but not obligatory for adrenocorticotrophic hormone (ACTH) gene synthesis (9). It is comprehended that a harmful stimulus can suppress the HPA axis feedback information which is a possible function of nature and intensity of the stimulus (10). Spinal anesthesia avoids the risks of general anesthesia, and various additives such as epinephrine, phenylephrine, clonidine, opioids, etc. added to local anesthetics were associated with adverse effects (11-13). In a variety of clinical settings dexamethasone administered preoperatively improved postoperative analgesia and decreased opioid consumption and their associated adverse effects (14).

Our hypothesis was that administration of a single dose of intrathecal dexamethasone 0.1 mg/kg preoperatively enhances perioperative analgesia in elderly patients with a PrFF.

## 2. OBJECTIVE

The purpose of this article was to evaluate if a single shot of dexamethasone with levobupivacaine administered intrathecally reduces postoperative pain and cognitive complications in patients with proximal femoral fractures.

## 3. PATIENTS AND METHODS

### Patients

This study was approved by the local Ethics committee and registered at clinicaltrials.gov (NCT03856502). The study was performed at a level II trauma center which is a part of a teaching hospital with a catchment population of around 300,000 patients, the first author's affiliation. Around 500 PrFF are performed yearly in the center. All participants gave oral and written informed consent before randomization. Emergency patients with PrFF receiving spinal anaesthesia for surgical treatment were screened for inclusion. Inclusion criteria were all cooperative patients with a proximal femoral fracture of one leg, aged 50+, with an American Society of Anesthesia (ASA) class <3. Patients were excluded if they had pre-existing cognitive impairment, diabetes mellitus, neurological conditions or tumors, neuroendocrine disorders or tumors, ASA ≥4 and unwillingness to participate in the study. Patients were excluded if spinal anaesthesia failed, patients were unsuitable for spinal anaesthesia or if they received an additional peripheral block.

The study design was a randomized controlled trial with two parallel groups. The group assignment was determined by a computer generated algorithm (Randlist®, Datainf, Thübringen, Germany) A researcher who participated in data collection performed randomization in two groups (sizes 1:1). Participants were randomized to receive spinal anaesthesia before surgery by either one shot levobupivacaine solution (LSA) or one shot levobupivacaine solution with additional low dose Dexamethasone (DLSA).

Patients read and signed the informed consent after the study has been clearly explained to them.

Proximal femoral fractures were treated either by a partial hip arthroplasty or by intramedullary nailing, depending on the localisation of the fracture. Subtrochanteric fractures were treated with additional cerclage wiring and using an extended length intramedullary nail.

### Anesthetic procedure

All spinal anaesthesia were performed by the principal investigator (LŠ). Spinal anesthesia was performed in the sitting position medially or paramedially in the middle lumbar segments (L2-3 or L3-4) via an BD Spinal Needle Quincke Type Point 22-27 G. The skin was anesthetized using lidocaine 10 mg/ml with adrenaline.

One study group (DLSA) received 8 mg of dexamethasone (Dexamethasone Sodium Phosphate, KRKA) and 12,5 mg of 0,5 % levobupivacaine (Chirocaine, Abbott). The control group of thirty patients received 12,5 mg of 0,5 % levobupivacaine intrathecally, the LSA group. Block onset, duration of analgesia as well as duration of surgical procedure was calculated in minutes (min), and was measured from the application, throughout the surgical procedure and in the postoperative recovery.

Motor block was assessed using a modified Bromage scale (0 = able to lift whole extended leg or standing up, 1 = flexion of the knee, 2 = flexion of the ankle, 3 = no flexion of the knee or ankle). If there was a difference in motor block between the legs, the leg with the most intense block was reported.

Plasma cortisol was measured at five time-points: T1- before anesthesia and infusion administration, T2- one hour after surgery, T3- third postoperative day at 6 am, T4- fifth postoperative day at 6 am and T5- on tenth postoperative day at 6 am. Plasma cortisol was assayed by Roche Elecsys Immunoassay System in laboratory reference points (185-624) nmol/L using 0.5 mL of patients' blood.

Postoperative cognitive impairment was evaluated using simplified Confusion Assessment Method (CAM) score scale (15) in four measure points: T1- one hour after surgery, T2- third postoperative day at 9 am, T3- fifth postoperative day at 9 am and T4- on tenth postoperative day at 9 am to follow cortisol measurements as well. It is a clinical instrument for delirium assessment used by non- psychiatric medical staff. Delirium is described in terms of 4 diagnostic criteria; 1) acute onset or fluctuating course, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness (alert, lethargic, stupor or coma) and is defined as present when 1 plus 2 or either 3 or 4 is positive. CAM scale criteria was used to exclude delirium. Preoperative cognitive evaluation was based on anesthesiologist guided conversations with the patient and information given by the patient's closest relative or guardian. Memory and speech were assessed by object naming and verbal fluency by having patients recall the items in any order and name in 60 seconds as many words as possible that began with a specific letter. Higher scores represented greater verbal fluency and better memory. Attention was measured by response time on a dual task having patients naming presented items while using distractors at the same time (16).

Participants were assessed for postoperative pain using a Visual Analogue Scale (VAS) ranging from 0 to 10, including worst pain experienced during rehabilitation. If the participant was asleep at the time of pain query, the pain score was assigned "0".

Visual Analogue Scale (VAS), was used for evaluating overage pain intensity every three hours when patients were awake in five measure points: T1- before anesthesia and infusion administration, T2- one hour after surgery, T3- third postoperative day, T4- fifth postoperative day and T5- on tenth postoperative day to follow cortisol measurements. Hospitalization was calculated by the number of days preoperatively from the day of admission to the day of surgical treatment and post-operatively from the day of surgical reconstruction to the day of hospital discharge in the time period of up to 30 days.

Weight bearing was allowed as tolerated from postoperative day one. Heparin was administered for thromboprophylaxis.

**Outcome measures**

The predefined, primary end point of the study were plasma cortisol concentration and incidence of cognitive disturbances. Secondary outcomes included duration of analgesia, postoperative pain intensity at first hour postop, as well as the third, fifth and tenth days after surgery and length of hospital stay. Data was interpreted by investigators blinded to the treatment received (DT,AK).

**Ethical statement**

The research approved by Ethical Committee of the University hospital "Sveti Duh", Zagreb, Croatia, reference number 3612, October 30<sup>th</sup> 2012 and the Croatian School of Medicine University of Zagreb, number: 380-591-0106-13-244212.

**Statistical analysis**

Normality distribution was tested using the Kolmogorov-Smirnov test. Categorical variables were shown by using absolute frequencies and ratios, quantitative variables were expressed as median [interquartile range] for non-normally distributed variables and mean ( $\pm$ standard deviation) for normally distributed variables. The data for descriptive variables were analyzed by chi-square test, whereas differences in quantitative variables were tested by Mann-Whitney U test. Particular clinical parameters were evaluated by Spearman's correlation analysis. Multivariate relationship of particular clinical variables related to the group with cognitive impairment was performed using binary logistic regression analysis. With an  $\alpha = 0.05$  and a power = 0.8 we estimated that a total of 60 participants were required and that 30 patients per study group were needed to detect the dif-

Variable	Group				P	
	DLSA		LSA			
Age, years (mean $\pm$ SD)	81.63 ( $\pm$ 6.94)		79.69 ( $\pm$ 10.17)		0.370	
Gender n, %	Female	19	63,30%	26	86,70%	0.037
	Male	11	36,70%	4	13,30%	
ASA status n, %	2	22	73,30%	19	63,30%	0.405
	3	8	26,70%	11	36,70%	
Fracture type	Extracapsular	23	76,70%	16	53,30%	0.058
	Intracapsular	7	23,30%	14	46,70%	
Cognitive alterations	None	21	70,00%	12	40,00%	0.0195
	POCD	8	26,67%	13	43,33%	
	Delirium	1	3,33%	5	16,67%	
Preoperative hospital stay (hours)	$\leq$ 48 h	11	36,70%	5	16,70%	0.08
	>48 h	19	63,30%	25	83,30%	
Hospitalisation days (mean $\pm$ SD)	15.9 (6.0)		17.4 (4.0)		0.045	

**Table 1. Demographic data and outcome measures**

ference between two groups for the predefined plasma cortisol levels.  $P < 0.05$  was considered to be statistically significant. Statistical analysis was performed by the IBM SPSS Statistics v23 (IBM, Armonk, NY, US).

**Data availability**

Please provide a Data Availability statement under this subsection. Certain data types must be deposited in an appropriate public structured data, and the accession number(s) provided in the manuscript. At publication, full access is required. If full data access is required for peer review, authors must make it available.

**4. RESULTS**

Sixty patients with PrFF were included in this randomized, prospective, clinical trial. All screened patients could be included (Figure 1).

Average age was 80.65 ( $\pm$ 8.5) years. Preoperatively, there were no significant differences in age, ASA clas-

Timeline		Mean ( $\pm$ SD) nMol/L	P
Preoperative	DLSA	731.23 ( $\pm$ 170.33)	0,511
	LSA	757.00 ( $\pm$ 216.06)	
1h postop	DLSA	410.13 ( $\pm$ 190.25)	0,088
	LSA	479.37 ( $\pm$ 166.30)	
3 days postop	DLSA	522.63 ( $\pm$ 140.29)	0,865
	LSA	524.80 ( $\pm$ 138.28)	
5 days postop	DLSA	493.87 ( $\pm$ 122.42)	0,796
	LSA	526.10 ( $\pm$ 281.01)	
10 days postop	DLSA	433.03 ( $\pm$ 115.13)	0,745
	LSA	433.10 ( $\pm$ 159.11)	

**Table 2. Plasma cortison values**

Prediction of cognitive disorder	OR	95% CI		p
		lower	upper	
Extracapsular proximal femoral fracture/ Intracapsular proximal femoral fracture	2,84	0,42	19,13	0,283
LSA / DLSA	7,67	1,39	42,36	0,019
VAS preoperatively	2,04	0,86	4,83	0,104
Cortisol preoperatively	1,00	0,99	1,00	0,365
Age (years)	1,12	1,00	1,25	0,051
Female / male	1,20	0,16	8,77	0,860

**Table 3. Intrathecal dexamethasone as a predictor of postoperative cognitive function**

sification, fracture type and preoperative hospital stay duration between the groups (Table 1).

**Primary outcome measure** The overall incidence of cognitive alterations, POCD and delirium, was significantly lower in the DLSA group ( $p=0.0195$ ) (Table 1). Majority of patients were operated on after the 48h mark, without a significant difference between the groups (Table 1). There were no differences in cortisol levels between the two groups at any time-point (Table 2 and Figure 2). Intrathecal dexamethasone was the only significant predictor of postoperative delirium, OR 7.76 ( $p=0.019$ ) (Table 3).

**Secondary outcome measure**

Analgesia lasted longer in the DLSA group, 540 mins [264] than in the LSA group 330 [122] ( $p<0.001$ ). From the third postoperative day onwards, pain levels were significantly lower in the DLSA group (Table 4). DLSA patients had a lower mean number of hospitalization days (Table 1).

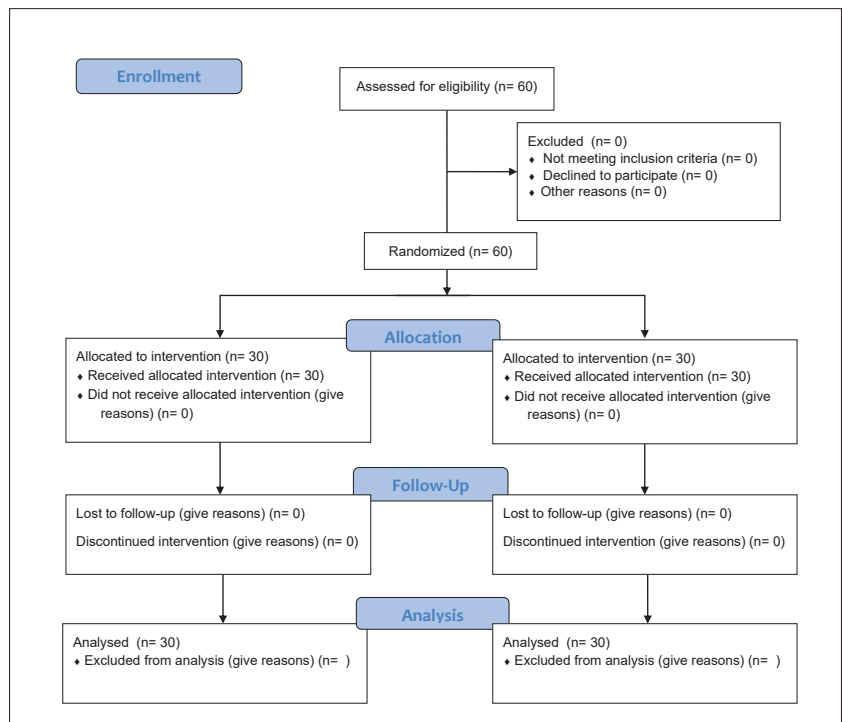
**5. DISCUSSION**

This study demonstrates that single low dose of dexamethasone with levobupivacaine administered intrathecally reduces plasma cortisol levels, provides longer lasting analgesic effect, lowers the incidence of cognitive complications and shortens hospitalization.

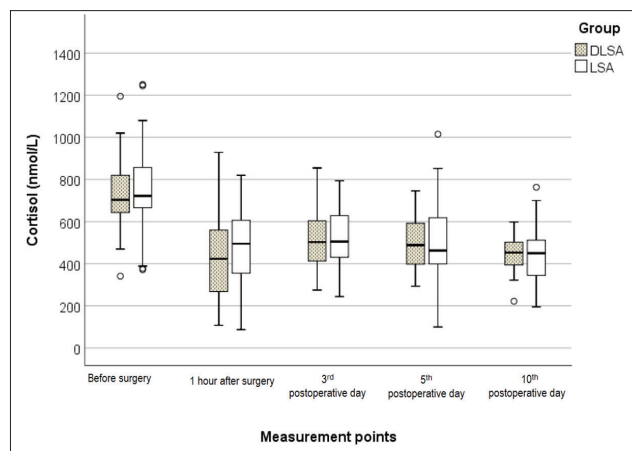
Pain sensation varies in this type of fractures and time of surgical reconstructions depending on intensity, quality and duration of pain stimuli involving nociception, inflammation and nerve cells remodeling (11, 16). According to the demographic study findings, proximal femoral fractures are more usual in older female population with significant neuroendocrine stress response to tissue damage, perioperative pain and psychological stress. Although dexamethasone has been used intrathecally for many years, it has not been evaluated when it was given in conjunction with levobupivacaine intra-

Timeline		Median[IQR]	p
	LSA	8.0 [2.0]	
1h postop	DLSA	0.0 [0.0]	0.061
	LSA	0.0 [0.0]	
3 days postop	DLSA	1.5 [1.0]	<0.001
	LSA	3.0 [2.0]	
5 days postop	DLSA	1.0 [2.0]	<0.001
	LSA	3.0 [1.0]	
10 days postop	DLSA	0.0 [1.0]	0.002
	LSA	1.0 [1.0]	

**Table 4. Comparison of pain levels using the Visual-Analog-Scale (VAS) between the groups**



**Figure 1. Flow of patients during study**(Color figure can be viewed at [Wileyonlinelibrary.com](http://Wileyonlinelibrary.com))



**Figure 2. Graphical analysis of the differences between the groups in plasma cortisol fluctuations. DLSA the study group that received dexamethasone and levobupivacaine in spinal anaesthesia, LSA the control group that received levobupivacaine in spinal anaesthesia**



thecally. Single shot effect of intrathecally administered dexamethasone with levobupivacaine affecting postoperative pain, consciousness and outcome in emergency patients with femoral fractures have not yet been evaluated in recent literature. Intrathecal addition of dexamethasone to bupivacaine for elective orthopedic surgery on lower limbs has been shown to significantly prolong duration of sensory block and to decrease opioid requirements in postoperative management (17).

Glucocorticoids are part of induction to anesthesia in different clinical protocols achieving much improved analgesia and minimized inflammation with reduced opioid requirements and less adverse events after surgery (11, 14, 18, 19). Why dexamethasone prolongs regional analgesia is a subject of debate. Dexamethasone relieves pain by reducing inflammation and blocking transmission of nociceptive C-fibers and by suppressing ectopic neural discharge (20) and also that dexamethasone increases the activity of inhibitory potassium channels on nociceptive C fibres, decreasing their activity (21).

Our study findings suggest higher pain intensity and increased cortisol concentrations, occurring on the third postoperative day were directly in correlation with more complex degrees of cognitive impairment in the LSA group, not in the DLSA group. The difference in VAS scores and different in-hospital stay might signify reduced perioperative stress effect when dexamethasone was added intrathecally with enhancement of treatment outcome. Szucs et al. (22) demonstrated significant improvement in postoperative pain with intravenously administered dexamethasone.

Nikkel et al. (23) demonstrated average time to surgery was 1.8 days for PrFF and a longer time to surgery was associated with longer hospital stay. The percentage of patients with most comorbid conditions increased with increasing length of stay. A shorter hospital stay (<5 days and <10 days) was also associated with decreased 30 day mortality.

Although guidelines recommend the surgery to be performed within 24hrs of admission (24), and studies demonstrate a clear benefit of early surgery (25), and no downside of after-hours surgery (26) in the present study hospitalization lasted shorter in the group that received dexamethasone, but was overall long with 73,33% of patients waiting for surgical treatment more than 48h from admission because of preoperative preparation.

#### Limitation of the study

This study has some limitations. No long-term follow-up has been performed, however, outcome measures were short-term outcomes during in-hospital stay. The in-hospital time to surgery is long compared to the literature and the guidelines. The same study in a setting where these times are shorter might affect the results, especially due to the role of cortisone in a stress reaction such as a hip fracture. Both intramedullary nailing and arthroplasty have been included in the study. Given the complications are similar (27), we do not expect there would be a difference in results if controlled for this particular variable.

## 6. CONCLUSION

Single shot intrathecal administration of dexamethasone with levobupivacaine used in anesthesia for proximal femoral fractures reduces the stress response by decreasing plasma cortisol concentrations prolonging analgesia. Complications such as delirium and POCD occurred with significantly lower frequency allowing better postoperative rehabilitation and shortening the hospitalization.

- **Author's contribution:** All authors were involved in all steps of preparation this article. Final proofreading was made by the first author.
- **Conflict of interest:** None declared.
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