



International Journal of Pharmacology

ISSN 1811-7775

science
alert

ansinet
Asian Network for Scientific Information

Comparison of Five Percent Prilocaine-lidocaine Cream and Intravenous Fentanyl in Reducing the Spinal Puncture Pain

Erdem Nail Duman and Mesut Karaca

Department of Anesthesiology, Faculty of Medicine, Karadeniz Technical University, Turkey

Abstract: One of the major disadvantages of the spinal anesthesia is that the patients feel anxiety and pain during the spinal needle puncture. It is aimed to compare the analgesic effects of 5% prilocaine-lidocaine cream with $1 \mu\text{g kg}^{-1}$ intravenous fentanyl applied before spinal puncture. Seventy-five male patients of ASA I-II, with the age range 20-65 were included and randomly divided into three groups in the study. Forty-five minutes before the spinal needle puncture 2.5 g 5% prilocaine-lidocaine cream was applied on the intervention area of the Group A patients. Ten minutes before the spinal puncture $1 \mu\text{g kg}^{-1}$ fentanyl intravenous bolus was applied to the Group B patients; but no analgesics or local anesthetics were applied to the Group C patients. The anxiety level of the patients was measured with APAIS-A anxiety score and the sedation level was measured with Ramsay Sedation Scale. The pain felt by the insertion of the spinal needle was assessed with 0-4 range Verbal Rating Scale. Additionally, patient's satisfaction, quality of performance and irritation movement were evaluated. Verbal Rating Scale scores and irritation movements were significantly lower in Group A. Patient's satisfaction was significantly higher in Group A. Quality of performance was significantly higher in Group A than the rest of the groups and in Group B than Group C. As a result, it is concluded that by considering the parameters of analgesic activity, patient's satisfaction, irritation movements and quality of performance; 2.5 g, 5% prilocaine-lidocaine cream is superior to intravenous $1 \mu\text{g kg}^{-1}$ fentanyl in reducing the spinal puncture pain.

Key words: Spinal anesthesia, 5% prilocaine-lidocaine cream, fentanyl, acute pain, patient's satisfaction

INTRODUCTION

Although spinal anesthesia is a fast and reliable method for inferior body interventions, some of the patients are still hesitate because of vaccinophobia (Gajraj *et al.*, 1995). Relieving the puncture pain not only increase the patient's satisfaction and comfort, but also let anesthetist apply spinal puncture fast and easily. There are various methods to alleviate superficial pain during spinal punctures. The methods like 5% prilocaine-lidocaine cream, local anesthetic infiltration and 5% prilocaine-lidocaine cream application before infiltration have been suggested to ease the skin and sub-skin level spinal puncture pain, however some clinics directly apply puncture without any pre-application (Kelsaka *et al.*, 2006; Ozyurt *et al.*, 2004; Elson and Paech, 1995).

It has reported that the injection of local anesthetics before regional anesthesia may cause pain during puncture, may not provide proper analgesia and may cause disappearance of anatomical landmarks (Kobayashi *et al.*, 1999). Therefore, attention towards topical anesthesia has been raised again.

Five percent prilocaine-lidocaine cream is an effective topical anesthetic mixture used for relieving the pain caused by repetitive insertions like venous and intra-arterial cannula insertions for pediatric and adult patients, excision of cutaneous lesions and minor surgical procedures, epidural injections and lumbar function (Gajraj *et al.*, 1994).

Intravenous opioids are frequently preferred in analgesia for interventions aiming diagnose and treatment. Intravenous fentanyl is the most frequently preferred opioid in this field because it has powerful analgesic and sedative features; it can be applied systemically and easily; it has short-lasting influence; it has antagonist and it has few side effects when it is applied in proper doses (Bailey *et al.*, 2000).

Although 5% prilocaine-lidocaine cream and fentanyl have been used in clinical practice for a long time, literature review has not hit any studies examining their analgesic efficiency in reducing spinal puncture pain. The aim of this study was to compare analgesic effects of 2.5 g topically applied 5% lidocaine-prilocaine cream with $1 \mu\text{g kg}^{-1}$ intravenous fentanyl in the reduction of the

spinal puncture pain of the cases planned to be operated under spinal anesthesia.

MATERIALS AND METHODS

After obtaining ethics committee approval (2009/101) and written informed consents of each patient, 75 male patients with the age range of 20 to 65, from ASA (American Society of Anesthesiologists) I-II risk group, who were planned to have elective urological surgery under spinal anesthesia, were chosen as the sample of this prospective study. The study was completed at the end of 2010.

The patients with no contraindications to spinal anesthesia, with no opioid and local anesthetic allergies and with no lumbar anomaly were included in this study. By drawing envelopes method, the patients in the sample were randomly divided into 3 equal groups of 25 patients as; Group A (5% prilocaine-lidocaine cream group), Group B (Fentanyl group) and Group C (Control group).

All the patients included in the study were informed about the spinal anesthesia and then about how to rate the pain they would feel during the insertion of the spinal needle into skin using Verbal Rating Score (VRS) (0: No pain, 1: Mild pain, 2: Moderate pain, 3: Severe pain, 4: Horrible pain).

Since increasing anxiety and fear may cause increase in pain, all patients were given intramuscular 0.07 mg kg⁻¹ midazolam as premedication 45 min before the surgery. Anxiety and sedation levels of all the patients were measured and recorded as pain scores may be affected from these parameters. The anxiety levels were determined 5 min before the puncture with Amsterdam Preoperative Anxiety and Information Scale-Anxiety (APAIS-A) (1: I am worried about the anesthetic, 2: The anesthetic is on my mind continually, 3: I am worried about the procedure, 4: The procedure is on my mind continually). Each question was scored between 1 (not at all) and 5 (extremely) (Moerman *et al.*, 1996). On the other hand, the sedation levels were measured with Ramsay Sedation Scale (RSS) four times as; 45 and 15 min before the puncture, just before and after the puncture. (1: Patient is anxious and agitated or restless, or both, 2: Patient is cooperative, oriented and tranquil, 3: Patient responds to commands only, 4: Patient exhibits brisk response to light glabellar tap or loud auditory stimulus, 5: Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus, 6: Patient exhibits no response) (Ramsay *et al.*, 1974).

To the cases in Group A, 45 min before the spinal puncture, 2.5 g; 5% prilocaine-lidocaine cream (AstraZeneca, Istanbul, Turkey) was applied onto 3×3 cm area where spinal needle puncture would be performed

(L4-L5 intervertebral space) and the area was covered with a non-permeable tape. Prior to the puncture the tape was removed and the cream was wiped away. It was evaluated and recorded with 2-point-scale (0: No side-effect, 1: Side effect(s) exist(s)) whether there were any side effects (erythema, paleness and edema) on the area where 5% prilocaine-lidocaine cream was applied.

To the cases in Group B, 10 min before the puncture, intravenous bolus 1 µg kg⁻¹ fentanyl (Johnson and Johnson, Istanbul, Turkey) was applied. The probable side effects of fentanyl (apnea, hypotension, bradycardia, nausea-vomiting, chest rigidity) were evaluated and recorded with 2-point-scale (0: No side-effect (s), 1: Side effect (s) exist (s)).

To the cases in Group C, no analgesics or local anesthetics were applied.

To all patients in the study group, 20 Gauge intravenous cannula was inserted in forearm veins and 5 mL kg h⁻¹, 0.9% NaCl infusion was started when they were in waiting room. Then the patients were taken into operation room and non-invasive Mean Arterial Pressure (MAP), ECG with D II derivation, Heart Rate (HR) and peripheral oxygen saturation (SpO₂) values were monitored. In order to detect probable hemodynamic changes induced by anesthesia or spinal puncture pain MAP, HR and SpO₂ values were recorded immediately before and immediately after the spinal puncture.

Afterwards, the patients were placed in right lateral decubitus position. They were reminded that they were expected to evaluate the pain caused by spinal needle puncture with respect to 0-4 range VRS. The skin area aligning L4-L5 intervertebral space was cleaned and antiseptized by povidone iodine with standard procedure. Then spinal anesthesia application was performed with 22 Gauge, Quincke type spinal needle.

Immediately after the puncture, the patients evaluated the pain felt during the insertion of the spinal needle into skin with respect to VRS and the patient satisfaction with 2 point scale (0: Bad, 1: Good). The results were recorded. On the other hand, the anesthetist evaluated and recorded the quality of the performance with 4 level scale (0: Bad, 1: Medium, 2: Good, 3: Excellent) and the irritation movement during the insertion of the needle with 2 level scale (0: No irritation, 1: Irritation exists).

Statistical analysis: The obtained data were entered in SPSS 13 program. First the normality of the data was tested with Kolmogorov-Smirnov test (Gaddis and Gaddis, 1990). The data exhibiting normal distribution were compared with ANOVA (with Post Hoc Bonferroni) while the data with non-normal distribution were tested with Kruskal-Wallis (Mann-Whitney with Post Hoc Bonferroni correction) test. For the comparison of the

changes in measured data by time within each group; Variance Analysis (with Post Hoc Paired t-test) was applied for repetitive measurement data with normal distribution and Freidman (with Post Hoc Wilcoxon Signed Ranks) test was used for data with non-normal distribution (Gaddis and Gaddis, 1990). Chi-Square test was used to compare qualitative data. The obtained data were presented with arithmetic Average±Standard deviation (sd), number (n) and percent (%) of the subjects in the tables. The statistical significance value was accepted as p<0.05 and for multiple comparisons the significance reference value was accepted as p<0.05/number of comparisons.

RESULTS

The mean ages of the groups were 46.72±12.84 years for Group A; 48.36±13.21 years for Group B and 47.52±13.49 years for Group C. There was not any significant difference among the groups in terms of age (p>0.05) (Table 1). When the ASA classifications were compared, there was no significant difference between the groups (p>0.05) (Table 1). When within group comparisons were considered, a slight but not statistically significant decrease was observed between the pre and post MAP values in Group C; pre MAP was 112.92±19.98 mmHg, post MAP was 103.32±26.90 mmHg (p>0.05) (Table 2). There were no significant differences between the hemodynamic values (MAP, HR and SpO₂) measured before and after the spinal puncture in all groups (Table 2).

When VRS values of the groups compared, there were statistically significant differences among the groups (p<0.05). The average mean VRS score of Group A was smaller than both Group B (p = 0.005) and Group C

(p = 0.005). There was no statistically significant difference between VRS scores of the Group B and Group C (p>0.05) (Fig. 1).

The mean patient satisfaction score in Group A was higher than both Group B (0.022) and Group C (p = 0.002).

There was no statistically significant difference between patient satisfaction scores of the Group B and Group C (p = 0.538) (Fig. 2).

When Group A, Group B and Group C were compared with respect to irritation movement; there were statistically significant differences among them (p<0.05). No irritation movement was seen in Group A. Similar to VRS and satisfaction scores, there was no significant difference between irritation movement scores of the Group B and Group C (p = 0.148) (Fig. 3).

The quality of the performance in Group A was evaluated as *Excellent* for 16 patients (64%), Good for 8 patients (32%) and Bad-Medium for only 1 patient (4%) by the anesthetist performing the puncture. However, the evaluation of the anesthetists yielded different distributions in Group B (Excellent for 2 patients (8%), Good for 15 patients (60%) and Bad-Medium for 8

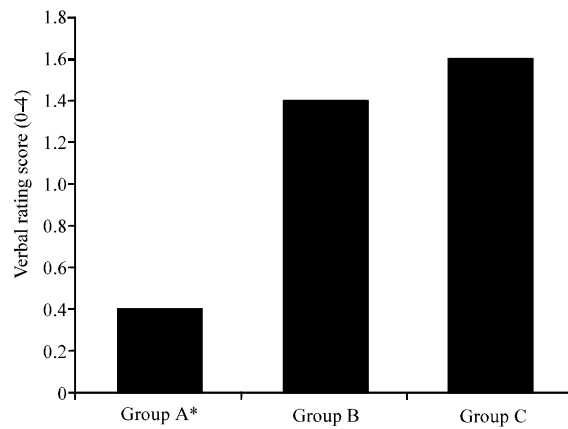


Fig. 1: Comparison of the VRS values of the groups *There are statistically significant changes between Group A and the other two groups (p<0.05)

Table 1: Demographic data of the patients

Parameter	Group A (n = 25)	Group B (n = 25)	Group C (n = 25)	p-value
Age (year)	46.72±12.84	48.36±13.21	47.52±13.49	0.908
ASA				0.846
I	16 (64%)	15 (60%)	14 (56%)	
II	9 (36%)	10 (40%)	11 (44%)	

p<0.05 significance

Table 2: Comparison of the MAP, HR and SpO₂ values of the groups

Measurement time	Group A		Group B		Group C	
	Mean±SD	p-value	Mean±SD	p-value	Mean±SD	p-value
MAP	Pre	103.40±15.00	100.00±13.72	0.474	112.92±19.98	0.103
	Post	104.92±12.07	99.6±12.32		103.32±26.90	
HR	Pre	73.16±14.69	81.12±18.70	0.884	81.76±15.50	0.156
	Post	73.28±12.47	81.36±20.01		79.80±14.56	
SpO ₂	Pre	99.04±0.978	97.84±1.46	0.158	98.68±1.03	0.294
	Post	98.88±1.054	98.12±1.36		98.84±1.06	

p<0.05 significance, MAP: Mean arterial pressure, HR: Heart rate, SpO₂ :Peripheral oxygen saturation, SD: Standard deviation

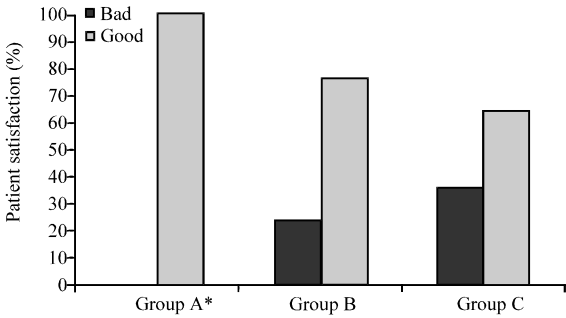


Fig. 2: Comparison of the patient satisfaction data of the groups. *There are statistically significant changes between Group A and the other two groups ($p < 0.05$)

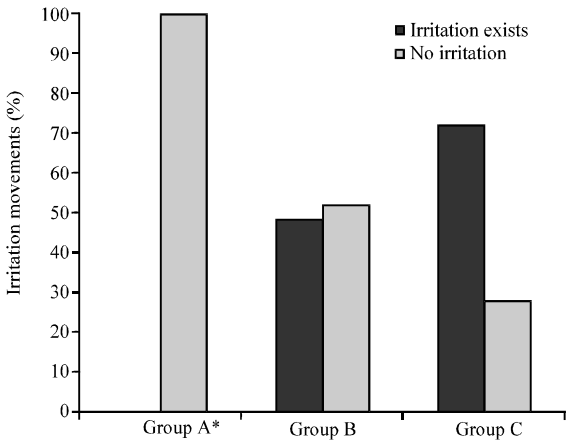


Fig. 3: Comparison of the irritation movements data of the groups. *There are statistically significant changes between Group A and the other two groups ($p < 0.05$)

patients (32%) and Group C (Good for 8 patients (32%) and *Bad-Medium* for 17 patients (68%)) (Fig. 4). Quality of performance was significantly higher in Group A than the rest of the groups and in Group B than Group C.

In Group No. A none of the patients showed any local skin reactions (erythema, paleness, and edema) on the area where 5% prilocaine-lidocaine cream was applied.

Similarly none of the patients in Group B showed fentanyl-bound side effects (apnea, hypotension, bradycardia, nausea-vomiting, chest rigidity). There were no statistically significant differences among the groups for APAIS-A anxiety scores ($p > 0.05$).

When the groups were compared in terms of RSS scores, there were no statistically significant differences. The mean sedation score of all three groups were 2.

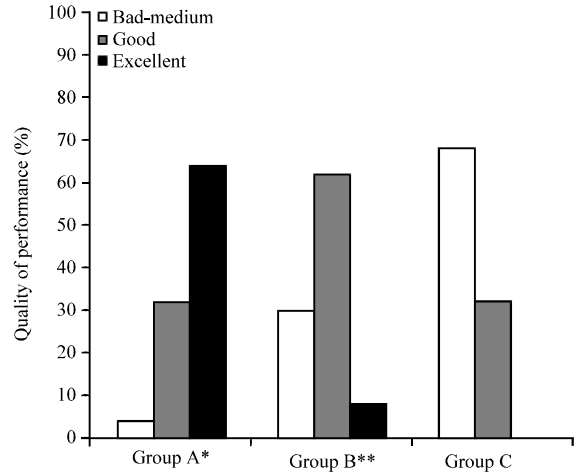


Fig. 4: Comparison of the quality of performance data of the groups. *There are statistically significant changes in all parameters between Group A and the other two groups ($p < 0.05$). **There are statistically significant changes in all parameters between Group B and Group C ($p < 0.05$)

DISCUSSION

The effects of 2.5 g, 5% prilocaine-lidocaine cream applied on puncture area and intravenous fentanyl in reducing the pain caused by spinal puncture were compared in this study in terms of various parameters. Five percent prilocaine-lidocaine cream application is found to be superior when compared to intravenous fentanyl application.

Needles used for regional anesthesia cause various levels of pain and anxiety on patients. Such pain and anxiety of patients lead abnormal motor and psychological responses which hinder the application of the puncture and may cause patients refuse regional anesthesia method (Gajraj *et al.*, 1995). Therefore, in the literature various methods are used to reduce this pain during spinal punctures.

In this study; 45 min before the puncture to provide amnesia, control anxiety and movements intramuscular 0.07 mg kg⁻¹ midazolam was applied. Applying sedation before painful interventions provides certain advantages like; relieving the fear and anxiety, minimizing the unintended motor and psychological responses, increasing the pain threshold of patients, causing amnesia, reducing discomfort due to body posture and minimizing the hemodynamic changes caused by autonomic activation (Habib *et al.*, 2004). Midazolam is a popular sedation agent for day case surgery because it

has fast and short influence; in four hours following the application the mental functions are fully retained and it sustains cardiovascular stability (Habib *et al.*, 2004).

It is preferred to use APAIS-A test to measure the anxiety because APAIS-A is a simple test and it takes little time to apply. It was determined that 5 min before the puncture; APAIS-A anxiety scores were low and in acceptable range for all three groups. RSS was used to determine the sedation level of the patients. It was observed that all of the pre-application sedation scores of the patients were at level 2. It was thought that 0.07 mg kg⁻¹ midazolam intramuscularly applied 45 min before the spinal anesthesia puncture provided proper level of sedation as it was recommended in the study done by Habib *et al.* (2004).

Gursoy *et al.* (2007) reported higher pain scores on female patients than male patients and remarked that men and women differently response to painful stimuli. Concerning this piece of finding, only male patients were included in this study.

While there are various methods to ease the skin and sub-skin originated superficial pain during spinal punctures, some clinics directly apply puncture without any local application or analgesia for several reasons like; the duration of the puncture is rather short, the practitioner of the puncture does not take the pain seriously or concerns with the toxicity of the applied agents (Kelsaka *et al.*, 2006). Methods like application of 5% prilocaine-lidocaine cream (used as one of the methods in this study), local anesthetic infiltration or 5% prilocaine-lidocaine cream before local anesthetics infiltration have been recommended to reduce the skin and sub-skin level pain caused by spinal needle puncture.

It is a known fact that infiltration of local anesthetics also gives pain (Kobayashi *et al.*, 1999). In addition, infiltration of local anesthetics onto spinal puncture area may make difficult spinal anesthesia puncture by disappearing anatomic landmark points which are normally palpable (Ozyurt *et al.*, 2004). Consequently, infiltration of local anesthetics may cause patients experience anxiety, pain and other similar problems caused by spinal needle before the puncture. This makes the process only an unworthy waste of time and money. So this technique was not used in this study as a comparison method to reduce the pain induced by spinal puncture.

The mentioned disadvantages of local analgesic infiltration have caused topical anesthesia has become one of the most frequently preferred methods. Because of its low side-effect profile and widely accepted efficiency, 5% prilocaine-lidocaine cream has been used for analgesic purposes before intervention procedures with pediatric and adult patients such as; establishing

vascular access, spinal and epidural anesthesia, dermal punctures, arterial catheterization and some peripheral nerve blocks (Gajraj *et al.*, 1994; Buckley and Benfield, 1993). In this study, this method has also provided advantages and efficiency as mentioned before both by Gajraj *et al.* (1994) and Buckley and Benfield (1993). On the other hand, the main disadvantages of 5% prilocaine-lidocaine cream can be listed as; (1) It must be smeared well before the puncture so it cannot be used in emergency cases, (2) In elective cases it is hard to save time for the operation rooms where there are too much patients having the operations and (3) It is expensive.

Fentanyl, a potent opioid agent, is frequently preferred during anesthesia practices in or out of operating room, all diagnostic or therapeutic painful interventions in emergency units. Since fentanyl has antagonists and it causes side effects very rarely when overdose is not given and it is given with dose titration, it can be used in painful interventions of suitable patients with performing necessary monitoring (Bailey *et al.*, 2000). For interventional procedures, 0.5 to 1.5 mcg kg⁻¹ dose of intravenous fentanyl is recommended by DRUGDEX in MICROMEDEX(R), Healthcare Series Integrated Index (DRUGDEX® System, 2011); so 1 mcg kg⁻¹ intravenous fentanyl is preferred in this study.

Although, there are lots of studies in the literature evaluating the efficiency of 5% prilocaine-lidocaine cream and infiltrative local anesthetics in alleviating spinal needle puncture pain, there are not any studies conducted with fentanyl or any other opioid agent. Fentanyl, which is extremely safe, powerful and which has short action time, can be an alternative analgesic agent to prevent spinal needle-bound pain when it is applied in proper doses. Therefore, the application of 2.5 mg 5% prilocaine-lidocaine cream as topical anesthetic was compared with the application of intravenous 1 µg kg⁻¹ fentanyl before spinal puncture in terms of pain score, patient's satisfaction, quality of performance and irritation movements.

There are various studies comparing the effects of 5% prilocaine-lidocaine cream with infiltrative local anesthetics in preventing spinal needle puncture pain. Koscielniak-Nielsen *et al.* (1998) reported lower pain scores with 5% prilocaine-lidocaine cream. In that study the effects of 5% prilocaine-lidocaine cream, 2 mL lidocaine infiltration with 2% adrenaline and placebo were compared in preventing superficial pain caused by spinal needle puncture. Coherently, Zencirci *et al.* (2006) noted that 5% prilocaine-lidocaine cream applied 30 min before the spinal anesthesia is a noninvasive method and can be an alternative method of lidocaine infiltration for preventing spinal needle puncture pain. In the study

conducted with female subjects with ages ranging from 17 to 28; Sharma *et al.* (1996) compared the activity of 3 mL 1% lidocaine infiltration and 5% prilocaine-lidocaine cream and determined that pain scores were lower in the group in which 5% prilocaine-lidocaine cream applied 30 min before the puncture. Kelsaka *et al.* (2006) reported that lidocaine infiltration and 5% prilocaine-lidocaine cream application provide equal level of analgesia in alleviating superficial pain caused by spinal puncture however infiltration of lidocaine with sodium bicarbonate addition is the most efficient method.

When this study was evaluated in terms of pain scores; there were significant differences among the VRS scores of the three groups. The mean pain score of Group A was significantly lower than Group B and Group C. However, there were no significant differences between VRS pain scores of Group B and Group C. Backed with the results, it is concluded that topically applied 2.5 g 5% prilocaine-lidocaine cream provides sufficient analgesia to alleviate spinal needle pain as also reported by various studies above.

Topically applied 5% prilocaine-lidocaine cream 30 min before the intervention (Zencirci *et al.*, 2006) and 15 and 45 min before the intervention (Ozyurt *et al.*, 2004) provide sufficient analgesic effect in alleviating of the spinal needle puncture pain. Along with these studies, application of 5% prilocaine-lidocaine cream 45 min before the intervention was chosen and sufficient analgesic activity was obtained. It is thought that the dermal analgesia which is required for insertion of the spinal needle can be obtained by 5% prilocaine-lidocaine cream application 45 min before the intervention.

In the literature, no studies evaluating the efficiency of fentanyl in preventing the pain caused by regional anesthesia was found. Within the monitoring period of this study, it was observed that the pain scores of the Group B were statistically significantly higher than Group A but non-significantly lower than the Group C. Thus, it is concluded that intravenous fentanyl in 1 $\mu\text{g kg}^{-1}$ dose was insufficient in alleviating the spinal needle puncture pain.

Among the studies reviewed from the literature, only the study by Koscielniak-Nielsen *et al.* (1998) was inquired about patient satisfaction. In this study, the effects of 5% prilocaine-lidocaine cream, 2 mL lidocaine infiltration with 2% adrenaline and placebo on preventing the superficial pain caused by spinal anesthesia application were compared. Koscielniak-Nielsen *et al.* (1998) detected that satisfaction scores of 5% prilocaine-lidocaine cream group was higher than the rest and they noted that this application reduces spinal puncture anxiety of the patients. In this study; mean patient satisfaction score in Group A was significantly higher

than both Group B and Group C, similar to the results of Koscielniak-Nielsen *et al.* (1998). However, there was no statistically significant difference between Group B and Groups C. Concerning the inverse proportion between patient satisfaction results and pain scores, it was thought that there is correlation between analgesic activity and patient's satisfaction. In other words, 5% prilocaine-lidocaine cream increases patient's satisfaction by providing sufficient analgesic activity.

In the literature review, among the studies towards alleviating the spinal puncture pain no researches evaluating quality of performance was found. According to the results of this study the quality of performance scores in Group A was higher than the scores of Group B and Group C. In addition, it was higher in Group B than the Group C.

It is possible to observe certain local skin reactions on the related area such as; edema, paleness, erythema and itching following to the application of 5% prilocaine-lidocaine cream. Ozyurt *et al.* (2004) reported that no local skin reaction was observed on any of the patients who were applied 5% prilocaine-lidocaine cream before spinal anesthesia. Parallel to that study, no skin reaction was observed on the patients in Group A in our study. Additionally, no side effects were observed in Group B, either.

It is possible to experience serious increases in MAP and HR caused by spinal puncture pain or anxiety. In literature; among the studies towards alleviating the spinal puncture pain only Zencirci *et al.* (2006) evaluated hemodynamic parameters like this study. They have reported that they observed no significant changes between pre intervention and post intervention values of MAP, HR and SPO2 in 5% prilocaine-lidocaine cream group. In this study, also no significant changes between pre application and post application values of MAP, HR and SPO2 in the all three groups were observed.

When it comes to irritation movements, literature review hit no data about it. No irritation movements were observed in Group A; while 48% of the patients in Group B and 72% of the patients in Group C exhibited irritation movements. It was determined that 5% prilocaine-lidocaine cream is fully effective in terms of preventing irritation movements.

CONCLUSION

In reducing the spinal puncture pain; application of 2.5 g, 5% prilocaine-lidocaine cream 45 min before the intervention is found to be better than 1 $\mu\text{g kg}^{-1}$ intravenous fentanyl. Especially indicating sufficient

analgesic activity; better patient's satisfaction was provided by 5% prilocaine-lidocaine cream. As no irritation movement was observed in 5% prilocaine-lidocaine cream group, the quality of performance was also better. As a conclusion, 5% prilocaine-lidocaine cream is found to be superior to 1 µg kg⁻¹ intravenous fentanyl in reducing spinal puncture pain and increasing the quality of intervention and patient's satisfaction.

REFERENCES

- Bailey, P.L., T.D. Egan and T.H. Stanley, 2000. Intravenous Opioid Anesthetics. In: Anesthesia, Miller, R.D. (Ed.). Churchill Livingstone, Philadelphia, PA., USA., pp: 273-376.
- Buckley, M.M. and P. Benfield, 1993. Eutectic lidocaine/prilocaine cream. A review of the topical anaesthetic analgesic efficacy of a Eutectic Mixture of Local Anaesthetics (EMLA). *Drugs*, 46: 126-151.
- DRUGDEX® System, 2011. Micromedex® healthcare series integrated index vol. 149. Klasco, R.K. (Ed.). Thomson Healthcare, Greenwood Village, Colorado.
- Elson, J.A. and M.J. Paech, 1995. EMLA cream prior to insertion of elective of epidurals. *Anaesth. Intensive Care*, 23: 339-341.
- Gaddis, G.M. and M.L. Gaddis, 1990. Introduction to biostatistics: Part 5, Statistical inference techniques for hypothesis testing with nonparametric data. *Ann. Emerg. Med.*, 19: 1054-1059.
- Gajraj, N.M., J.H. Pennant and M.F. Watcha, 1994. Eutectic Mixture of Local Anesthetics (EMLA) cream. *Anesth. Analg.*, 78: 574-583.
- Gajraj, N.M., S.K. Sharma, A.J. Souter, Y. Pole and J.E. Sidawi, 1995. A survey of obstetric patients who refuse regional anaesthesia. *Anesthesia*, 50: 740-741.
- Gursoy, A., D.T. Ertugrul, M. Sahin, N.B. Tutuncu, A.N. Demirel and N.G. Demirag, 2007. The analgesic efficacy of lidocaine/prilocaine (EMLA) cream during fine-needle aspiration biopsy of thyroid nodules. *Clin. Endocrinol.*, 66: 691-694.
- Habib, N.E., N.M. Mandour and H.G. Balmer, 2004. Effects of midazolam on anxiety level and pain perception in cataract surgery with topical anesthesia. *J. Cataract Refractive Surg.*, 30: 437-443.
- Kelsaka, E., F. Guldugus, B. Sarihasan and S. Tepe, 2006. Comparison of EMLA and lidocaine with or without sodium bicarbonate in prevention of spinal needle insertion pain. *Anestezi Dergisi*, 14: 76-79.
- Kobayashi, Y., Y. Kamada, T. Ichimiya and A. Namiki, 1999. Is local anesthesia necessary for spinal needle insertion? *Masui*, 48: 1033-1036.
- Koscielniak-Nielsen, Z., L. Hesselbjerg, J. Brushoj, M.B. Jensen and H.S. Pedersen, 1998. EMLA patch for spinal puncture: A comparison of EMLA patch with lignocaine infiltration and placebo patch. *Anaesthesia*, 53: 1218-1222.
- Moerman, N., F.S. van Dam, M.J. Muller and H. Oosting, 1996. The Amsterdam Preoperative Anxiety and Information Scale (APAIS). *Anesth. Analg.*, 82: 445-451.
- Ozyurt, G., E. Basagan-Mogol and B. Kerimoglu, 2004. EMLA cream application prior to spinal anaesthesia. *SSK Goztepe Tip Dergisi*, 19: 167-169.
- Ramsay, M.A., T.M. Savege, B.R. Simpson and R. Goodwin, 1974. Controlled sedation with alphaxalone-alphadolone. *Br. Med. J.*, 22: 656-659.
- Sharma, S.K., N.M. Gajraj, J.E. Sidawi and K. Lowe, 1996. EMLA cream effectively reduces the pain of spinal needle insertion. *Reg. Anesth.*, 21: 561-564.
- Zencirci, B., H. Oksuz and M. Ezberci, 2006. The efficacy of EMLA cream in alleviating the pain of spinal needle as compared with lidocaine infiltration and placebo. *Turkiye Klinikleri J. Anesthesiol. Reanimation*, 4: 106-109.