СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted* **ISSN Online 2406-0895**

Original Article / Оригинални рад

Marija Jović[1,♣], Radmilo Janković[2], Nebojša Videnović[3], Marija Stošić[4], Ines Veselinović[4], Biljana Stošić[2]

Comparative analysis of effects of three different doses of fentanyl and standard dose of bupivacaine on a spinal block in patients with hip endoprosthesis surgery

Компаративна анализа три различите дозе фентанила у комбинацији са стандардном дозом бупивакаина код спиналног блока код болесника подвргнутих елективној операцији уградње вештачког кука

[1]Leskovac General Hospital, Department of Anesthesiology and Reanimatology, Leskovac, Serbia;
[2]University of Niš, Faculty of Medicine, Clinical Center of Niš, Anesthesiology Clinic, Niš, Serbia;
[3]University of Priština – Kosovska Mitrovica, Faculty of Medicine, Department of Anesthesiology and Reanimatology, Priština–Gračanica Clinical Hospital Center, Gračanica, Serbia;
[4]PhD student, University of Niš, Faculty of Medicine, Clinical Center of Niš, Anesthesiology Clinic, Niš, Serbia

Received: July 29, 2020
Revised: January 20, 2021
Accepted: February 7, 2021
Online First: March 5, 2021
DOI: https://doi.org/10.2298/SARH200729010J

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.
Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.
When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

♣**Correspondence to:**
Marija JOVIĆ
Đorđa Andrejevića Kuna 39
16000 Leskovac, Serbia
E-mail: **mladenovicmarija@yahoo.com**

Comparative analysis of effects of three different doses of fentanyl and standard dose of bupivacaine on a spinal block in patients with hip endoprosthesis surgery

Компаративна анализа три различите дозе фентанила у комбинацији са стандардном дозом бупивакаина код спиналног блока код болесника подвргнутих елективној операцији уградње вештачког кука

SUMMARY

Introduction/Objective Spinal anesthesia is often used for hip endoprosthesis surgery. Significant surgical stress response consisting of hormonal, metabolic and inflammatory changes can be initiated by the hip replacement surgery. Intrathecal opioids, as adjuvants to local anesthetics, make spinal block sufficient even with lower doses of the local anesthetics, and the incidence of the side effects reduce to minimum.

Methods This study included 162 patients of either sex, ASA 1- 2, scheduled for total hip arthroplasty. The patients had spinal anesthesia with 10mg of 0.5% bupivacaine with 20 μg (Group I), or 25 μg (Group II) or 30μg fentanyl intrathecally (Group III).

Results Mean time to achieve maximum motor and sensory blockade was with no significant difference among the groups. Time of motor block duration was shorter in the Group III. Four hours after the operation, patients in the Group I had significantly higher cortisol serum levels. Blood glucose levels were with no significant difference among the groups. Levels of CRP increased remarkably postoperatively in the Group I. Incidence of hypotension, bradycardia, nausea and vomiting was significantly higher in the Group III. Pruritus and shevering were not recorded among the groups. The first time an analgetic was needed postoperatively was the longest in the Group III.

Conclusion The dose of 10mg of bupivacaine combined with 25 μg fentanyl was the optimal option to achieve hemodynamic stability, sufficient sensory and motor blockade, and reduce the stress response and incidence of the opioids side effects such as vomiting, nausea, pruritus etc.

Keywords: spinal anesthesia; bupivacaine; fentanyl; postoperative analgesia

САЖЕТАК

Увод/Циљ Спинална анестезија честа је анестезиолошка техника која се користи током хируршке интервенције уградње вештачког кука. Овај хируршки третман може изазвати системски одговор на хируршки стрес, односно, хормонске, метаболичке и запаљенске промене. Интратекално дати опиоиди као адјувант локалног анестетика остварују синергистички ефекат са њим чинећи спинални блок потпунијим чак и при примени нижих доза локалног анестетика, а инциденцу нежељених ефеката своде на минимум.

Методе Студијом је обухваћено 162 болесника, оба пола, *ASA* 1-2, подељени у три групе методом случајног избора. Испитаници су добијали 10 *mg* 0,5% раствора бупивакаина и 20 *μg* (Група I) или 25 μg (Група II) или 30 μg (Група III) фентанила интратекално.

Резултати Статистички значајно није било разлике у времену потребном за постизање потпуне моторне и сензитивне блокаде међу групама, док је време трајања моторне блокаде било знатно краће у Групи III. Постоперативно током прва четири сата болесници Групе I имали су највећу вредност кортизола у серуму. Ниво гликемије у крви није имао статистички значајну промену вредности. Вредности *CRP* биле су током постоперативног периода највише у болесника Групе I. Инциденца хипотензије, брадикардије, мучнине и повраћања била је највећа у Групи III. Свраб и дрхтање нису описани ни у једној од испитаних група. Постоперативно, најдужи период до потребе за аналгетиком описан је у болесника Групе III.

Закључак Применом 25 *μg* фентанила, као адјуванта локалном анестетику, 10 *mg* 0,5% бупивакаину, постиже се адекватна хемодинамска стабилност, моторна и сензитивна блокада, смањује стрес одговор организма на хируршки третман и редукује инциденца нежељених ефеката опиоида, мучнина, повраћање, свраб итд.

Кључне речи: спинална анестезија; бупивакаин; фентанил; постоперативна аналгезија

INTRODUCTION

Significant surgical stress response consisting of hormonal, metabolic and inflammatory changes can be initiated by the hip replacement surgery [1, 2]. The controlled trauma of a surgical insult activates the afferent nerve signals from the surgical site and stimulates releasing corticotrophin- releasing hormone and arginine vasopressin. These peptides stimulate secretion of adrenocorticotropic hormone which stimulates cortisol secretion [3]. The effects of cortisol in the setting of surgical stress include suppression of insulin and mobilization of energy stores, increased proteolysis, sodium and water retention leading to preservation of blood pressure, suppression of the immune inflammatory response and delayed wound healing through its effects on collagen synthesis. Cortisol enables the synthesis and release of catecholamines and contributes to normal vascular permeability, vascular tone, and myocardial contraction by regulating β- receptor synthesis and regulation [4, 5].

Spinal anaesthesia is often used for hip endoprothesis surgery. During a spinal anaesthesia there are many side effects as a result of sympatical nervous system blockade. Post spinal anesthesia hypotension is caused by the decrease in the sympathetic outflow causing arterial vasodilatation, a decrease in venous return and consequently the activation of the Bezold Jarish reflex that elicts a triad of bradycardia, vasodilatation and further hypotension [6]. The incidence of hypotension during the spinal anesthesia is about 16% to 33% [7]. Compensatory mechanisms are generally more effective in young patients [8]. In elderly patients there are reduced physiological reserve and associated comorbidites [9]. Acute hypotension reduces cerebral perfusion, which leads to transient ischemia and activates the vomiting center [10]. To reduce the incidence and severity of hypotension, various strategies have been developed: preloading/ coloading fluids, use of vasoconstrictors and low doses of local anesthetics [11, 12].

Spinal anesthesia can provide good perioperative pain control. The pre- surgery block contributes to intra- operative analgesia and reduces the need for other analgetics [13].

The use of the lower doses of local anesthetics combined with opioids, while providing a spinal block, may result in a better hemodynamic response of the patients and minimal incidence of the side effects [14, 15]. Besides analgesia, this anesthetic technique protects

patients by reducing the immune response and the incidence of the postoperative complications.

The aim of study is to compare the efficiency of three different intrathecal doses of fentanyl (20μg, 25μg and 30μg) added to standard dose of local anesthetic (2mg 0.5% bupivacaine) during the elective hip replacement surgery. The efficiency of the opioid used refers to less surgical stress, less side effects and longer duration of analgesia.

METHODS

All procedures performed in the study involving human participants were done in accordance with the ethical standards of the Helsinki declaration and its later amendments. Furthermore, the research was approved by the Ethics Committee of the Faculty of Medicine University of Niš on September 12, 2017; ref. №.: 12-8765/ 8. Informed consent was obtained from all individual participants included in the study.

This study included 162 patients of either sex, ASA 1- 2, scheduled for total hip arthroplasty. All patients had surgical treatment in the morning. The patients were randomized into three groups:

Group I: Patients received 10 mg (2 ml) 0.5% bupivacaine and 20μg (0.4 ml) of fentanyl intrathecal;

Group II: Patients received 10mg (2ml) 0.5% bupivacaine and 25μg (0.5ml) of fentanyl intratecal;

Group III: Patients received 10mg (2ml) 0.5% bupivacaine and 30μg (0.6ml) of fentanyl intratecal.

Sensory blockade was evaluated by the bilateral pin- prick method. Motor blockade was evaluated by the modified Broomage test (0= without paralysis; 1= unable to lift extended legs; 2= unable to flex knee; 3= unable to flex feet or complete motor blockade).

Serum levels of cortisol, glucose and CRP (C- reactive protein) were measured in all groups preoperatively and 4h, 12h and 24h after surgery.

The cardiovascular status of the patients was monitored by non- invasive methods such as: ECG monitoring, systolic, diastolic and mean arterial pressure, every five- minute interval.

The side effects on the central nervous system and gastrointestinal system such as: shivering, nausea, vomiting, pruritus were followed up and recorded intra- operatively or postoperatively.

The intensity of pain was assessed in 30^{th}, 60^{th}, 90^{th}, 120^{th}, 180^{th}, 240^{th} and 300^{th} minute after the anesthesia was given by:

- visual analog scale (VAS) (0- without pain to 10- the worst pain) and
- numerical scale (0- without pain to 10- the worst pain).

Duration of sensory blockade and the first time an analgesic drug was needed postoperatively were also recorded.

RESULTS

There was no statistically significant difference regarding ages, body mass index (BMI) and duration of surgery in all the groups ($p < 0.05$) (Table 1).

Mean time to achieve maximum motor blockade was with no significant difference among the groups. The time of motor blockade duration was significantly shorter in the Group ($p < 0.05$) (Table 2).

Mean time to achieve maximum sensory blockade was comparable among the three groups ($p < 0.05$) (Table 3). It was with no significant difference among the groups.

At the 4^{th}, the 12^{th} and the 24^{th} postoperative hour, the hormones of the surgical stress response were recorded. The study showed that patients in the Group I had significantly higher cortisol serum levels at 4^{th} hour after the surgery (Table 4).

Blood glucose levels were not significantly different among the groups. Levels of CRP increased remarkably postoperatively in the Group I (Table 5).

Incidence of hypotension, bradycardia, nausea and vomiting were significantly higher in the Group III ($p < 0.05$) (Table 6). Pruritus and shivering were not recorded among the groups.

The longest time untile new analgetic was needed postoperatively was in the Group III (Figure 1).

DISCUSSION

The intensity of sympathetic nervous system blockade depends on the local anesthetic dosage. A degree of sympathetic blockade and consequent hypotension after spinal anesthesia can be reduced by using small doses of local anesthetic. On the other side, it was reported more breakthrough pain with bupivacaine doses of 5 mg or less [16]. This tendency to adopt a higher dose approach is likely to be attributable to concerns that duration of spinal anesthesia may not be sufficient for the proposed surgery when bupivacaine < 10mg is used [17].

The success of spinal anesthesia with low dose of local anesthetic can be improved by addition of opioids. Intrathecally fentanyl doses not make additional effects on the sympathetic blockade, but makes duration of analgesia longer [18, 19].

In this study maximal dose of the intrathecal solution of 0.5% bupivacaine was 2ml (10mg) with 30µg (0.6 ml) fentanyl. This dose was defined by the results of the previous studies [19, 20]. Lower doses of local anesthetics combined with opioids may result in inadequate sensory or motor blockade. Intra- operatively, analgesia was adequate in all groups. Similar results had Ben David et al. with intrathecal dose of 4mg bupivacaine with 20µg fentanyl [20].

Bibhush [21] compared three different doses (12.5 mg, 10 mg and 5 mg) of 0.5% bupivacaine, with 25µg fentanyl. Results of this study showed that the dose of 5mg of bupivacaine in combination with 25µg of fentanyl intrathecally had inadequate motor blockade, while the dose of 10 mg of bupivacaine increased intensity and duration of both,

sensory and motor blockade. The time was 241.96 min. In this study the duration of motor blockade was 141.67 ± 15.3 min.

In this study, increasing the dose of fentanyl from 0.4ml (20μg) to 0.5 ml (25μg) and 0.6 ml (30μg) resulted in increase of the maximum level of sensory blockade. The time of achieving maximal analgesia was with no significant difference among the groups. Similar results had Kuusniemi [22].

Cortisol, has been researched in order to find the best anesthetical approach to reduced surgical stress response. Opioids, fentanyl and morphine, can reduce surgical stress response. Kwon et al. [23] hypothesized that circadian rhythm of cortisol might affect postoperative cortisol levels depending on the surgery start time. Cortisol recovery to preoperative level was faster in the afternoon surgery than in the morning surgery group. In this study, all patients had surgical treatment in the morning. Postoperative cortisol increased, similar to previous studies, except in the Group II, where the values were the same as before surgery. Cortisol serum level was significantly higher in the Group I at 4^{th} postoperative hour. Postoperatively, at 12^{th} hour, there was a remarkable increase of the cortisol serum levels in all groups.

CRP serum levels were without any significant differences among the groups. At 4^{th} postoperative hour, the level of serum CRP was significantly higher in the Group I. Even after 12h it showed higher levels.

Impaired metabolism of glucose has influence on wound infection, and can cause cardiac and thromboembolic complications. Hahn et al. [24] mention the reduction of the postoperative complications in patients who were not diabetics. Blood level of glucose is very important during peri- operative and postoperative. In this study blood glucose levels were not significantly different among the groups.

As a result of study, Knigin et al. [25] described spinal hypotension in 43,4% of patients. Rao et al. [26] hypotension described in 7 of 30 patients in group with 8mg bupivacaine combined with 25μg fentanyl. Malhotra et al. [27] the highest incidence of hypotension had in group with 12,5mg of bupivacaine combined with 25μg fentanyl. Hypotension was described in 60 patients (37%) in this study. In Group I it was described in 17 (31.5%) patients. In Group II hypotension was described in 18 (33.3%) patients and in Group III in 25 (46.3%). Better

haemodynamic stability they had in patients with 10mg bupivacaine and 20μg fentanyl. Ali et al. [28] reported pruritus with higher doses of fentanyl (25μg). Akanmu et al. [29] described pruritus and shivering only in patients who recived 10mg of bupivacaine with 25μg of fentanyl. Pruritus and shivering were not recorded among the groups in this study.

In our study, the longest time of analgesia was observed in the Group III, 272 ± 21 min. Akanmu et al. [29] found that analgesia lasted the longest in patients who recived 10mg of bupivacaine with 25μg of fentanyl, and it was 276.23 ± 26.21min.

CONCLUSION

Spinal anesthesia using standard doses of local anesthetics for hip endoprosthesis surgery in geriatric population, often causes hemodynamic instability due to reduced physiological reserve and comorbidities of patients. In order to prevent negative side effects and complications, but achieve appropriate sensory and motor blockade, the use of lower doses of local anesthetics combined with opioids was implemented in practice.

The dose of 10 mg (2 ml) of bupivacaine combined with 25 μg (0.5 ml) fentanyl, in this study, was the optimal option to achieve hemodynamic stability, sufficient sensory and motor blockade, and reduce the stress response and the incidence of the opioids side effects such as vomiting, nausea, pruritus, etc.

Conflict of interest: None declared.

REFERENCES

1. Kendrisic M, Surbatovic M, Djordjevic D, Jevdjic J. Surgical stress response following hip arthroplasty regarding choice of anaesthesia and postoperative analgesia. Vojnosanit Pregl. 2017;74(12):1162–1169. DOI: 10.2298/VSP160416153K.
2. Iwasaki M, Edmondson M, Sakamoto A, Ma D. Anesthesia, surgical stress and "long-term" outcomes. Acta Anaesthesiol Taiwan. 2015;53:99–104. Pubmed PMID: 26235899; DOI: 10.1016/j.aat.2015.07.002.
3. Prete A,Yan Q, Al-Tarrah K, Akturk KH, Prokop JL, Alahdab F, et al. The cortisol stress response induced by surgery: A systematic review and meta-analysis. Clin Endocrinol. 2018;89(5):554–567. PubMed PMID: 30047158; DOI 10.1111/cen.13820.
4. Khoo B, Boshier RP, Freethy A, Tharakan G, Saeed S, Hill N, et al. Redefining the stress cortisol response to surgery. Clin Endocrinol. 2017;87(5):451–458. PubMed PMID: 28758231; DOI: 10.1111/cen.13439.
5. Kwon HS. Perioperative glucocorticoid management based on current evidence. Anesth Pain Med 20089 [Preprint]. 2020 [cited 2021 Jan 15]. Available from: http:/www.anesth-pain-med.org/content/10.17085/apm20089
6. Ashoor MT, Hussien SN, Anis GS, Esmat MI. Dexamethasone blunts postspinal hypotension in geriatric patients undergoing orthopedic surgery: a double blind, placebo-controlled study. BMC Anesthesiology. 2021;21(11):1–9. DOI: 10.1186/s12871-021-01232-w.
7. Hofhuizen C, Lemson J, Snoeck M, Scheffer JG. Spinal anesthesia-induced hypotension is caused by a decrease in stroke volume in elderly patients. Local Reg Anesth. 2019;12:19–26. PubMed PMID: 30881108; DOI: 10.2147/LRA.S193925.
8. Ferré F, Martin C, Bosch L, Kurrek M, Lairez O, Minville V. Control of spinal anesthesia-induced hypotension in adults. Local Reg Anesth. 2020;13:39–46. DOI: 102147/LRA.S240753.
9. Zdravcevic SK. Subarahnoidalna, epiduralna i kaudalna anestezija. U: Jukic M, Husedzinovic I, Kvolik S, Kogler MV, Peric M, Zunic J, autori. Klinicka anesteziologija. Zagreb: Medicinska naklada; 2013. str. 643–659.
10. Vukotic DA, Green D, Jevdjic DJ, Vukotic VM, Petrovic N, Stevanovic DP. Comparison of efficacy and safety of preemptive infusion protocols of ephedrine and phenyephrine-prevention of hypotension and effects on hemodynamic parameters during spinal anesthesia for caesarean section. Srp Arh Celok Lek. 2020;148(3–4):173–179. DOI: 10.2298/SARH190607009V.
11. Elagamy EA, Kamaly MA, Shahin IM, Saleh M. Norepinephrine versus ephedrine for hypotension prophylaxis during cesarean section under spinal anesthesia. Ain-Shamas J Anesth. 2021;13(3):1–6. DOI: 10.1186/s42077-020-00124-4.
12. Isngardi I, Hartono R, Husodo PD, Prasedya SE. Low dose hyperbaric bupivacaine 5mg combined with 50mcg fentanyl for cesarean section in maternal heart disease. Anaesth Pain Intensive Care. 2019;23(3):274–278. DOI: 10.35975/apic.v23i3.1135.
13. Simic D, Simic I, Stevic M, Jovicic N, Mitrovic M, Budic I, et al. The role of regional anesthesia in the postoperative analgesia in pediatric patients. Srp Arh Celok Lek. 2019;147(5–6):316–320. DOI: 10.2298/SARH180116067S.
14. Cenkowski JM, Maguire D, Kowalski S, Al Gurashi AF, Funk D. Hemodynamic effects of low-dose bupivacaine spinal anesthesia for cesarean section:A randomized controlled trial. Saudi J Anesth. 2019;13(3):208–214. PubMed PMID: 31333365; DOI: 10.4103/sja.SJA_799_18.
15. Regmi SDB, Deo PG, Shrestha S, Shrestha S, Mishra TR. Low dose hyperbaric bupivacaine with fentanyl in spinal anesthesia in elective cesarean section. JCMC. 2019;9(28):79–82. DOI: 10.3126/jcmc.v9i2.24560.
16. Velde VM . Low-dose spinal anesthesia for cesarean section to prevent spinal-induced hypotension. Curr Opin Anesthesiol. 2019;32(3):268–270. DOI: 10.1097/ACO.0000000000000712.
17. Shelton C,White S. Anaesthesia for hip fracture repair. BJA Education. 2020;19(20):321–328. DOI: 10.1016/j.bjae.2020.02.003.
18. Andrés RG, Marcela HP, Paola VD, Marco BN, Marcela OV, Miguel RA. Low dose intrathecal morphine for hip arthroplasty. Rev Chil Anest. 2020;49:548–559. DOI: 10.2523/revchilanestv49n04.11.
19. Tighe SQ. Ultra-low dose spinal anaesthesia for hip fracture surgery fracture surgery. Anaesthesia. 2016;71:1237–1248. PubMed PMID: 27611045; DOI: 10.1111/anae.13613.

20. Ben DB, Frankel R, Arzumonov T, Marchevsky Y, Volpin G. Minidose bupivacaine-fentanyl spinal anesthesia for surgical repair of hip fracture in the aged. Anesthesiology. 2000;92:6–10. PubMed PMID: 10638892; DOI: 10.1097/00000542-200001000-00007.
21. Bibhush S, Subhash PA, Amatya R. Comparison of intrathecal bupivacaine with or without fentanyl for urosurgeries. JSAN. 2014;1:18–21. DOI: 10.3126/jsan.v1i1.13584.
22. Kuusniemi KS, Pihlajamaki KK, Pitkanen MT, Helenius HY, Kirvelä OA. The use of bupivacaine and fentanyl for urologic surgery. Anesth Analg. 2000;91:1452–1456. PubMed PMID: 11093999; DOI: 10.1097/00000539-200012000-00029.
23. Kwon YS, Jana JS, Hwang SM, Tark H, Kim JH, Lee JJ. Effects of surgery start time on postoperative cortisol, inflammatory cytokines and postoperative hospital day in hip surgery. Medicine. 2019;98:24. PubMed PMID: 31192911; DOI: 10.1097/MD.000000000015820.
24. Hahn RG, Ljunggren S. Preoperative insulin resistance reduces complications after hip replacement surgery in non-diabetic patients. BMC Anesthesiol. 2013;13(1):39. PubMed PMID: 24188443; DOI: 10.1186/1471-2253-13-39.
25. Knigin D, Avidan A, Weiniger FC. The effect of spinal hypotension and anesthesia-to-delivery time interval on neonatal outcomes in planned cesarean delivery. Am J Obstet Gynecol. 2020;223(5):747–760. DOI: 10.1016/j.ajog.2020.08.005.
26. Rao GD, Shalini A, Pasha N. Comparative study of isobaric levobupivacaine and hyperbaric bupivacaine for subarachnoid block in elective cesarean sections. Anesth Pain Intensive Care. 2020;24(2):215–222. DOI: 10.3575/apic.v24i2.
27. Malhotra A, Singh U, Singh M, Sood D, Grewal A, Mahajan A. Efficacy of premixed versus succedent administration of fentanyl and bupivacaine in subarachnoid block for lower limb surgeries:A randomized control trial. Indian J Anaesth. 2020;64(3):175–179.
28. Ali AM, Ismail S, Sohaib M, Aman A. A double-blind randomized control trial to compare the effect of varyng doses of intrathecal fentanyl on clinical efficacy and side effects in parturients undergoing cesarean section. J Anesthesiol Clin Pharmacol. 2018;34(2):221–226. PubMed PMID: 30104833; DOI: 10.4103/joacp.JOACP_271_16.
29. Akanmu NO, Soyannwo AO, Sotunmbi TP, Lawani-Osunde SA, Desalu I, Adekola OO, et al. Analgetic effects of intrathecally administred fentanyl in spinal anaesthesia for lower limb surgery. Maced J Med Sci. 2013;6(3):255–260.

Table 1. Patient characteristics

Group (number of patients)	Age (years)	Sex (M / F)	BMI (kg / m^2)	Duration of surgery (min)
I (n = 54)	69.1 ± 8	30/24	25.5 ± 3.1	104.4 ± 9.6
II (n = 54)	66.6 ± 7.5	38/16	24.3 ±3.8	106.9 ± 8.6
III (n = 54)	67.5 ± 7.7	34/20	24.4 ± 3.4	105.6 ± 8.6

There was no statistically significant difference regarding ages, body mass index (BMI) and duration of surgery in all the groups ($p < 0.05$).

Table 2. Characteristics of motor blockade

Group	Time to achieve motor blockade I (min)	Time to achieve motor blockade II (min)	Time to achieve motor blockade III (min)	Time to achieve motor blockade IV (min)	Time duration of motor blockade (min)
I	2.2 ± 0.6	3.2 ± 0.8	4 ± 1	4.7 ± 1	166.0 ± 7.8
II	2.4 ± 0.7	3.4 ± 0.7	4.5 ± 0.6	4.6 ± 0.6	141.7 ±15.3
III	2.1 ± 0.6	3 ± 0.7	3.9 ± 0.7	5 ± 0.6	128.7± 15.1

Mean time to achieve maximum motor blockade was with no significant difference among the groups. The time of motor blockade duration was significantly shorter in Group II ($p < 0.05$).

Table 3. Characteristics of sensory blockade

Group	Time for distribution of sensory blockade until T10 (min)	Time to achieve maximal sensory blockade (min)
I	4.3 ± 0.5	6.4 ± 0.4
II	4.4 ± 0.8	6.6 ± 0.7
III	4 ± 0.7	6.2 ± 0.9

Mean time to achieve maximum sensory blockade was with no significant difference among the groups ($p < 0.05$).

Table 4. Average serum cortisol levels (nmol/l) in the groups with 20 μg, 25 μg and 30 μg intrathecal fentanyl, 4h, 12h, and 24h postoperatively

Group	Preoperatively (nmol / l)	Postoperatively (nmol / l)		
		4h	12h	24h
I	472.4 ± 167.6	593.2 ± 277.3	850 ± 265.1	698 ± 105.3
II	692.6 ± 219.7	636.7 ± 184.2	789 ± 278.2	490.3 ± 170.6
III	558.5 ± 353.1	441.8 ± 249.4	765 ± 149.4	441.6 ± 277.3

Patients in Group I had significantly higher cortisol serum levels at 4th hour after the surgery ($p < 0.05$).

Table 5. Levels of CRP (mg/L) 4h, 12h, and 24 h postoperatively

Group	Preoperatively (mg / L)	Postoperatively (mg / L)		
		4h	12h	24h
I	18.9 ± 3	108.4 ± 1.1	78.7 ± 26.6	65.3 ± 28.9
II	5.9 ± 2.2	5.3 ± 1.7	21.3 ± 11.2	11.2 ± 8.9
III	16.1 ± 2.5	18.7 ± 1.6	56.8 ± 15.6	44.9 ± 21.4

Levels of CRP increased remarkably postoperatively in the Group I ($p < 0.05$).

Table 6. Prevalence of side effects

Group	Hypotension		Bradycardia		Nausea		Vomiting	
	Number of patients (n)	%	Number of patients (n)	%	Number of patients (n)	%	Number of patients (n)	%
I	17	31.5	11	20.4	0	0	0	0
II	18	33.3	13	24.1	2	3.1	0	0
III	25	46.3	18	33.3	4	7.4	2	3.7

Incidence of hypotension, bradycardia, nausea and vomiting were significantly higher in Group III ($p < 0.05$).

Duration (min)

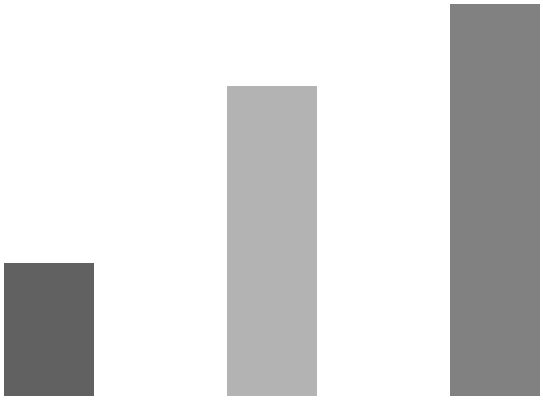

Figure 1. New analgesic needed postoperatively; the longest time until new analgesic was needed postoperatively was in the Group III ($p < 0.05$).

