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Effects of adjuvant Dexketoprofen in regional intravenous anesthesia

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Abstract: Background and objectives: In our study, it is aimed to investigate the effectiveness of the use of local anesthetics by the addition of adjuvant drugs to the patients who had hand surgery with regional intravenous anesthesia. In this context, contributions of non-steroidal anti-inflammatory agent to the local anesthetics as adjuvant medication during and after surgery for the patients and their positive and negative effects on the patients were evaluated. Methods: The Study was designed to cover backward date range of January 2010-August 2011 period of University Hospital Operating Room records of the hand surgery patients operated with regional intravenous anesthesia (RIVA) and those were evaluated. Total 44 patients' records retrospectively evaluated. The patients treated with prilocaine were selected as control group (Group 1), the other 22 patients treated with prilocaine and Dexketoprofen were selected as the adjuvant drug added group for the RIVA process (Group 2). The sensory and motor block onset and end times of the patients, the surgical wound pain VAS values and also VAS scores that could be derived from tourniquet pain were examined. Results: We found the positive impact on the patients, in terms of pain, as statistically significant, by the use of non-steroidal anti-inflammatory drug as an adjuvant, during and after surgery, for the RIVA technique. In this study, the starting and ending times of sensory and motor block, surgical wound VAS scores, tourniquet VAS scores measurements were taken. The mean onset time of sensorial block of Group I was calculated as 9.4 min, whereas Group II, mean onset time of sensorial block was calculated 7.09 min. In Group 2, 40 Minutes after the tourniquet had a lower VAS scores. Conclusion: It is concluded that, in the first 24 hours in RIVA, intraoperative and postoperative analgesic requirement was reduced by Dexketoprofen.

Keywords: Prilocaine, Dexketoprofen, Regional Intravenous Anesthesia

1. Introduction

In fact, the regional intravenous anesthesia (RIVA) techniques are based on hundreds of years ago. Currently it has an important role in extremities surgery and historically first applied in 1908 by Karl Agust Bier and named as Bier block. It has been revised by Morrison in 1931 and by Holmes in 1963 and came to the present times(1).

Regional intravenous anesthesia is a type of regional block formed by injection of a solution containing local anesthetic through a vein of the extremities which the blood circulation was obstructed by a tourniquet. The action mechanism, increased vascular permeability caused by ischemia and anoxia due to cessation of blood circulation in the vessels and leaking of local anesthetic solution and blocking the nerve fibers. Used agent makes a temporary functional impairment to the tissue without creating permanent damage. The method is simple and fast effective. Technical failure rate is low, and has a high degree of reliability. Therefore are often preferred particularly in short surgical procedures of upper and lower extremities.(1-4) Due to its easy use, reducing perioperative morbidity, shortening the duration of hospital treatment and staying periods, the low consumption of medication and supply materials, the low cost of anesthesia are the advantages; but, the more volume of local anesthetic used in regional intravenous anesthesia, tourniquet obligation, having pain after tourniquet and having the risk of local anesthetic toxicity are the disadvantages. It is preferred to general anesthesia although there is a risk of rare

complications. Today, especially in the upper extremities surgery RIVA applications are frequently used.(1-4)

It is known that addition of local anesthetics the various adjuvant drugs (morphine, meperidine, fentanyl, alfentanyl, sufentanyl, tramadol HCL, non-steroidal anti-inflammatory drugs, neuromuscular blocking agents, ketamine and clonidine) to increase the effectiveness of RIVA, to eliminate the tourniquet pain, and insufficient of postoperative analgesia.(5-16)

In this study, we aimed to determine the measurable or observable states of the RIVA method used in our clinic, for the local anesthetic and adjuvant-added situation, the changes in hemodynamics, efficacy on the pain, side effects occurred on intraoperative and postoperative patients.

2. Materials and the Method

Prior to the start of the study, Ethics Committee approval and the written Patients' Consents were obtained. Orthopedics and Traumatology, Plastic and Reconstructive Surgery, Hand Surgery Clinics, between the ages of 18-65, ASA (American Society of Anesthesiology) physical status of I-II, surgery performed, 44 hand surgery patients' files were evaluated retrospectively.

According to the files examined: All patients prior to RIVA process, the information were given by the anesthetist about the anesthetic technique, intravenous access established to the arm that shall not be operated, in the preparation room with 20 G branules 5 mL/kg crystalloid infusion started, and half an hour before the operation anxiolytic midazolam, 0.05 mg/kg intravenous application were observed. For the upper extremity to be operated on the back of hand the venous vascular access with the opening branules 22 G were detected, the operating table were recorded from the patients' demographic data, as well as non-invasive blood pressure, electrocardiogram (ECG) and pulse oximetry monitoring (Dräger Fabius GS premium) were provided. It is seen that, Baseline mean arterial pressure (MAP), heart rate (HR) and peripheral oxygen saturation (SpO_2) values were recorded, and RIVA process were applied to all patients as a technical standard.

In our study, while examining the patient files, RIVA applied patients' files are randomly divided into 2 groups.

Group 1: It was called as Control Group. For these patients 3 mg/kg prilocaine (Citanest flacon-Astra Zeneca 20 ml of a 2% drug) above completed to 40 ml. with 0.9 % NaCl solution, were applied.

Group 2: It was called as Dexketoprofen group. For these patients 3 mg/kg prilocaine 25 mg Dexketoprofen (50 mg Dexketoprofen Trometamol containing Arveles 50 mg/2 ml ampoule-IE Ulagay drug) above completed to 40 cc with 0.9 % NaCl solution, were applied.

For both groups the timing have been started from the end of injection; while under tourniquet after discontinuation of injection every 3 major nerves (radial, median, ulnar) distribution region in the period between the loss of perception of the sense of needle penetration, with the Pinprick test, have been recorded and named as the time of the emergence of surgical analgesia (sensory block onset time).

The presence of motor block was evaluated in the form of exists or not exists, after the drug injection, the time until the lack of movement in the fingers of patients, were recorded as motor block onset time. Before and after the tourniquet was placed and the injection of the prepared solution, at the beginning of the operation, at the operation 5^{th} min., 10^{th} min., 20^{th} min., 30^{th} min., 40^{th} min., 50^{th} min.,60^{th} min., end of operation, removal of the tourniquet, post-operation 1^{st} hour, 4^{th} hours, 8^{th} hours, 16^{th} hours, 24^{th} hours, Heart Rate (HR), Mean arterial pressure (MAP), SpO_2 values, sense of pain (Visual Analogue Scale - VAS) and sedation scores (Ramsey sedation Score = RSS) were recorded.

After the removal of a tourniquet; the recovery period of pain sensation at the radial, median and ulnar nerve dermatomes by Pinprick test were determined as the sensorial block recovery period, and the period till the time until the starting of movement in the fingers of patients, were recorded as motor block recovery time.

Postoperative pain onset time; was defined as accepting the sense of burning at the surgical region. It was planned to apply perioperative intravenous 0.01 mg Fentanyl (Fentanyl citrate 20 ml flk-Abbot) and if it was postoperative to give oral Paracetamol 500 mg tablets (Tamol 500 mg tb-Sandoz) after reaching VAS>4 value. In addition, the patient and surgeon satisfaction parameters of the groups (0: not satisfied at all, 5: very satisfied) were also recorded.

In the study, statistical analyzes were performed with SPSS 15.0 software package program. Statistical analysis, descriptive statistical methods (mean, standard deviation) as well as Matching variant analysis for repeated measurements of multiple groups, Newman Keuls' multiple comparison test for sub-group comparisons, one-way variance analysis for comparison of groups, Tukey's multiple comparison test for sub-group comparisons, Q-square test for qualitative data comparisons were used. The significance of $p < 0.05$ were evaluated for the results.

3. Results

For a total of 44 RIVA applied patients there were no statistically significant difference between the two groups, Group I and Group II, age, height, gender, weight, based on the values and the types of the surgery ($p > 0.05$) in terms of demographic and clinical characteristics. There were no statistically significant difference between the groups if they were compared in terms of operation and the mean tourniquet timings ($p > 0.05$).

The mean onset time of sensorial block of Group I was calculated as 9.4 min, whereas Group II, mean onset time of sensorial block was calculated 7.09 min. Statistical comparison of the groups showed that, the mean onset time

of sensorial block of Group I, were statistically significant higher than that of Group II (p<0.05) (Table 1)

Table 1. *Sensorial and motor block onset time of the block groups (*p<0, 05)*

	Group	n	Average time	Σ_x	p
Motor block onset time (min.)	I	22	13, 6091	3, 09027	0, 103
	II	22	13, 0455	2, 61418	
Sensorial block onset time (min.)	I	22	8, 8091*	1, 35960	0, 001*
	II	22	7, 4909	1, 41929	

The mean onset time of motor block of Group I was calculated as 13.6 min, whereas Group II, mean onset time of motor block was calculated 13.04 min. Motor block mean onset time of Group I was found statistically insignificant as per the Group II. (p > 0.05)

The mean sensorial block recovery time of Group I was calculated as 3.4 min, whereas Group II, mean sensorial block recovery time was calculated as 5.09 min. Statistical comparison of the Groups showed that, the mean sensorial block recovery time of Group II, were statistically significant longer than that of Group I (p<0.05) (Table 2) The mean recovery time of motor block of Group I was calculated as 8.9 min, whereas Group II, mean recovery time of motor block was calculated 9.1 min. Motor block mean recovery time of Group I was found statistically insignificant as per the Group II. (p > 0.05)

Table 2. *Sensorial block and motor block recovery periods of the Groups (*p<0,05)*

	Group	n	Average time	Σ_x	p
Motor block recovery time (min.)	I	22	8, 9191	1, 89027	0, 192
	II	22	9, 1455	2, 21418	
Sensorial block recovery time (min.)	I	22	3, 4091*	1, 25960	0, 001*
	II	22	5, 0909	1, 61929	

The average time to first postoperative analgesic requirement of Group I was calculated as 95.24 min, whereas Group II, average time to first postoperative analgesic requirement was calculated as 158.68 min. Statistical comparison of the Groups showed that, the average time to first postoperative analgesic requirement of Group I, were statistically significant lower than that of Group II (p<0.05 meaningful) (Table 3) Before tourniquet, after drug administration, at the beginning of the operation, at the operation 5th min., 10th min., 20th min., 30th min., 40th min., 50th min., post-operation 1st hour, 2nd hours, 4th hours; the Mean arterial pressures (MAP) were not showing statistically significant differences between Group I and Group II (p>0.05). Before tourniquet, after drug administration, at the beginning of the operation, at the operation 5th min., 10th min., 20th min., 30th min., 40th min., 50th min., end of operation, removal of the tourniquet, post-operation 1st hour, 4th hours, 8th hours, 16th hours, 24th hours; the Mean SpO_2 values were not showing statistically significant differences between Group I and Group II (p>0.05).

Table 3. *First postoperative analgesic requirement periods of the Groups (*p<0,05)*

	Group I	Group II		Σ_xp
The average time to first analgesic requirement (min.)	95, 24	158, 68	3,9	0,001*

Group I and Group II statistical comparison of the mean wound VAS values; significant difference between the mean VAS values were observed for wound VAS 40th min., 50th min., post-operation wound VAS zero min., 30th min., 1 hour, 2nd hours, 4th hours, and 6th hours (p <0.05). Before tourniquet, at the operation 1st min., 5th min., 10th min., 20th min., post-operation 12th hours, and post-operation 24th hours wound VAS values were not showing significant differences between the groups (p>0.05).

Group I and Group II statistical comparison of the mean tourniquet VAS values; statistical difference between the groups were not observed for tourniquet VAS values of 1st min., 5th min., 10th min., 20th min., 30th min., and 40th min., mean measurements (p>0.05).

Group I and Group II statistical comparison of the mean tourniquet VAS values; statistical difference between the groups observed for tourniquet VAS value of 50th minute was found significant. (p <0.05)

If Group I and Group II were compared with the average values in terms of patient satisfaction significant

differences between the groups were observed. (Table 4) ($p<0.05$). If Group I and Group II were compared with the average values in terms of surgeon satisfaction significant differences between the groups were observed. (Table 4) ($p<0.05$)

Table 4. *Groups, patient and surgeon satisfaction (*p<0,05)*

	Group	n	Level	Σ_x	p
Patient satisfaction	I	22	3, 0000*	00000	0, 001*
	II	22	3, 8636	77432	
Surgeon satisfaction	I	22	3, 0909*	29424	0, 001*
	II	22	3, 7273	55048	

Ramsey sedation score values of Group I and Group II did not show differences statistically. ($p> 0.05$)

4. Discussion

RIVA, due to its low cost comparing to general anesthesia, ease of applicability, providing bloodless environment during the operation as the surgeon prefers, having rare postoperative complications, due to the time-saving and fast recovery, has been the preferred method of operations for the distal extremities. (Especially the hand, wrist and forearm)(1-10). In RIVA technique, inexperience, pose a technical reason for the failure. In experienced hands, the possibility of technical failure is quite small. Loosen of the tourniquet and removing it before the safe range may cause to local anesthetic toxicity.(11) One of the discussions in RIVA technique which of the local anesthetic to be used. Historically the most commonly used local anesthetic is Lidocaine, the majority of European countries prefer Prilocaine due to its fewer toxicity (17-19). In our study, we preferred records of group of patients used local anesthetic, at 3 mg / kg Prilocaine.

To decrease the toxic side effects the dose and concentration of the local anesthetic was reduced, currently in order to increase the efficacy some adjuvant drugs usage are studied. There are researches by the use of adjuvant drugs to increase the depth of anesthesia, hemodynamic stabilization, by providing the appropriate comfortable surgery environment for the patient and the surgeon, using morphine, clonidine, meperidine, fentanyl, sufentanyl, tramadol, NSAIDs, dexamethasone, and even the various studies conducted on the use of local anesthetic drugs (10, 13, 17). We have started to our studies by comparing non-steroidal anti-inflammatory analgesic effective dexketoprofen having opportunity to study with intravenous use as an adjuvant drug with only prilocaine using groups. After that Erciyes et al,(17) gave 6 mg of morphine mixing with prilocaine. They mentioned that analgesia starting period was shorter and the duration of anesthesia was longer for the morphine added group. In our study, we have compared addition of 25 mg of prilocaine to dexketoprofen group with prilocaine alone.

Sakirgil et al, in their study, added morphine (0.1 mg/kg) to ropivacaine. The surgical analgesia onset time was longer, and had a longer duration of analgesia (20). In the study made by Acalovschi et al,(5) meperidine was used as adjuvant. Anesthesia start time was shorter, the motor block and the block recovery slowing were provided. However, the authors observed and reported side effects such as nausea, dizziness, light-headedness, temporary swelling and itching at the arm, and injection site pain (4). In our study, intraoperative and postoperative adverse events in patients undergoing RIVA applications were not observed.

Fahim et al in their study, reported that lidocaine sufentanyl added group sensorial and motor block onset time were shorter compared to lidocaine group but reported dizziness following the removal of tourniquet(21). Acalovschi et al have added 100 mg of tramadol to lidocaine and reported the shortening of the sensory block duration(18). Tan et al have added 50 mg of tramadol to lidocaine and reported the shortening of the sensory block starting period(22). Again, Ozcan et al have added 50 mg of tramadol to lidocaine and reported the shortening of the sensory block duration (23). Bigat et al compared Tenoxicam which was a non-steroidal anti-inflammatory drug with dexamethasone. And reported prolong duration of sensorial and motor blockade with the use of dexamethasone with local anesthetics(10).

Güldoguş et al, compared the local anesthetic agent, muscle relaxant atracurium with the fentanyl group, and reported that there was no difference between the groups used and the local anesthetic alone, the long duration of motor paralysis prolong the duration of postoperative recovery, and reported adverse effects were seen(11, 14). But in our study no difference was observed between dexketoprofen group and the control group for the mean motor block recovery durations ($p>0.05$). Kurt et al, in their study with lidocaine atracurium or alfentanyl addition, was noted that the sensorial block onset time was short, the motor block onset time, intraoperative and postoperative pain scores postoperative first analgesia durations were similar for all groups.(24)

Non-steroidal anti-inflammatory agents such as tenoxicam, ketorolac may also prolong the duration of postoperative analgesia by the addition to local anesthetic used to decrease tourniquet pain (15, 25). Gentili et al

reported that clonidine reduces tourniquet pain in RIVA(26). In our study also, when Dexketoprofen adjuvant drugs were used, the mean values of Dexketoprofen group's 50th-minute tourniquet pain, was found at significantly lower statistical values ($p < 0.05$).

Gentili et al investigated the effects of the addition of 0.5% lidocaine and clonidine on tourniquet pain. Researchers have found that when clonidine is used a lower tourniquet VAS value were observed; however following the removal of a tourniquet they did not find statistically significant differences on postoperative pain and additionally they found sedation in clonidine group (26). For our patient groups the intraoperative sedated agents are not used. 30 minutes prior 0.05 mg/kg intramuscular midazolam made for the preoperational anxiolytic activity. of, considering the systemic effects of local anesthetic sedation scores were monitored and in none of the cases Ramsey sedation score above 2 were observed. There were no statistically significant differences in sedation scores between the two groups. ($p> 0.05$)

In the literature the studies, for RIVA, dexmedetomidine having sedation activity addition into the local anesthetics are available, and was reported dexmedetomidine selective α2-agonist activity was reported to be 8 times more than the clonidine (27, 28). It has been reported that, the dexmedetomidine's α2-adrenergic receptor stimulation to the spinal cord at the level of the use of analgesic effect of intraoperative and postoperative opioid or non-opioid analgesics might have reduce the requirement (28). If the value of postoperative VAS was over 4, oral paracetamol of 500 mg po was given. In our study, time to first analgesic requirement in Group I was in average 95.24 minutes, while in Group II, it was 158.68 minutes, respectively. In our study it was concluded that, addition of dexketoprofen, significantly prolonged the duration of the first analgesic requirement.

In our study, the average sensory block onset time was 8.8 minutes in Group I and was 7.4 minutes in Group II respectively ($p <0.05$). In the study made by Suer et al, for RIVA for a group only 0.5 % per 0.6 mg/kg prilocaine was using and for the other group it was using 0.25 % prilocaine added by 0.1 mg/kg of morphine and was more rapid onset time of sensorial block was observed for the morphine group (5). In Turan et al study, neostigmine added to prilocaine in RIVA and sensory block onset time was shortened (29). In Fahim et al (21) study 0.5 mg / kg of dexmedetomidine added to lidocaine was found shortening the starting time of the sensorial block.

In our RIVA applied retroactively cases of file scanning sensorial block recovery time was found as 3.4 minutes in Group I, and was found as 1.5 minutes in Group II, respectively and statistically significant difference was found ($p <0.05$). Fahim et al (21) with the Memiş et al (30) in their study, lidocaine added to the dexmedetomidine group had a longer duration of sensory block return. In the studies done by Fahim et al (21), and Memis et al (30), it was determined that sensorial block return period was longer than in the lidocaine added dexmedetomidine group. However, Esmaoglu et al (31) study showed that by adding 1 µg/kg dexmedetomidine into lidocaine will result with no significant differences observed for the two groups' sensorial block starting periods. In our study, RIVA applied cases motor block recovery time for patients treated in our study group I, was 8.9 minutes, and was 9.1 minutes for Group II patients and no significant difference was found. Similarly, The study of Esmaoglu et al, (31) by adding by adding 1 µg/kg dexmedetomidine into lidocaine, block starting period of the two groups did not show differences between the groups. However for the studies of Memis et al (30), and Fahim et al (21), motor block starting period of dexmedetomidine added to lidocaine group was found shorter starting period.

5. Conclusion

Addition of 25 mg of dexketoprofen to local anesthetic solution at RIVA, showed faster perioperative surgical analgesia formation, and later postoperative pain occurrence has been observed.

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