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Original Article

The analgesic effect of dexketoprofen trometamol when added to lidocaine for intravenous regional anesthesia

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Abstract

Aim: The purpose of this study was to evaluate the duration of onset and regression time of sensory and motor blocks, tourniquet pain, and postoperative analgesia with the addition of dexketoprofen trometamol to lidocaine solution in intravenous regional anesthesia (IVRA) for hand surgery.

Material and Methods: This study was designed as a retrospective analysis. Records, including perioperative anesthesia notes, of 290 patients evaluated and 75 identified as eligible that underwent IVRA with an upper extremity Bier block and a corresponding tourniquet time of less than 1 hour were reviewed. Patients undergoing IVRA with lidocaine (3 mg/kg) were compared with those receiving dexketoprofen trometamol (50 mg) as an adjuvant in IVRA (the D-IVRA group) or as intravenous analgesia in the non-operated arm (the D-IV group) . All hemodynamic values, sensorial/motor block onset and regression times, VAS values, intraoperative and postoperative analgesic requirements, and all complications were recorded.

Results: Sensory block onset time was shorter and motor block regression time longer in the D-IVRA group. After tourniquet deflation, all perioperative VAS scores in the D-IVRA group were lower than those of the control group. VAS scores were lower in the D-IVRA group compared to the D-IV group, especially at 30 min and 1 h postoperatively.

Conclusion: The addition of dexketoprofen trometamol to lidocaine in IVRA may increase the quality of anesthesia and analgesia in hand surgery.

Keywords: Dexketoprofen trometamol; lidocaine; IVRA; local anesthetics; NSAIDs

INTRODUCTION

Bier block, or intravenous regional anesthesia (IVRA), were first described for anesthesia of the hand and forearm by August Karl Gustav Bier in the early 1900s. The method has continued to be used as a simple, safe and low-cost anesthesia technique with success rates ranging between 94% and 98% (1). However, in addition to these advantages, IVRA also has several disadvantages. In particular, the technique is limited by tourniquet pain, insufficient block duration, and the inability to provide postoperative analgesia (1). Other disadvantages of IVRA include local anesthetic toxicity and the short duration of postoperative analgesia. Various nonsteroidal anti-inflammatory drugs (NSAIDs) have been combined as additives with local anesthetics to reduce tourniquet pain, prolong post-deflation analgesia, and improve block quality (2-4). However, additional intravenous (iv) use of any form of analgesic may be needed to support IVRA (2,3,5,6).

Dexketoprofen trometamol is a relatively new NSAID with analgesic and antipyretic properties available in both oral and parenteral forms. It functions directly, by inhibiting cyclooxygenase and prostaglandin synthesis, and indirectly, by affecting mediators such as quinine. The high lipid solubility of dexketoprofen trometamol also helps to accelerate absorbance of the drug (7).

Our primary endpoint in this study was to evaluate the effects of dexketoprofen trometamol on the quality of analgesia and anesthesia in IVRA. Our secondary endpoint was to assess the duration of onset and regression time of sensory and motor blocks of dexketoprofen trometamol in IVRA.

In the light of these properties, we hypothesized that the use of dexketoprofen trometamol in IVRA in particular may increase the quality of anesthesia and analgesia.

MATERIAL and METHODS

Patient and study design

Following approval from the Karadeniz Technical University ethical committee (2012/118), we performed a retrospective review of the surgical and anesthesia records of 290 patients evaluated and 75 identified as

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eligible undergoing carpal tunnel syndrome and trigger finger surgery with IVRA. Data were elicited for all patients undergoing IVRA with a tourniquet time of less than 1 hour, classified as ASA 1 or 2 based on preoperative physical status assessment according to American Society of Anesthesiologists (ASA) criteria, aged between 18 and 55, and weighing between 50 and 100 kg. Patient demographics were documented, including sex, age, weight, and type of procedure performed. Patient data were then classified depending on whether or not IVRA was performed with dexketoprofen trometamol. Ninety cases were selected in this way. Ten patients were subsequently excluded due to missing data in the records and five due to progression to general anesthesia because of prolongation of surgery and IVRA proving inadequate. The study was thus completed using the records of the remaining 75 patients (Figure 1). Patients were allocated into three groups based on the drugs used. The control group consisted of patients undergoing IVRA with lidocaine 3 mg/kg + isotonic NaCl (total 40 ml) only (n=25). Patients undergoing IVRA with the addition of one ampoule of dexketoprofen trometamol (Arveles 50 mg/2 ml UFSA İlaç Sanayi Tic. A.Ş, Istanbul, Turkey) to 3 mg/kg lidocaine + isotonic NaCl (total 40 ml) constituted the D-IVRA group (n=25). Patients given one ampoule of dexketoprofen trometamol iv to support anesthesia in the non-operated arm and who underwent IVRA with 3 mg/kg lidocaine + isotonic NaCl (total 40 ml) constituted the D-IV group (n=25).

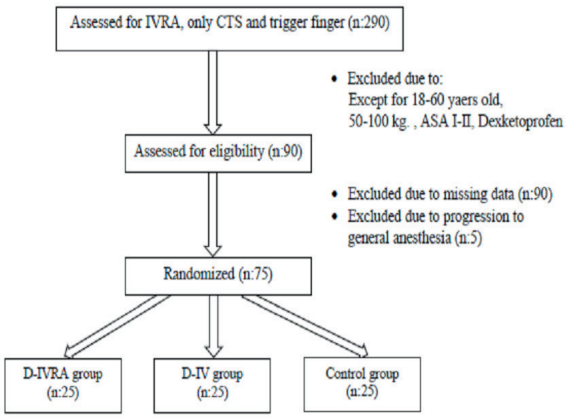

Figure 1. Study flow chart

The anesthesia records of each patient were used to identify anesthesia procedures, tourniquet inflation and deflation times, motor and sensorial block onset and regression times, all hemodynamic and VAS values, perioperative additional non-routine analgesic requirements, (paracetamol IV 100 mg, and contramal IV 50 mg if necessary), and the presence of any intraoperative or immediate (prior to discharge) postoperative complications related to any kind of lidocaine toxicity. In addition to these records, two samples of D-IVRA mixes from the patients with the highest and lowest weight values were reconstituted for this study, and pH measurements were performed. Two separate mixtures were prepared for the two patients weighing 50 and 100 kg (150 mg lidocaine+50 mg dexketoprofen trometamol and 300 mg lidocaine +50 mg dexketoprofen trometamol, total 40 ml each). The pH of the mixture was measured potentiometrically using a PH meter (HANNA Instruments/ H1 211/ORP Met). The results were expressed as pH values.

Biostatistical analysis

Ten minutes after tourniquet deflation was selected as the point when the effect of the techniques applied in the three groups could be best assessed.

The sample size was calculated by considering the outcomes of previous study (2). The alpha error=0.05, beta error=0.20 and the effect size=0.8 were selected both for the primary and secondary endpoints of the study. The required sample size was determined as n=21 for each group. However, by considering the potential data loss during the study period, the final sample size was obtained as 25 patients for each group (n=75; total sample size).

Data were analyzed using Statistical Package for Social Sciences (SPSS) for Windows version 13.0. Data obtained by measurement were expressed as mean plus standard deviation, and those obtained by counting as %. Significance was set at $p<0.05$. The chi-square test was used to compare qualitative data, and the Kolmogorov-Smirnov test was used to compare compatibility of the data with normal distribution. Student's t-test was used for normally distributed data at two-way comparisons, and the Mann-Whitney test was used for non-normally distributed data. Analysis of variance (ANOVA) was used in repeated measurements if data compared from the beginning onward were normally distributed, while the Friedman test was used for non-normally distributed data. ANOVA was used for normally distributed data in comparisons between the three groups, and the Kruskal-Wallis test was used for non-normally distributed data. The Bonferroni-corrected Mann-Whitney U-test was used in post-hoc two-way comparisons. Data obtained by measurement were expressed as mean plus standard deviation, and data obtained mathematically as %. Significance was set at $p<0.05$.

RESULTS

No difference was determined between the groups in terms of age, gender, ASA, length of operation, or tourniquet duration ($p>0.05$) (Table 1). All cases were hemodynamically stable, and all MAP levels were similar ($p>0.05$, for all values).

Initial heart rate values were similar. Heart rate values at 10 min after the commencement of the surgery ($p=0.012$), at tourniquet deflation ($p=0.023$) and at the 5 min after deflation ($p=0.030$) were all lower in the D-IVRA group compared to the control group. There was no difference between the D-IVRA and D-IV groups or between the D-IV and control groups.

D-IVRA group sensory block onset times were shorter than those of the control and D-IV groups ($p=0.001$), while

there was no difference between the control and the D-IV groups (p>0.05). No difference was observed between the groups in terms of sensory block regression times (p>0.05) (Table 2).

No difference was determined in terms of onset time of motor block (p>0.05). Motor block regression time was longer in the D-IVRA group compared to the control and D-IV groups (p<0.001). No difference was observed between the control and D-IV groups (p>0.05) (Table 2).

Initial VAS values were similar. VAS values in the D-IVRA group were lower at tourniquet deflation (p<0001), and at 5 min (p=0.033), 10 min (p=0.005), 15 min (p=0.003) and 30 min (p=0.012) and at 1 hour (p=0.028) after deflation compared to those of the control group. VAS values in the D-IVRA group at 30 min (p=0.024) and 1 hour (p=0.033) after deflation were lower than those in the D-IV group (Figure 2).

Table 1. Demographic data, length of surgery and tourniquet duration

	D-IVRA group (n=25)	Control group (n=25)	D-IV group (n=25)	p
Age	36.12±13.624	32.16±11.316	40.08± 14.719	P=0.116
Gender (%) male/female	76 / 24	68 / 32	80 / 20	P=0.611
ASA-1/ASA-2 (%)	72 / 28	80 / 20	80 / 20	P=0.738
Op. length	40.60 ±8.916	40.24 ±8.227	42.92± 10.360	P=0.539
Tourniquet Duration	56.80± 10.075	55.24 ±9.382	60.40± 11.551	P=0.204

* (p>0.05 for all comparisons)
** Abbreviations: ASA: American Society of Anesthesiologists; D-IVRA: Intravenous regional anesthesia - lidocaine +dexketoprofen trometamol, Control: Intravenous regional anesthesia - lidocaine + saline, D-IV: Intravenous regional anesthesia - lidocaine + intravenous dexketoprofen trometamol

Table 2. Onset and regression times of sensory and motor blocks (min)

Variable	D-IVRA	D-IV	Control	p
Sensory block onset time	3.40±1.041	4.76±1.422	4.76±1.451	*p:0.001
Sensory block regression time	4.16±1.546	3.40±2.082	3.92±1.801	P>0.05
Motor block onset time	8.68±2.940	10.00±3.096	9.36±3.882	P>0.05
Motor block regression time	9.00±1.581	5.16±2.764	4.56±2.162	*p<0.001

* p<0.05, D-IVRA with the D-IV and control groups

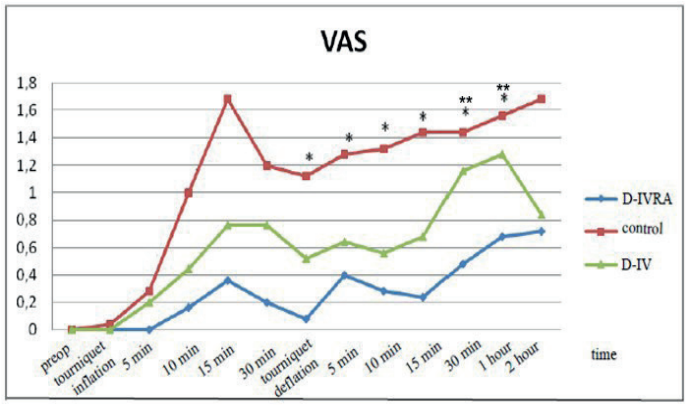

Figure 2. Visual analogue scale (VAS) values in the study groups (VAS; min 0- max 10) (*; p<0.05, D-IVRA with the control group, **; p<0.05, D-IVRA with the D-IV group)

Intraoperative additional analgesic requirement levels were 20% in the D-IVRA group, 32% in the control group and 20% in the D-IV group. Postoperative additional analgesic requirement levels were 12% in the D-IVRA group, 40% in the control group and 28% in the D-IV group. These differences were not statistically significant (p>0.05). (Figure 3).

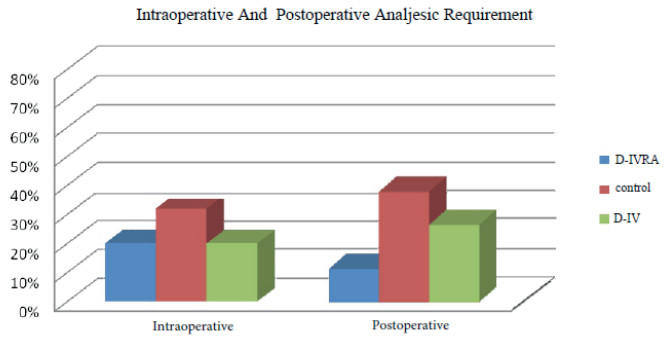

Figure 3. Intraoperative and postoperative additional analgesic requirements in the study groups

No patients exhibited any signs of lidocaine toxicity. Two patients (in the D-IV and control groups) with

postoperative hypotension had a history of hypertension, as they were on betablockers.

The pH value of the iv form of dexketoprofen trometamol was approximately 7.0-8.0. The pH values of the lidocaine-dexketoprofen trometamol mixture were 6.7 and 6.82, and the pH of lidocaine solution alone was 6.7.

DISCUSSION

The main findings of the present study are as follows: The addition of dexketoprofen trometamol to lidocaine for IVRA shortened sensory block onset time, prolonged motor block regression time and improved anesthesia via reduced VAS scores without causing any side-effects.

Various different adjuvant NSAIDs including ketorolac, lornoxicam, tenoxicam and paracetamol are currently added to lidocaine to reduce tourniquet and postoperative pain (2,3,5,6). Although several mechanisms have been proposed, the pharmacological effects of NSAIDs are attributed to cyclooxygenase and prostaglandin inhibition [8]. Surgical trauma also leads to the release of chemical mediators that activate nociceptors, such as bradykinin, serotonin, substance p, and histamine (9). These have been shown to inhibit COX-2, which plays a particular role in inflammation-related pain (10).

The tourniquet pain resulting from compression in the peripheral nerve is ischemic in nature, begins in the early period, and worsens progressively (2,11). Nerve compression, tourniquet diameter, inflammation pressure and adjuvants used in IVRA all affect tourniquet pain (4). The incidence and severity of tourniquet pain which may arise from oxidative stress during ischemia is correlated with tourniquet duration. The incidence of tourniquet pain is 15% in operations involving tourniquet duration of 30 min. However, the incidence exceeds 50% when the duration rises to 70 min (12). Drugs with antioxidant characteristics may be beneficial in tourniquet pain. Lornoxicam and diclofenac have been shown to exhibit antioxidant properties (13,14). The question therefore arises of whether dexketoprofen trometamol also exhibits antioxidant properties, similarly to other NSAIDs.

Numerous studies have shown that the use of an additional NSAID in IVRA may affect block onset and regression times. Şen et al. reported faster sensorial and motor block onset times when they added lornoxicam in IVRA, and attributed this to the pH of the solution, as well as to the effects of classic NSAIDs (2). Those authors measured the pH of the iv form of lornoxicam as 8.7, that of the lornoxicam-lidocaine mixture as 7.6, and that of the lidocaine solution alone as 6.7 (2). They then suggested that the alkalization of the solution by the addition of lidocaine-lornoxicam may shorten the block onset time through an increase in non-ionized form. However, the previous literature suggests that the adjuvant use of NSAIDs or opioids is more effective in upper extremity operations (in contrast to lower extremity blocks) than in alkalization in IVRA (15). We encountered no previous studies showing that dexketoprofen trometamol changed pH when used as an adjuvant. However, the pH change in the mixture in the present study was very low. The positive effect observed on the block cannot be explained in terms of alkalinization. NSAIDS have been shown to exert a greater analgesic effect when concentrated at a peripheral site than when the same drug is administered systemically (5) NSAIDs have been shown to reduce the synthesis of inflammatory mediators and afferent nociceptive signals originating from the procedure site. The principal analgesic effect of NSAIDs is attributed to COX2 inhibition. The addition of NSAIDs to IVRA appears to result in an immediate onset of action. The involvement of another mechanism may therefore be assumed. For example, A-delta fibers and unmyelinated C-fibers may play a role in tourniquet pain due to the enhancement by ischemia of circumferential pressure on the peripheral nerves (6). In addition, opening of the K channels in the primary afferent nerve ending results in antinociception and constitutes a significant step in the peripheral antinocicepive activity of a number of NSAIDS. These largely exhibit their antinociceptive effects in peripheral sites. This may account for the greater analgesic effect of NSAIDs such as dexketoprofen trometamol in IVRA compared to systemic administration for tourniquet pain (6).

Several previous studies have used NSAIDs as an adjuvant in IVRA or iv through the non-operated arm (2,3,5,6). In two separate studies, Borazan et al. and Jones et al. used dexketoprofen trometamol and tenoxicam, respectively, as adjuvants in IVRA and iv through the non-operated arm. The drug used by Borazan et al. was found to be effective in both routes, while Jones et al. reported greater efficacy in IVRA (4,16). The effectiveness of iv use via the non-operated arm is thought to derive from a decrease in nociceptive signals from the surgical area [9]. Dexketopropofen trometamol accelerated the block onset of IVRA, prolonged the duration of block, and reduced analgesia requirements, while iv use only reduced analgesia requirements (17,18).

In the light of all these studies, since the aim of using NSAIDs with IVRA is to increase block quality along with a positive contribution to analgesia, it seems more reasonable to use NSAIDs together with local anesthetics rather than in the form of iv administration. VAS values in the present study were better in the D-IVRA group than in the control group at all times and better than in the D-IV group at most times. These data support the idea of an efficient adjuvant effect of dexketoprofen trometamol.

We determined a shorter sensory block onset time in the D-IVRA group, while regression time was unchanged. Motor block onset time was unchanged, while regression time was prolonged. Yurtlu et al. reported significantly higher intraoperative fentanyl requirements and postoperative paracetamol consumption in a control group compared to D-IV and D-IVRA groups (17). In the present study, the variation between intra- and postoperative analgesic requirements was not significant.

One of the principal limitations of this study is its retrospective nature. The fact that the positive effect on our VAS scores was not reflected in analgesic consumption may be attributed to the retrospective nature of the study and to the fact that perioperative analgesic management could not be standardized.

CONCLUSION

In conclusion, IVRA block containing dexketoprofen was successful, and its use in combination with lidocaine was even more effective in terms of block quality and analgesia.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: Approval the Karadeniz Technical University ethical committee (2012/118).

REFERENCES

1. Memis D, Turan A, Karamanlioglu B, at all. Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. Anesth Analg 2004;98:835-40.
2. Sen S, Ugur B, Aydin ON. The analgesic effect of lornoxicam when added to lidocaine for intravenous regional anaesthesia. Br J of Anaesth 2006;97:408-13.
3. Loser B, Petzoldt M, Loser A, at all. Intravenous regional anesthesia: A historical overview and clinical review. J Anesth Hist 2019;5:99-108.
4. Borazan H, Sahin O, Uluer MS, at all. Comparison the effects of prilocaine and the addition of dexketoprofen and dexamethasone to prilocaine for intravenous regional anesthesia. Agri 2014;26:65-72.
5. Choyce A, Peng P. A systematic review of adjuncts for intravenous regional anesthesia for surgical procedures. Can J Anaesth 2002;49:32-45.
6. Sen H, Kulahci Y, Bicerer E, at all. The analgesic effect of paracetamol when added to lidocaine for intravenous regional anesthesia. Anesth Analg 2009;109:1327-30.
7. Mauleon D, Artigas R, Garcia ML, at all. Preclinical and clinical development of dexketoprofen. Drugs 1996;52:24-45.
8. Barbanoj MJ, Gich I, Artigas R, at all. Pharmacokinetics of dexketoprofen trometamol in healty volunteers after single and repeated oral doses. J Clin Pharmacol 1998;38:33-40.
9. Reuben SS, Steinberg RB, Kreitzer JM, at all. Intravenous regional anesthesia using lidocaine and ketorolac. Anesth Analg 1995;81:110-3.
10. Turan A, Memis D, Karamanlıoglu B, at all. Intravenous regional anesthesia using lidocaine and magnesium. Anesth Analg 2005;100:1189-92.
11. Gokin AP, Philip B, Strichartz GR. Preferential block of small myelinated sensory and motor fibers by lidocaine: in vivo electrophysiology in the rat sciatic nerve. Anesthesiology 2001;95:1441-54.
12. Valli H, Rosenberg PH, Kyttä J, at all. Arterial hypertension associated with the use of a tourniquet with either general or regional anaesthesia. Acta Anaesthesiol Scand 1987;31:279-83.
13. Rokyta R, Holecek V, Pekárkova I, at all. Free radicals after painful stimulation are influenced by antioxidants and analgesics. Neuro Endocrinol Lett 2003;24:304-9.
14. Kaplan O, Naziroglu M, Guney M, at all. Non-steroidal anti-inflammatory drug modulates oxidative stress and calcium ion levels in the neutrophils of patients with primary dysmenorrhea. J Reprod Immunol 2013;100:87-92.
15. Sahmeddini MA, Khosravi MB, Seyedi M, at all. Comparison of magnesium sulfate and tramadol as an adjuvant to intravenous regional anesthesia for upper extremity surgeries. Anesth Pain Med 2017;27:7:57102.
16. Jones NC, Pugh SC. The addition of tenoxicam to prilocaine for intravenous regional anaesthesia. Anaesthesia 1996;51:446-8.
17. Yurtlu S, Hancı V, Kargi E, at all. The analgesic effect of dexketoprofen trometamol when added to lidocaine for intravenous regional anaesthesia: a prospective, randomized, plasebo controlled study. J Int Med Res 2011;39:1923-31.
18. Akdogan A, Eroglu A. Comparison of the Effect of Lidocaine Adding Dexketoprofen and Paracetamol in Intravenous Regional Anesthesia. Biomed Res Int 2014;2014:938108.