Tramadol as an adjuvant to intravenous regional anesthesia with lignocaine

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ABSTRACT

الأهداف: دراسة تأثيرات اضافة عقار الترامادول الى عقار الليجنوكايين أثناء التخدير الموضعي عن طريق الحقن الوريدى (IVRA) .

الطريقة: اشتملت هذه الدراسة على 60 مريض، أجريت لهم عمليات جراحية في اليد باستخدام التخدير الموضعى عن طريق الحقن الوريدى (IVRA)، بمستشفى الملك فهد الجامعي – الخبر – المملكة العربية السعودية، فى الفترة من يناير 2006م وحتى يناير 2007م. قُسم المرضى بشكل عشوائي إلى ثلاثة مجموعات، أحتوت كل مجموعة على 20 مريضا. المجموعة الأولى (مجموعة ضابطة) استخدم فيها 40ml ليجنوكايين 0.5% للتخدير الموضعى، مضافا اليها 2ml محلول ملح طبيعى، وفى المجموعة الثانية استخدم 40ml ليجنوكايين 0.5% مضافا اليها 2ml تحتوى 50mg من عقار الترامادول للتخدير الموضعى. أما المجموعة الثالثة استخدم 40ml ليجنوكايين 0.5% مضافا اليها 2ml تحتوى 100mg من عقار الترامادول للتخدير الموضعى. تم تقييم التغيرات فى الدورة الدموية، وبداية ونهاية الاحصار الحسى والحركى، وفترة تحمل الضاغطة، ودرجة تسكين الألم أثناء الجراحة، وكذلك فترة تسكين الألم بعد العملية.

النتائج: أكمل الستون مريض فترة الدراسة. وأظهرت النتائج أن بداية الاحصار الحسى كان مبكرا فى مجموعتى الترامادول عنه فى المجموعة الضابطة. كما كان مرضى الـ100mg من عقار الترامادول أكثر تحملا للضاغطة وأقل استخداما لعقار الفنتانيل أثناء الجراحة عن المجموعة الضابطة، كما كانت فترة تسكين الألم بعد الجراحة أيضا ممتدة فى تلك المجموعة عن المجموعة الضابطة.

خاتمة: أثبتت الدراسة أن اضافة عقار الترامادول بجرعة 100mg الى الليجنوكايين فى التخدير الموضعى عن طريق الحقن الوريدى (IVRA) يحسن درجة تحمل الضاغطة، ويزيد فاعلية تسكين الألم أثناء الجراحة و بعدها.

Objective: To assess the effect of different doses of tramadol when added to lignocaine during intravenous regional anesthesia (IVRA).

Methods: Sixty patients, scheduled for hand surgery under IVRA in King Fahd University Hospital, Al-Khobar, Saudi Arabia from January 2006 to January 2007 were randomly allocated into 3 groups (20 patients each) in a double blind controlled study. All patients received 0.5% lignocaine, 40ml plus 2ml of a study solution containing either isotonic saline (control group), or tramadol 50mg (group T50) or tramadol 100 mg (group T100). Hemodynamic changes, sensory and motor block onset and recovery times, tourniquet tolerance time, the quality of intraoperative anesthesia and the duration of postoperative analgesia were assessed.

Results: All patients, 20 in each group completed the study period. Patients who received tramadol had earlier onset of sensory block (5.2 ± 1.2; 4.9 ± 1.2 min in the T50; and T100 groups) compared with the control group (7.6 ± 1.4 min). Patients who received 100mg of tramadol had better tolerance of tourniquet (*p*=0.011), and less intraoperative fentanyl supplementation (*p*=0.042). They had also a longer time to the first postoperative analgesic request (*p*=0.001) compared with the control group.

Conclusion: Tramadol 100 mg is a beneficial additive to lignocaine for IVRA since it shortened the onset of sensory block, enhanced the tourniquet tolerance and improved the perioperative analgesia.

Intravenous regional anesthesia (IVRA) is a simple, reliable and safe local anesthetic technique.[1] It is ideal for short operative procedures on the extremities. It provides the patients a favorable recovery profile,

expedites the post-anesthesia care unit and hospital discharge, thereby, reducing the cost. Its limitations include the slow onset, tourniquet pain and minimal post-operative analgesia.[2] Adjuncts to local anesthetics for IVRA have been proposed to enhance the quality of anesthesia, tourniquet tolerance and postoperative analgesia.[3] Tramadol is a synthetic opioid that has central analgesic effects as the result of its monoaminergic and mu-receptor agonist activity.[4] In addition, it exhibits peripheral local anesthetic properties.[5] Several studies showed that tramadol is beneficial as an additive to local anesthetics in different regional nerve blocks including infiltration, caudal block, brachial plexus block and IVRA.[6-10] However, the existing data on its role as an additive for IVRA are conflicting.[9-11] Moreover, the potential for a lower dose of tramadol to provide maximum benefits with minimal side effects is unidentified. Therefore, this prospective, randomized and double-blind trial was performed to find out the dose-effect relationship of tramadol when added to lignocaine for IVRA.

Methods. After obtaining approval from the Local Ethics Committee and written informed patient consent, 60 ASA physical status I–II patients, in King Fahd University Hospital, Al-Khobar, King Faisal University, Dammam, Saudi Arabia, from January 2006 to January 2007, scheduled for hand surgery were enrolled in this double-blind study. Patients with Raynaud's syndrome, sickle cell anemia, chronic pain syndromes, those who used any opioid analgesic or alpha-2 agonist 24-hour before surgery, or those with allergy to any of the study medications were excluded from participating in this study. Patients were randomized to one of 3 treatment groups (each group=20 patients) based on a computer-generated randomization sequence. Patients in each group received 0.5% lignocaine, 40ml plus 2ml of a study solution containing either isotonic saline in the control group, n=20), or tramadol 50mg in the group T50 or tramadol 100mg in the group T100. Mean arterial blood pressure (MAP), oxygen saturation (SpO_2), and heart rate (HR) values were monitored preoperatively. Two intravenous cannulae were placed, one in a vein on the dorsum of the operative hand for the IVRA, and the second in the opposite hand for administering supplemental medications and fluids during the operation. After a pneumatic double tourniquet had been placed around the upper arm, the extremity was elevated and exsanguinated with an Esmarch bandage. The proximal cuff was then inflated to 250 mm Hg (or 100 mm Hg above the systolic blood pressure), and circulatory isolation of the arm was verified by inspection, absence of radial pulse, and loss of the pulse oximetry tracing in the ipsilateral index finger.

The IVRA was performed using 40mL of lignocaine 0.5% plus 2ml of the test solution and injected over 90 seconds by an anesthesiologist who was blinded to the group allocation. Sensory block was assessed every 30 seconds after injection of the lignocaine using a standardized pinprick technique with a 22-gauge short beveled needle. The patient's response was evaluated in the dermatomal sensory distribution of the medial and lateral antebrachial cutaneous, ulnar, median, and radial nerves. Motor function was assessed by asking the subject to flex and extend their wrist and fingers at 30 s intervals, and complete motor block was recorded when no voluntary movement was present. The onset time for sensory blockade is defined as the time elapsed from injection of the lignocaine until a complete sensory block was achieved in all dermatomes, and the onset time for motor blockade was the time elapsed from injection of lignocaine to achieving a complete motor block. When an adequate surgical block was achieved, the operative tourniquet (namely distal cuff) was inflated to 250 mm Hg and then the proximal cuff was released and the surgery was started. The HR, MAP and SpO_2 values were collected before and after tourniquet application, at 10 minutes intervals for 60 minutes after injection of the test solution; and after release of the tourniquet by an anesthesiologist who was unaware with the administered medication. The initial time to tourniquet pain, denoted as the time elapsed between the distal cuff inflation and the patient's first complaint of tourniquet pain, was recorded. Tourniquet-related pain was assessed using a visual analog scale (VAS), with 0 = no pain and 10 = worst pain imaginable. When the tourniquet pain score was >4, the patient was given intravenous bolus of fentanyl (0.5 µg/kg) that was repeated after 5 minutes if pain was not relieved. The total intraoperative fentanyl consumption was also calculated. At the end of surgery, tourniquet was deflated following a gradual deflation technique over 1-2 min. Sensory recovery time was reported as the time elapsed after tourniquet deflation until recovery of sensation in all dermatomes using pinprick at 30 s intervals. Motor block recovery time was marked as the time elapsed after tourniquet deflation until full movement of the fingers. The time until the initial analgesic requirement was recorded as the time elapsed after tourniquet release until the patient's first request for analgesics. Patients were given diclofenac, 75 mg intramuscular if the pain VAS was >4, and the total diclofenac consumed was calculated. All the evaluations were carried out by an observer who was unaware with the patient's group allocation. The incidence of nausea, vomiting, skin rash, tachycardia (HR >100 bpm), bradycardia (HR <50 bpm), hypotension (MAP <60 mm Hg), hypertension (MAP >120 mm Hg), headache, dizziness, tinnitus, and hypoxemia (SpO_2 <90%), in

addition to any surgical complications during the first postoperative 24 hours were recorded.

Statistical analysis. Sample size was selected to detect a mean reduction of 20% in the tourniquet tolerance time. Seventeen patients in each group were required based on type I error of 0.05 and type II error of 0.20. Power analysis was based on the study of hospital data of intravenous regional anesthesia. Data were tested for normal distribution using the Kolmogorov-Smirnov test. Except for gender and the incidence of complications which were analyzed using Chi-square test, data were expressed as the mean ± SD and analyzed by one-way analysis of variance (ANOVA) test, and the differences were then calculated by post hoc testing (Newman-Keuls test). The p value of <0.05 was considered significant. Analysis was performed using the Statistical Package for Social Sciences Version 6.0 for windows (Statsoft, Inc).

Results. Twenty patients were included in each group. Among the patients, none was excluded from the study because of technical failure. No treatment was needed for hypotension or bradycardia in any patient. Saturation of oxygen in arterial blood flow (SpO_2) (96% mean value throughout the study) was always within the clinically acceptable range. Patients in the 3 groups did not differ as regard the demographic or operative data (**Table 1**). The surgical procedures were matched in the 3 groups. There were no statistical differences in the HR, MAP and SpO_2 at any intraoperative and postoperative period between the groups. As shown in **Table 2**, the onset of sensory block was signficantly shorter in the groups T100 and T50 compared with the control group ($p<0.001$). Sensory recovery time and motor onset and recovery times were not different between the groups. The initial time to tourniquet pain was signficantly longer in group T100 compared with the control group ($p<0.05$). In the T100 group, the total dose of fentanyl administered was significantly lower than the control group ($p<0.05$). The duration of postoperative analgesia was significantly longer in the group T100 compared with the control group. However, this was not translated as a reduction in the postoperative consumption of diclofenac, which was similar in the 3 groups. One patient in the control group and 3 patients in each of the tramadol groups had postoperative nausea or vomiting necessitating treatment with granisetron one mg intravenously.

Discussion. The results of this study confirmed the local anesthetic properties of tramadol. Our main findings showed that tramadol 100mg addition to lidocaine for IVRA was the favorable dose since it reduced the onset time of sensory block, increased the initial time to tourniquet pain, decreased the intraoperative

Table 1 - Demographic data and operative characteristics (N=20 each group).

Parameter	Control group	T50 group	T100 group	*P* value
Age (years)	34.1 ± 10.5	31.3 ± 8.4	34.9 ± 11.7	0.52
Gender (Male/Female)	16/4	18/2	14/6	0.28
Weight (kg)	76.3 ± 7.9	73.4 ± 6.0	71.4 ± 6.3	0.08
Duration of surgery (min)	49.2 ± 12.6	44.5 ± 8.8	47.1 ± 9.9	0.42
Tourniquet time (min)	59.8 ± 12.3	54.7 ± 10.8	57.9 ± 9.4	0.33

Data are mean ± SD (except for Gender). Group T50 and group T100 are groups that received tramadol 50 mg and 100 mg respectively.

Table 2 - Characteristics of the block and postoperative analgesia (N=20 each group).

Parameters	Control group	T50 group	T100 group	P value
Onset time of sensory block (min)	7.6 ± 1.4	5.2 ± 1.2*	4.9 ± 1.2*	<0.001
Onset time of complete motor block (min)	14.3 ± 4.5	13.6 ± 4.0	13.1 ± 4.0	0.633
Onset time of tourniquet pain (min)	42.0 ± 7.7	46.5 ± 9.4	51.3 ± 10.8*	0.011
Intraoperative fentanyl requirements (µg)	63.3 ± 39.5	52.5 ± 32.4	32.8 ± 35.2*	0.042
Sensory block recovery time (min)	4.4 ± 1.3	4.3 ± 1.4	4.6 ± 1.2	0.819
Complete motor block recovery time (min)	4.9 ± 1.2	4.7 ± 1.1	5.0 ± 1.4	0.639
Duration of postoperative analgesia (min)	125 ± 54	160 ± 81	215 ± 85*	0.001
Postoperative diclofenac consumption (min)	124 ± 55	113 ± 52	98 ± 43	0.263

Data are mean ± SD. *$p<0.05$ in comparison with the control group.
Group T50 and group T100 are groups that received tramadol 50 mg and 100 mg.

fentanyl consumption, and prolonged the time to first postoperative analgesic request. Our results agree with Alayurt et al[10] reported that tramadol 100mg added to lidocaine for IVRA shortened the onset of sensory block, enhanced the tourniquet tolerance and extended the intraoperative analgesia similar to sufentanil and clonidine. Also, Acalovschi et al[9] found that tramadol 100mg added to lidocaine for IVRA in volunteers resulted in a faster onset time of sensory block. On the contrary, Langlois et al[11] demonsterated that the same additive and dosage did not decrease the tourniquet pain or prolong the postoperative analgesia. However, the tourniquet inflation time in their study was shorter (proximal tourniquet 21 ± 4, distal tourniquet 27 ± 4 min) than in our study (51.3 ± 10.8 min) and the study of Alayurt et al,[10] where it was 52 ± 15 min. The incidence and intensity of the tourniquet pain is correlated with the duration of application and a longer tourniquet inflation time could have revealed the analgesic effect of tramadol.[12] Moreover, this contradiction can be explained by the marked interindividual and interethnic variability of the cytochrome P450 enzyme (CYP2D6) activity which is the major metabolic isoform for oxidation of tramadol.[13] Tramadol is a central analgesic with an opioid agonist activity with some selectivity formu-receptors.[4] Also, it inhibits norepinephrine uptake and stimulates serotonin release intrathecally, which are transmitters in the descending pathways which enhance analgesia.[4,5] Several experimental and clinical studies have shown that tramadol might have a potential peripheral local anesthetic effect.[14-16] Tsai et al[14] demonstrated the blockage of neural conduction by the direct application of tramadol on sciatic nerves of rats. Pang et al[15] showed that tramadol significantly reduced propofol injection pain and produces a local anesthetic effect following intradermal injection.[15,16] Altunkaya et al[6] concluded that tramadol 5% has a local anesthetic effect similar to prilocaine 2% when used intradermally for excision of cutaneous lesions. Explanations for the local anesthetic action of tramadol remain unclear. Mert et al[17] compared the nerve conduction blockade by tramadol and a local anesthetic and concluded that tramadol has a local anesthetic activity similar to lignocaine.[17] Moreover, Güven et al[18] demonstrated that tramadol may block K+ channel more than lignocaine. A further experimental study suggests that the nonspecific voltage dependent K+ channels and the nitrergic system might have a role in the antinociceptive effect of tramadol.[19] A recent experimental study suggested that tramadol acts on voltage dependent Na+ channels like local anesthetics and adrenergic pathways, like vasoconstrictors as mechanisms of local tramadol effects.[20]

Tourniquet-related pain is a main factor limiting the extensive use of IVRA techniques in surgical procedures involving the extremities.[21] This distress may be caused via multiple factors including neuropathic pain produced by nerve compression stimulation of the nerve endings in the cutaneous tissue,[22] skeletal muscle ischemia,[23] and local metabolic changes.[24] Tramadol may be effective in the management of tourniquet pain since it has been successfully used in the treatment of neuropathic pain.[25] In addition, it has been found that it is more effective than morphine in relieving severe ischemic pain in an experimental study on rats.[26]

This study had few limitations. Although our findings suggested that a local mechanism could be at least partly responsible for the analgesic effect of tramadol added to lignocaine during IVRA, it is still possible that tramdol analgesic effect occurs through systemic absorption. In addition, we did int measure plasma tramadol level. Further studies are required to compare groups receiving tramadol either systemically or added to IVRA and measure its plasma level may help to clarify this issue. Our study confirmed the favourable effects of tramadol as an adjuvant to lignocaine for IVRA. Tramadol 100 mg was the effective dose that shortened the onset of sensory block, improved patient's tolerance of tourniquet and reduced the intraoperative analgesic consumption.

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