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Klinik Araştırma

Comparison of the Effects of Bupivacaine and Levobupivacaine Used in Spinal Anesthesia on Propofol Requirement in BIS Guided Sedation

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SUMMARY

Objective: This study was designed to compare the effects of equivalent doses of bupivacaine and levobupivacaine on propofol requirement in BIS guided sedation under spinal anesthesia.

Material and Methods: Spinal anesthesia was performed on seventy patients scheduled for elective lower limb surgery with 3 mL's of either isobaric bupivacaine (Group B) or plain levobupivacaine (Group L). Five minutes after induction of spinal anesthesia, propofol infusion was started at 100 µg/kg/min and titrated to maintain bispectral index (BIS) score in the range of 65-75. Onset (to reach BIS ≤ 75) and recovery (the time from cessation of propofol infusion until BIS=90) time for sedation, and total propofol consumption during this time interval were recorded as well as time to recovery from sensory and motor block, length of stay (LOS) and sedation scores (OAA/S) in the postanesthesia care unit (PACU). Data were analyzed with One way ANOVA, Mann Whitney-U, Student's t and x^2 tests.

Results: BIS was significantly decreased in Group B compared to Group L at 10 and 15 min after spinal anesthesia ($p<0.01$). The maximum sensory block level was higher, while time to reach maximum motor block level was shorter in Group B ($p<0.05$, $p<0.001$ respectively). Offset time of sensory and motor block, recovery time and LOS in PACU were significantly increased in Group L ($p<0.05$).

Conclusion: Plain bupivacaine provides higher sensory block with faster onset of motor block, independent of propofol requirement as assessed by BIS monitorization.

Key words: spinal anesthesia, local anesthetics, bupivacaine, levobupivacaine, sedatives, propofol, sedation

ÖZET

Spinal Anestezide Kullanılan Bupivakain veya Levobupivakainin, BIS Kontrollü Sedasyonda Propofol Tüketimine Etkisinin Karşılaştırılması

Amaç: Bu çalışmada, spinal anestezi altında BİS kontrollü propofol sedasyonunda bupivakain ile levobupivakainin eş değer dozlarının propofol gereksinimi üzerine etkilerini karşılaştırmayı amaçladık.

Gereç ve Yöntem: Elektif alt ekstremite cerrahisi geçirecek yetmiş olguya izobarik 3 mL bupivakain (Grup B) veya levobupivakain (Grup L) ile spinal anestezi uygulandı. Spinal anestezinin beşinci dakikasında propofol infüzyonu 100 µg kg^{-1} dk^{-1}'dan başlatılıp BİS 65-75 olacak şekilde titre edildi. Başlangıç zamanı (BİS 75'e düşünceye kadar geçen süre), derlenme süresi (propofol kesildikten BİS 90 olana kadar geçen süre), bu sırada tüketilen toplam propofol miktarı ile derlenme ünitesinde kalma süresi, sedasyon düzeyi (OAA/S), duyusal ve motor blok dönme zamanları kaydedildi. İstatistiksel analizde One way ANOVA, Mann Whitney-U, Student's t and x^2 testleri kullanıldı.

Bulgular: Spinal anestezi sonrası 10. ve 15. dk.'larda BİS değerlerinin Grup B'de, Grup L'ye göre anlamlı düşük olduğu saptandı ($p<0.01$). Maksimum duyusal blok seviyesi Grup B'de Grup L'ye göre anlamlı yüksek, maksimum motor blok düzeyine ulaşma süresinin ise Grup L'de Grup B'ye göre anlamlı uzun olduğu belirlendi ($p<0.05$, $p<0.001$). Duyusal ve motor bloğun tam dönme süresi, derlenme süresi ve derlenmede kalış süresi Grup L'de Grup B'ye göre anlamlı olarak uzundu ($p<0.05$).

Sonuç: Bupivakain BIS monitorizasyonu ile takip edilen sedasyonda propofol tüketiminden bağımsız olarak, yüksek duyusal blok seviyesi, erken motor blok başlangıcı sağlamaktadır.

Anahtar kelimeler: spinal anestezi, lokal anestezikler, bupivakain, levobupivakain, sedatifler, propofol, sedasyon

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INTRODUCTION

Improvement of operating conditions and patient comfort by sedation during local and regional anesthesia has recently gained wide acceptance.[1] Previous studies have demonstrated that spinal, epidural or intramuscular administration of local anesthetics may result in an increase in sedation level associated with a decrease in the required doses of sedative-hypnotic drugs.[2] Besides, higher-level spinal anesthesia has been reported to increase sensitivity to the sedative effect of midazolam suggesting that neural block may itself has sedative properties or enhance the hypnotic effects of anesthetic drugs.[3-5]

The literature includes studies assessing the effect of the change in the local anesthetic and consequent varying levels of sensation under propofol sedation during spinal anesthesia. Yang et al. reported that varicose vein surgery patients having spinal anesthesia with hyperbaric tetracaine demonstrated lower propofol requirements than the ones for whom equal doses of isobaric tetracaine were used.[6] In another study, lower dose requirement of propofol during BIS guided sedation was demonstrated with higher dose of hyperbaric bupivacaine in comparison to lower dose administered.[7] However, there is not enough data about the effects of different local anesthetics administered intrathecally on the dose requirements of propofol during BIS guided sedation.

Levobupivacaine, introduced as the pure S (-) enantiomer of racemic bupivacaine into clinical practice, has been pointed out to be as equally effective as bupivacaine with regard its nerve blocking properties and hemodynamic effects.[8]

Therefore, we have conducted a prospective, clinical study to investigate the association between the levels of spinal anesthesia performed by two different local anesthetics with required dose of propofol during BIS guided sedation.

MATERIAL and METHODS

After obtaining patient informed consent and approval from the local hospital ethics committee, 70 patients (ASA physical status I or II; age, 18-65 years) scheduled for elective lower limb surgery under spinal anesthesia were enrolled into this prospective, randomized, double-blind, clinical trial. Those who had general contraindications for spinal anesthesia, including patient's refusal, history of allergic reaction to any of the study drugs, ongoing hypnotic therapy, and any documented preoperative systemic disease that can interfere with spinal anaesthesia were excluded from the study.

Patients did not receive any premedication. On admission to the operating room, they were prehydrated with 7-10 mL kg^{-1} h^{-1} infusion of lactated Ringer's solution and standard anesthesia monitorization was applied. BIS was monitored using a BIS sensor (A 2000 BIS Monitoring System, Aspect Medical System, The Netherlands) applied to the patient's forehead. Baseline measurements of heart rate (HR), blood pressure, peripheral oxygen saturation (SpO_2) and BIS were recorded at 5 min intervals thereafter. Spinal anesthesia was performed with the patient in the lateral decubitus position through L_{4-5} interspace using a 25 G spinal needle (Pencan®, B.Braun, Melsungen AG, Germany). Randomization was achieved using a sealed envelope for each patient from a list of black and white ones, so that 70 patients

matching the working criteria were assigned to one of the two groups, in other words to receive 3 mL intrathecal injection of either plain bupivacaine (Marcaine®, AstraZeneca İlaç AŞ, İstanbul, Turkey) (Group B) or plain levobupivacaine (Chirocaine®, AstraZeneca İlaç AŞ, İstanbul, Turkey) (Group L). Local anesthetic solution was injected over 15-20 seconds without aspiration, and the patient was placed in supine position immediately after the spinal injection.Then anesthetic level was tested by pinprick test until the sensory block remained same level at two consecutive times and motor block was evaluated using a modified Bromage scale (0=no motor block; 1=hip blocked; 2=hip and knee blocked; 3=hip, knee and ankle blocked). As soon as the level of sensory anesthesia induced by bupivacaine or levobupivacaine reached T_{12}, propofol infusion was started at 100 μg kg^{-1} min^{-1} and titrated to reach a BIS level of ≤ 75 (onset) and afterwards a BIS level of 65-75 was maintained throughout the surgery. When BIS score went out of these limits for more than 10 s, the dose of propofol was changed by 10 μg kg^{-1} min^{-1} every 20 s. Onset time and the propofol dose required for the onset were recorded. Surgery was started immediately after the induction of anesthesia. Anesthetic parameters were recorded every 5 min until the end of the study. A decrease in mean arterial pressure (MAP) and/or HR >25 % from basal values were considered as hypotension and bradycardia, respectively, and treated with ephedrine bolus 5 mg and atropine 0.5 mg respectively. A decrease in SpO_2 <95 % was treated by supplemental oxygen.

At the start of skin closure, propofol infusion was stopped to measure the time to reach a BIS level of 80 (recovery time). Recovery time and total propofol consumption were recorded. Postoperatively the patients were transferred to the postanesthesia care unit (PACU) for recovery, and sedation scores (Observer's Assessment of Alertness/Sedation (OAA/S)) as well as hemodynamic parameters were recorded every 10 min. Patients were asked to report pain, and any adverse effects (nausea, vomiting, bradycardia, hypotension, shivering). Two segment regression, duration of sensory and motor block were evaluated. Those patients meeting the standard discharge criteria (awake, oriented, stable vital signs, no active anesthetic problems) were sent to the PACU, and LOS in PACU were also recorded.

Propofol requirement in the two study groups was the primary outcome variable on which sample size estimation was based at the beginning of the study. A sample size of 29 per group was required to detect at least 50 % reduction in propofol requirement between these two groups with a power of 85 % at 5 % significance level. The reduction of 50 % was taken from both pilot study and clinical experience. Sample size estimation was performed by using NCSS and PASS 2000 software . Data analysis was performed by using SPSS 11.5 software (SPSS Inc., Chicago, IL, United States). Shapiro-Wilk test was used to test the normality of distribution for continuous variables. Data were expressed as mean±standard deviation or median (minimum-maximum), where applicable. Patient characteristics and times were analyzed for normality and the two groups were compared using Student's t-test. Non-parametric data were analyzed using Mann-Whitney U-test. Categorical data were analyzed using chi-square test. Repeated hemodynamic parameters were analyzed by Repeated Measures of

Variance Analysis with Bonferroni Adjustment for multiple comparisons; A p value less than 0.05 was considered statistically significant. The Bonferroni Correction was applied for all possible multiple comparisons controlling Type I error.

RESULTS

Five of the 70 patients originally included in the study were subsequently excluded, because of insufficient block (2 in Group L) or need for ephedrine treatment (3 in Group B). As shown in Table 1, physical and surgical characteristics were similar in both groups. Maximum sensory block level was higher, while time to reach maximum motor block level was shorter in Group B ($p<0.05$, $p<0.001$ respectively) (Table 2). Median anesthetic level at the end of 30 min was T_{12} (L_1-T_4) in Group L and T_8 (L_1-T_2) in Group B. Bromage score was 3 in all patients in Group B and in 25 patients in Group L. There was no significant difference in the propofol doses required to reach BIS=75 ($p>0.05$). BIS was significantly decreased in Group B compared to Group L at 10 and 15 min after spinal anesthesia ($p<0.01$). Onset time for sedation, total propofol consumption, se-

Table I. The physical and surgical characteristics of the groups.

	Group L (n=33)	Group B (n=32)	p
Age (yr)	50.6±12.0	45.0±13.2	0.077*
Sex(M/F)	12 (36.4) / 21 (63.6)	7 (21.9) / 25 (78.1)	0.199**
Weight (kg)	74.0±9.6	73.3±10.8	0.777*
Height (cm)	162.1±8.6	163.8±8.1	0.409*
ASA physical status I/II	23 (69.7) / 10 (30.3)	28 (87.5) / 4 (12.5)	0.081**
Duration of surgery (min)	75 (60-105)	80 (65-115)	0.107***
Tourniquet application (yes/no)	17 (51.5) / 16 (48.5)	18 (56.3) / 14 (43.7)	0.702**
Duration of tourniquet (min)	80 (64-95)	74 (65-105)	0.708***

*Values are mean ± SD or median (min-max) for continuous data and n (%) for nominal data. * Student's t test, ** Chi-square test, *** Mann Whitney U test.*

Table II. Characteristics of sensory and motor block in the groups.

	Group L (n=33)	Group B (n=32)	p
Maximum level of sensory block at 30 min	T_{12} (L_1 - T_4)	T_8 (L_1 - T_2)	0,033*
Time to onset of maximum motor block (min)	20 (5-30)	12.5 (5-30)	<0.001*
Time for 2 segment regression (min)	105 (62-205)	90 (65-163)	0.005*
Time to complete sensory block resolution (min)	320 (210-400)	261 (135-365)	<0.001*
Time to complete motor block resolution (min)	272 (160-360)	235 (120-315)	<0.001*

*Values are median (min-max), * Mann Whitney U test*

Table III. Total dose of propofol consumed, time to first pain medication, onset of sedation and recovery times, sedation scores and length of stay in PACU in the groups.

	Group L (n=33)	Group B (n=32)	p
Onset time for sedation (min)	24 (17–30)	22 (20–30)	0.121*
Propofol consumption (mg)	530 (300–850)	520 (360–880)	0.618*
Time to first pain medication (min)	240 (140–385)	231 (140–330)	0.927*
Sedation score in PACU	4.98±0.04	4.97±0.06	0.431**
Recovery time (min)	6 (4-13)	5 (3-10)	<0.001*
Length of stay in PACU (min)	180 (90-260)	117.5 (60-200)	<0.001*

*Values are mean ± SD or median (min-max) P<0.05: statistically significant, *Mann Whitney U test, **Student's t test. PACU= post anesthesia care unit*

dation scores in PACU, time to the requirement of the first pain medication did not differ between the groups (p>0.05) (Table 3). Two segment regression time, offset time of sensory and motor block, recovery time and LOS in PACU were significantly increased in Group L (p<0.05) (Table 2 and Table 3). There were no significant differences between groups in terms of hemodynamic parameters and adverse events.

DISCUSSION

This study demonstrated that the intrathecal administration of plain bupivacaine or levobupivacaine in patients undergoing lower extremity surgery provided no significant differences with regard to consumption of propofol as a sedative agent.

Local anesthetics administered via different routes have been shown to cause a decrease in the dose requirements of the anesthetic and hypnotic drugs in order to maintain a defined level of sedation. [5] Furthermore, neural blocks performed by local anesthetics cause somnolence even in the absence of systemic sedatives. [9] Eappen et al demonstrated that in rats subarachnoid bupivacaine reduced anesthetic requirements for thiopental.[10] In humans, Pollock et al reported that spinal anesthesia led to a significant decrease in BIS levels.[3]

Certainly, the most profound physiological effect of spinal anesthesia is to prevent or decrease afferent input from the anesthetized body region to the reticular activating system. This most speculated mechanism, called deafferentation, renders brain more susceptible to actions of sedative drugs, and high spinal anesthesia may be required to exert a significant effect on the brain.[7] Deprivation of the rostral portions of the neuraxis, which are normally required to keep brain in the awake state, has been implicated as a major cause of sleep.[11] Gentili et al reported that, the block extending especially to the upper thoracic segments, made 27 % of the patients unresponsive to verbal stimulation after 1 mg midazolam administration.[12]

In this study, median anesthetic levels established at 30 min after intrathecal injection were T_{12} (L_1-T_4) and T_8 (L_1-T_2) in the levobupivacaine and bupivacaine groups, respectively. This significant difference

between the block heights did not influence the propofol requirements for sedation in our patients. Moreover, this study did not demonstrate a correlation between block level and the propofol requirement, because our patients did not have such high spinal anesthesia levels.

There are studies comparing the efficacy of intrathecal levobupivacaine and bupivacaine in different patient groups. Similar sensory and motor block characteristics have been reported in some of these publications.[13] However, Van de Velde et al. found that levobupivacaine was less potent than bupivacaine at the ED_{50} and ED_{95} points of the dose response curves. [14] Based on our findings, we suggest that levobupivacaine may not be quite as potent as bupivacaine.

High spinal block may impair awareness because of hemodynamic changes or hypoxia due to extended motor blockade of the abdominal and intercostal muscles as well.[12] However, none of our patients complained of hypotensive episodes or hypoxia due to probably fine titration of propofol infusion rate according to BIS and oxygen supplementation. Moreover, hypotension was treated strictly with fluids and ephedrine. Significant increase in BIS, 7-10 minutes after ephedrine administration could not be excluded as a factor participating in the change of BIS in these patients.[15] Therefore, we excluded three patients from the bupivacaine group as a result of hypotension requiring ephedrine treatment.

Another explanation of sedation seen during spinal anesthesia is the possible alteration in the volume of distribution of the sedative drug caused by the cardiovascular effects induced by the block.[16] We did not measure the blood concentration of propofol, however, propofol was administered via an infusion, and it can be assumed that the predicted propofol concentrations would not differ relevantly, since we used an objective monitor of sedation (BIS) in patients who are homogeneous with regard to age, gender, weight and height.

Decrease in sedative requirements in patients undergoing subarachnoid block might reflect a direct action of the local anesthetic on the brain due to drug's rostral spread via cerebrospinal fluid.[7] However, this remains speculative, particularly in the -low- block groups. In a study by Pollock et al, delayed rostral spread of local anesthetics was suggested to be responsible for extreme variations from baseline BIS values in non sedated patients.[3] In other studies, 15-20 min was not found long enough for local anesthetics to spread rostrally in concentrations sufficient to influence the electrical activity of higher neuronal centers.[7] We started propofol infusion immediately, i.e. 5 min after successful intrathecal injection, and detected a significant decrease in BIS in Group B compared to Group L at 10 and 15 min after induction of spinal anesthesia. Although this finding may be attributable to early sedation caused by decreasing afferent spinal input which was more prominent in the bupivacaine group with a non significant but higher median spinal level, it is difficult to compare these results with those of the other studies because of the differences in timing of propofol infusion. Besides, one of the limitations of our study was, difficulty in assessing the level of block in sedated patients.

Consequently, we quantified sedation with neuraxial anesthesia by titrating dose

of propofol to maintain a target BIS score 65-75. We assessed definite height of the block at every 5 min for the first 30 min, before the surgery was begun. There are observations suggesting avoidance of repeated checks of block level which might influence the stability of the sedation level. However, in our study, onset time of sedation was 23.9±3.0 and 22.8±2.8 min in Group L and Group B, respectively thus, we did not interrupt the depth of sedation in our patients.

We continued to measure the sedation level of our patients in PACU for the first hour by using OAA/S. These values were not significantly different between the groups. This finding obviously suggests a complex relationship requiring further studies with higher doses, but one can assume that the level of spinal block may play an important role in sedation as indicated by shorter duration of sensory block associated with shorter recovery time in the bupivacaine group.

In conclusion, regarding the findings of our study we cannot conclude that higher sensory block is associated with a propofol sparing effect. Although plain bupivacaine might be particularly advantageous with regard to its block characteristics; further studies would be necessary to answer this question.

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