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ORIGINAL ARTICLE

Quality of lidocaine analgesia with and without midazolam for intravenous regional anesthesia

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Abstract
Purpose Midazolam has analgesic effects mediated by gamma aminobutyric acid-A receptors. This study was designed to evaluate the effect of midazolam on anesthesia and analgesia quality when added to lidocaine for intravenous regional anesthesia (IVRA).
Methods Forty patients undergoing hand surgery were randomly assigned to two groups to receive IVRA. The control group received 3 mg/kg lidocaine 2% w/v diluted with saline to a total volume of 40 ml, and the midazolam group received an additional 50 μg/kg midazolam. Sensory and motor block onset and recovery times, tourniquet pain, intraoperative analgesic requirements, sedation, and anesthesia quality were recorded. Postoperative pain and sedation scores, time to first analgesic requirements, analgesic use in the first 24 h, and side effects were noted.
Results Sensory and motor block onset and recovery times did not differ significantly between groups. Tourniquet pain scores were lower at 10, 15, 20, and 30 min ($P < 0.0001$) in the midazolam group. Three (15%) patients in the midazolam group required fentanyl for tourniquet pain compared with thirteen (65%) patients in the control group ($P = 0.02$). Patients in both groups received fentanyl once. Midazolam group showed that significantly less patients required diclofenac for postoperative analgesia ($P < 0.01$) and analgesic-free period during first postoperative 24 h was significantly longer (726.8 ± 662.8 min vs. 91.0 ± 35.9 min, $P < 0.0001$). Postoperative pain scores were lower ($P < 0.0001$) and sedation scores higher ($P < 0.05$) for the first 2 h in the midazolam group.
Conclusion Addition of midazolam to lidocaine for IVRA improves anesthesia quality and enhances intraoperative and postoperative analgesia without causing side effects.

Keywords Anesthetic techniques · Regional IV · Lidocaine · Midazolam

Introduction

Intravenous regional anesthesia (IVRA) is simple and effective for extremity surgery. However, IVRA has been limited by tourniquet pain and its inability to provide postoperative analgesia. Various adjuvant drugs have been evaluated in conjunction with local anesthetics to improve IVRA block quality with variable results [1, 2]. Midazolam, a benzodiazepine derivative, has analgesic effects mediated by gamma aminobutyric acid-A (GABA-A) benzodiazepine receptors in the spinal cord [3]. GABA receptors have also been found in peripheral nerves [4–6]. Midazolam reduces A-delta- and C-fiber-evoked activity [7]. Intra-articular administration of midazolam decreased postoperative pain after arthroscopic knee surgery [8]. Midazolam combined with bupivacaine improved analgesia quality when used in brachial plexus block [9, 10]. The addition of midazolam to lidocaine for IVRA has not been studied. This study was designed to evaluate the effect of midazolam on anesthesia and analgesia quality when added to lidocaine for IVRA. The primary aim was to assess

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tourniquet pain. The secondary aims were to assess intraoperative and postoperative pain and sedation, anesthesia quality, and onset and recovery times of sensory and motor block.

Materials and methods

Forty American Society of Anesthesiologists (ASA) physical status I–II patients scheduled for hand and forearm surgery (i.e., carpal tunnel, trigger finger, tendon release) were included in this prospective, randomized, and double-blinded study. Written informed patient consent and ethical committee approval was obtained. Exclusion criteria included patients with Raynaud disease, sickle cell anemia, chronic pain syndromes, psychological disorders, epilepsy, leukemia, autoimmune disease, diabetes, pregnant or breast-feeding women, ingestion of any analgesic or sedative 24 h before surgery, or a history of any drug allergy. Patients were allocated randomly into two groups according to a sealed envelope technique in a double-blind manner. No premedication was given. After the patients had been taken to the operating room, mean arterial blood pressure (MAP), peripheral oxygen saturation (SpO_2), and heart rate (HR) were monitored. Two cannulae were placed: one in a dorsal vein of the operative hand and the other in the opposite hand for crystalloid infusion. The operative arm was elevated for 2 min then exsanguinated with an Esmarch bandage; a double-cuff pneumatic tourniquet was then placed around the upper arm, and the proximal cuff was inflated to 250 mmHg (at least 100 mm Hg above the systolic blood pressure for all patients).

Circulatory isolation of the arm was verified by inspection, absence of radial pulse, and loss of pulse oximetry tracing in the ipsilateral index finger. IVRA was achieved with 3 mg/kg lidocaine 2% w/v diluted with normal saline to a total volume of 40 ml in the control group ($n = 20$) [2] or with 50 μg/kg midazolam plus 3 mg/kg lidocaine 2% w/v diluted with normal saline to a total volume of 40 ml in the midazolam group ($n = 20$). The solution was injected over 90 s by an anesthesiologists blinded as to group assignments. The sensory block was assessed by a pinprick performed with a 22-gauge short-beveled needle every 30 s. Patient response was evaluated in the dermatomal sensory distribution of the medial and lateral antebrachial cutaneous, ulnar, median, and radial nerves. Sensory block onset time was defined as the time elapsed from injection of drug to loss of pinprick sensation in all nerve distributions. The motor block was assessed objectively as follows: finger abduction (ulnar nerve), opposition of thumb to each finger (median nerve), and wrist and hand extension (radial nerve). Motor blockade was assessed on a 3-point scale (0 = normal finger motility, 1 = decrease motility, 2 = complete motor blockade). The motor block onset time was the time elapsed from injection of drug to complete motor block.

After sensory and motor blocks were achieved, the distal tourniquet was inflated to 250 mmHg and the proximal tourniquet was released. MAP, HR, SpO_2, subjective pain assessment using a numerical rating score (NRS) from 0 (no pain) to 10 (worst pain), and degree of sedation (scale 1–5; 1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, 5 = asleep but not responsive to any stimulus) [11] were monitored before and at 1, 5, 10, 15, 20, and 30 min after distal tourniquet inflation. These variables were measured after release of tourniquet and postoperatively at 1, 2, 4, 6, 12, and 24 h. When pain due to tourniquet was ≥4 on the NRS, patients were given fentanyl 1 μg/kg, which was repeated after 5 min if pain was not improved, and the number of patients requiring fentanyl was recorded. No additional sedative drugs were given during the intraoperative period. At the end of the operation, patients were asked to qualify the operative conditions, such as tourniquet pain or incisional pain, according to the following numeric scale: excellent (4) = no complaint from pain; good (3) = minor complaint with no need for supplemental analgesics; moderate (2) = complaint that needed a supplemental analgesic; and unsuccessful (1), patient was given general anesthesia. At the end of the operation, the surgeon who was blinded to group assignment was asked to qualify the operative conditions according to the following numeric scale: 0 = unsuccessful; 1 = poor; 2 = acceptable; 3 = good; and 4 = excellent [2].

The tourniquet was not deflated before 30 min and was not inflated more than 1 h. At the end of surgery, tourniquet deflation was performed by the cyclic deflation technique [the tourniquet was deflated three times with fixed periods of deflation (10 s) separated by 1 min periods of reinflation]. Sensory recovery time was defined as the time elapsed after tourniquet deflation up to recovery of pain in all dermatomes determined by pinprick test. Motor block recovery time was the time elapsed after tourniquet deflation up to finger movement.

Patients were administered diclofenac, 75 mg i.m., at 8-h intervals if the NRS pain score was >4. Analgesic-free period during first postoperative 24 h (the time elapsed after tourniquet release to first patient request of analgesic) was recorded. All evaluations were performed by an anesthesiology resident blinded as to the study group assignments. Headache, dizziness, skin rash, nausea, vomiting, and other side effects were recorded through 24 postoperative hours. A sample size of 20 patients per group was determined to be adequate to demonstrate a 25% reduction in tourniquet pain scores with $\alpha = 0.05$ and power of 80% [12]. The statistical evaluation was done by SPSS 10.0 for Windows (SPSS Inc.,

Chicago, IL, USA). Independent samples Student's t test was used to evaluate demographic data, intraoperative and postoperative hemodynamic data, time of onset and recovery of sensory and motor block, and operation and tourniquet duration. Z test was used to compare independent groups for proportions. The Mann–Whitney U test was used for intraoperative and postoperative NRS pain scores and sedation scores, analgesia duration, and anesthesia quality. Analysis of variance for repeated measures was performed on NRS pain scores, followed by Bonferroni test for multiple comparisons. Complications and operation type were compared with Fisher's exact test. Significance was determined at the $P < 0.05$ level.

Results

All 40 patients completed the study. Both groups had similar characteristics and operation data (Table 1). There was no significant difference between groups as regards MAP, HR, and SpO_2 at any intraoperative or postoperative period.

Sensory and motor block onset and recovery times were not significantly different between the two groups ($P > 0.05$; Table 2). NRS scores for tourniquet pain were significantly decreased in the midazolam group ($P < 0.0001$) at 10, 15, 20, and 30 min after tourniquet inflation (actual P value = 0.0001; Table 3). Three (15%) patients in the midazolam group required fentanyl for tourniquet pain compared with thirteen (65%) in the control group ($P = 0.02$). Patients in both groups received fentanyl once. No patient suffered from incisional pain during the intraoperative period in either group. Anesthesia quality [median (range)] as determined by the patient [4 (3–4) vs. 3 (3–4)] and the surgeon [4 (3–4) vs. 3 (2–4)] was statistically better in the midazolam versus control group ($P = 0.01$ and 0.003, respectively; Table 4).

Table 1 Patient characteristics and operative data

	Midazolam group ($n = 20$)	Control group ($n = 20$)
Age (Years)	42.5 ± 13.2	45.3 ± 12.6
Gender (M/F)	14/6	13/7
Weight (Kg)	78.2 ± 9.4	76.4 ± 10.5
Operation time (min)	34.1 ± 6.5	32.5 ± 8.6
Tourniquet time (min)	45.6 ± 7.4	43.9 ± 9.3
Types of surgical operation (carpal tunnel/trigger finger/tendon release)	14/5/1	12/6/2

Values are number or mean ± standard deviation

No significant differences were found between the two groups

Table 2 Onset and recovery times of sensory and motor block

	Midazolam group ($n = 20$)	Control group ($n = 20$)
Sensory block onset time (min)	4.7 ± 1.3	5.4 ± 1.4
Sensory block recovery time (min)	4.2 ± 1.2	3.7 ± 1.1
Motor block onset time (min)	4.9 ± 1.4	5.7 ± 1.5
Motor block recovery time (min)	4.6 ± 1.3	4.0 ± 1.2

Values are mean ± standard deviation

No significant differences were found between the two groups

Postoperative NRS pain scores were significantly lower ($P < 0.0001$) for the first postoperative 2 h in the midazolam group (actual P value = 0.006; Table 3). The time to first postoperative analgesic request was significantly longer ($P < 0.0001$) in the midazolam group (726.8 ± 662.8 min) compared with the control group (91.0 ± 35.9 min). Eleven patients in the midazolam group and 20 in the control group required diclofenac for postoperative

Table 3 Intraoperative and postoperative pain scores

	Midazolam group ($n = 20$)	Control group ($n = 20$)
Before tourniquet	0	0
After tourniquet		
1 min	1 (0–2)	1 (0–2)
5 min	1 (0–2)	1 (0–3)
10 min	1 (0–3)*	3 (1–4)
15 min	1 (0–3)*	3 (1–5)
20 min	1 (0–3)*	3 (1–5)
30 min	2 (1–4)*	3 (2–5)
After surgery		
1 h	1 (0–3)*	3 (1–5)
2 h	2 (0–4)*	3 (2–5)
4 h	3 (1–4)	3 (2–4)
6 h	3 (1–4)	3 (2–4)
12 h	2 (0–3)	2 (1–3)
24 h	1 (0–2)	1 (0–3)

Values are median (range)

* $P < 0.0001$ compared with the control group

Table 4 Quality of anesthesia assessed by patients and surgeon

	Midazolam group ($n = 20$)	Control group ($n = 20$)
Quality of anesthesia (patient)	4 (3–4)*	3 (3–4)
Quality of anesthesia (surgeon)	4 (3–4)**	3 (2–4)

Values are median (range)

* $P = 0.01$, ** $P = 0.003$ compared with the control group

pain ($P < 0.01$). The 11 (55%) patients in the midazolam group received diclofenac only once compared with 16 (80%) in the control group who received diclofenac once and four (20%) who received diclofenac twice although there was no significant difference. Postoperative sedation score values [median (interquartile range)] were significantly higher at both 1 and 2 h after surgery in the midazolam group [2 (2–3) vs. 1 (1–1) and 1 (1–2) vs. 1 (1–1), respectively] ($P < 0.05$) compared with the control group. No patient in the midazolam group required assistance for airway maintenance due to sedation. Intraoperative sedation scores did not differ between groups. No adverse effect was seen through the 24-h study period in either group; only three patients in the control group had nausea that required antiemetic treatment.

Discussion

The results of our study revealed that the addition of 50 μg/kg midazolam to lidocaine for IVRA decreases tourniquet pain, improves anesthesia quality, and reduces intraoperative and postoperative analgesic consumption without causing side effects. Tourniquet pain is a common problem complicating the use of a pneumatic tourniquet during surgical procedures involving the upper or lower limb [13]. Neuropathic pain produced by nerve compression plays an important role in the etiology of this discomfort [14]. The role of A-delta fibers and unmyelinated C fibers may be considered to be involved in tourniquet pain [15]. Moreover, the pneumatic tourniquet causes ischemia, which distorts nerve penetration by oxidative stress and affects blood–nerve barrier [16]. Benzodiazepines tend to suppress afferent evoked excitation in the substantia gelatinosa and motor horn, leading to an antinociceptive effect [17, 18]. Spinal administration of the GABA-A receptor agonists, muscimol and isoguvacine, attenuate behavioral allodynia and hyperalgesia after nerve injury [19]. The effect of midazolam on the GABAergic system might make it effective in alleviating neuropathic pain [7, 20, 21]. Koninen and Dickenson [7] demonstrated that midazolam reduced A-delta and C-fiber-evoked activity and reversed cold and mechanical allodynia after spinal nerve ligation. Midazolam-induced analgesia has also been linked to a non-μ-opioid mechanism, possibly via k-opioid receptors [22]. Moreover, midazolam exerts some antioxidant activity in vitro as measured by their protection of fluorescence decay of B-phycoerythrin [23]. Clinical studies have demonstrated an enhanced analgesic effect from midazolam when administered by the centroneuraxial route in combination with bupivacaine [24–26]. Batra et al. [8] demonstrated that intra-articular administration of midazolam reduced postoperative pain after day-case arthroscopic knee surgery. The addition of midazolam to bupivacaine for brachial plexus block quickened the onset of sensory and motor blocks and improved postoperative analgesia as manifested by lower pain scores, prolonged effect, and reduced requirements for rescue analgesics [9, 10].

This study showed that the addition of 50 μg/kg midazolam to lidocaine for IVRA enhanced intraoperative analgesia and improved anesthesia quality. This could be explained by the peripheral effect of midazolam as the tourniquet placement prevents whole-body distribution of midazolam through the bloodstream. The occurrence of sedation and enhanced postoperative analgesia after tourniquet deflation in the midazolam group could be explained by the systemic effect of midazolam in addition to the peripheral analgesic effect. In an animal model, systemically administered midazolam had antinociceptive effects on acute thermal-, acute mechanical-, and acute inflammatory-induced nociception [27]. Shrimali et al. [28] reported that midazolam given IV provides excellent analgesia for patients undergoing transrectal ultrasound-guided prostatic biopsy.

In our study, sensory and motor block onset times were shorter and recovery times prolonged in the midazolam group compared with the control group, but the differences did not reach statistical significance. A higher dose of midazolam could elicit a greater effect. Sajedi and Islami [29] showed that midazolam can improve the duration of sensory and motor blocks of lidocaine in a single epidural administration and demonstrated that the 5-mg dosage works better than the 3-mg dosage. The selected dose of midazolam used in our study was based on previous studies with no side effects detected [9, 10]. Further studies are required to evaluate the effect of varying doses of midazolam in other types of orthopedic surgical procedures and different peripheral techniques.

In conclusion, the addition of 50 μg/kg midazolam to lidocaine for IVRA improves the anesthesia quality and enhances intraoperative and postoperative analgesia without causing side effects.

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