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Effectiveness and safety of rocuronium or nitroglycerin plus ropivacaine on pain during intravenous regional anesthesia: A double-blind randomized controlled trial

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ABSTRACT

Objective: To compare the effects of adding rocuronium and nitroglycerin to ropivacaine in intravenous regional anesthesia (IVRA) on pain and hemodynamic parameters.

Methods: This randomized controlled trial was done in 2023. Participants were 177 candidates for forearm operation surgery under IVRA selected from Valiasr Hospital, Arak, Iran. They were allocated by block randomization to three different groups, namely nitroglycerin group, rocuronium group and control group. Hemodynamic parameters were recorded before tourniquet application up to postoperative recovery time. Sensory block and motor block onset and duration and pain were also evaluated. The data analysis was carried out by IMB SPSS software 20.0.

Results: 177 Eligible patients were included in study, with 59 in each group. Time to sensory and motor block onset in the nitroglycerin group was significantly less than the other groups and the time of motor block in the rocuronium group was statistically higher than the control and the nitroglycerin groups ($P<0.001$). Seven participants in the nitroglycerin group experienced headache and three from the rocuronium group experienced dizziness. The side effects occurrence in the nitroglycerin group was more prevalent than in the control and rocuronium groups ($P=0.009$).

Conclusions: Nitroglycerin significantly reduces the time to sensory and motor block onset, while rocuronium is more effective in prolonging the time of motor block. Although there is no difference between nitroglycerin and rocuronium respecting the pain score and opioid need administration, nitroglycerin is associated with a higher prevalence of medication side effects. Therefore, both nitroglycerin and rocuronium can be used as adjuvant for IVRA. The final choice

relies on patients' conditions and anesthesiologists' judgment.

KEYWORDS: Rocuronium; Nitroglycerin; Ropivacaine; Pain; Hemodynamic; Regional anesthesia; Intravenous anesthesia

1. Introduction

Intravenous regional anesthesia (IVRA) was developed first by Karl A. Bier as a safe, simple, and reliable method for minor

Significance

There is limited information about the combination effect of nitroglycerine and rocuronium with ropivacaine for intravenous regional anesthesia (IVRA). The combination of nitroglycerine with ropivacaine, significantly reduces the time to sensory and motor block onset in IVRA and the combination of rocuronium with ropivacaine is more effective in prolonging the time of motor block. Both nitroglycerin and rocuronium can be used as adjuvant therapy with ropivacaine in IVRA.

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surgeries, particularly applying to hand and forearm surgeries. Its rapid onset, high success rate, rapid recovery, and high controllability have turned IVRA into an appropriate anesthesia option for outpatients. The success rate of IVRA is 94%-98%[1, 2].

However, the most important limitation of IVRA is tourniquet pain after tourniquet deflation, particularly in prolonged surgeries[3,4]. Moreover, the toxic reaction of venous blockage may occur due to the incidental and unpredicted deflation of the tourniquet during surgery[5,6].

Different studies assessed the effects of adding medications such as morphine sulphate, meperidine, magnesium sulphate, ketorolac, dexmedetomidine, and ketamine to IVRA solution to prolong the duration of analgesia[3]. Some studies also assessed the analgesic effects of cutaneous nitroglycerine[7,8] and intravenous nitroglycerine in IVRA[9]. For example, Sen *et al.* reported that adding nitroglycerine to lidocaine better reduced pain in trigger finger, carpal tunnel, and tendon release surgeries[9]. Abbasivash *et al.* also found that intravenous nitroglycerine added to lidocaine for IVRA shortened the time to sensory and motor block onset and reduced tourniquet and postoperative pain without causing any complications[10]. Similarly, some studies reported that nitroglycerin increased the effects of anesthetic agents without significantly increasing the prevalence of complications, particularly hemodynamic complications[11-13]. Moreover, Moshiri *et al.* study on patients with forearm surgeries showed that dexmedetomidine shortened the duration of sensory and motor block onset, lengthily the duration of the motor block, and decreased postoperative pain and need for analgesics, while its effectiveness in reducing pain was more than nitroglycerin[11].

Rocuronium is a muscle relaxation drug for general anesthesia to relax airway muscles and facilitate endotracheal intubation for surgeries. It inhibits acetylcholine binding to cholinergic receptors at the motor end plate and its effects can be reversed using acetylcholine esterase inhibitors like pyridostigmine, neostigmine, and edrophonium[14,15]. Lapisatepun *et al.* found that adding rocuronium to lidocaine for upper limb IRVA can decrease the motor block onset duration and increase anesthesia quality beyond any considerable complication[16].

Previous studies mostly assessed the effects of nitroglycerine and rocuronium added to lidocaine and bupivacaine and there is limited information about the effects of these medications in combination with ropivacaine for IVRA. Therefore, we conducted the current study to narrow this gap. This study aims to evaluate the effectiveness of adding rocuronium and nitroglycerin to ropivacaine on pain and hemodynamic status for IVRA.

2. Patients and Methods

2.1. Study setting

A double-blind randomized clinical trial was carried out in 2023. Participants were 177 candidates for forearm surgery under IVRA. They were selected from Valiasr Hospital, Arak, Iran. The study flowchart was shown as Figure 1.

2.2. Ethical consideration

All included patients signed the written informed consent and the protocol of study is taken the Ethics Committee approval of Arak Medical University, Iran (code: IR.ARAKMU.REC.1402.033). In addition, this study is authorized by the Iranian Registry of Clinical Trials (No.IRCT20141209020258N183).

2.3. Inclusion criteria and exclusion criteria

Inclusion criteria were an age of 20-65 years, candidacy for forearm surgery, ASA I or II physical status based on American Society of Anesthesiologists (ASA) classification, consent for participation in the study, no allergy to the medications, no cyanosis in the afflicted hand, no substance abuse, no contraindication for intravenous anesthesia, just one bone fracture, and no affliction by Raynaud's disease, sickle cell anemia, neurological disorders in the forearm, and chronic pain syndrome. Exclusion criteria were a surgery duration of more than ninety minutes (which could lead to the complications of prolonged tourniquet use), a surgery duration of less than 35 minutes (which was associated with short tourniquet use), and ineffectiveness or termination of IVRA for any reason.

2.4. Intervention

After measuring and documenting vital signs and arterial oxygen saturation, two intravenous lines (through the dorsal veins of the afflicted and the non-afflicted forearms) were established for the administration of crystalloid solutions. Initially, midazolam 2 milligrams was administered as premedication and a double tourniquet was applied 3-4 centimeters above the elbow, the patient's arm was held up for two minutes for blood depletion, Esmarch bandage was used, the tourniquet cuff was blown up around 100 mmHg more than the baseline systolic pressure or 250 mmHg, and detached Esmarch bandage[17]. After ensuring pulse absence using a pulse oximeter, participants were randomly allocated to three groups (*i.e.*, control, nitroglycerin, and rocuronium) *via* block randomization method and the size of each block was considered six.

IVRA was induced using nitroglycerin 200 micrograms (Caspian Tamin Co, Iran) and 0.2% ropivacaine (Molteni Co., Italy) in

the nitroglycerin group (10) and rocuronium 0.06 milligrams per kilogram of body weight and 0.2% ropivacaine in the rocuronium group (13). The administration dose of ropivacaine in all groups was 35 milliliters (*i.e.*, 70 milligrams). The dose of the adjuvant medication was increased to five milliliters using distilled water. In the control group, 35 milliliters of 0.2% ropivacaine and five milliliters of normal saline were administered. Thus, the total volume of the medications in all groups was forty milliliters. The medications were administered through the intravenous catheter.

The onset of sensory block was checked every thirty seconds using a 22-gauge needle (pinprick). The response of patients in the sensory dermatome of interior and exterior biceps, ulnar, median, and radial nerves was assessed. Motor block was assessed by asking the patient to open and close his/her hand. The inability to perform any intentional motion in the limb was defined as an exact motor block. The sensory block time onset was the duration of the medication administration to the achievement of complete sensory block in all above-mentioned dermatomes. The duration of motor block onset was also considered as the distance between the administration of medications to the achievement of a complete motor block. After the complete sensory and motor block, the distal tourniquet was blown up to 250 mmHg, the tourniquet was exhausted, and the operation began.

Heart rate, means arterial blood pressure and oxygen saturation (SpO₂) were continuously assessed and documented before

tourniquet application up to the time of postoperative recovery. Any case of analgesia insufficiency was documented and alternative anesthesia methods were used. The tourniquet was never deflated before 35 minutes from its inflation and was not kept inflated for more than ninety minutes. If a surgery lasted more than ninety minutes, the patient was excluded from the study and underwent general anesthesia. After the surgery, the tourniquet was inflated using the intermittent method, and the time of sense regression (*i.e.*, the time interval between tourniquet deflation to pain sensation in response to painful stimuli inducted using a 22-gauge needle), the time of motor regression, and the time of the need for analgesia were measured and documented. The pain was assessed from tourniquet inflation to the end of surgery using a visual analogue scale. Subjects who have pain scores higher than 4, received fentanyl 1 microgram per kilogram of body weight, and the time of the first fentanyl administration was documented. After tourniquet deflation, pain was assessed every thirty minutes for two hours and then, every two hours for twelve hours. During the postoperative period, patients with a pain score of more than 4 received 25 milligrams of intramuscular pethidine and the time and the dose of pethidine administration were documented. An anesthesiologist administered the medications and an anesthesiology resident student who was unaware of the group assignment performed IVRA and the effects of the medications were recorded. Participants were also unaware of the group assignment and hence, the study was double-blind.

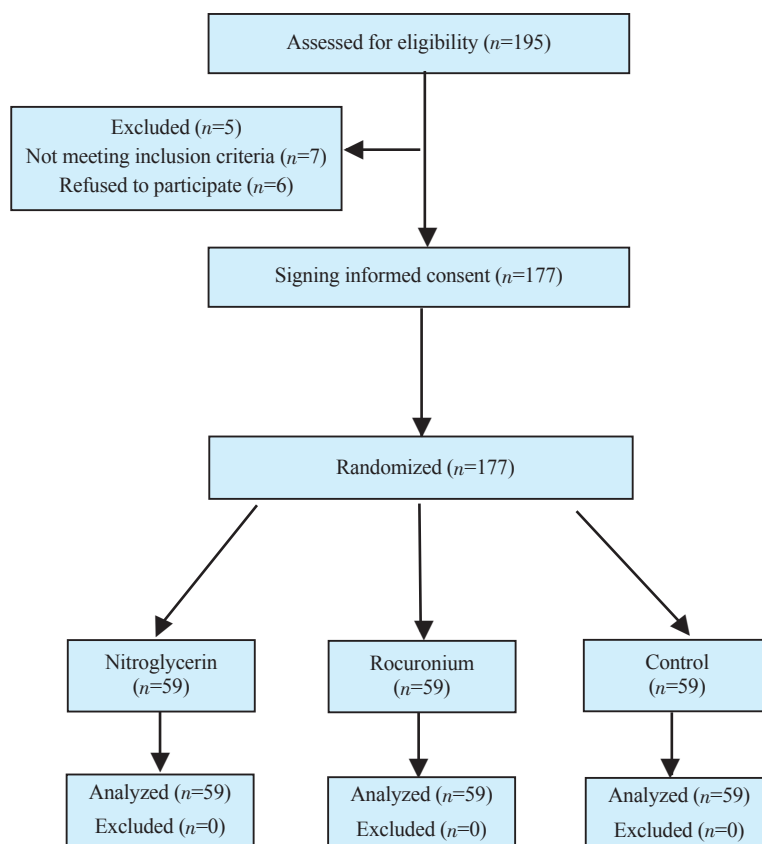


Figure 1. CONSORT diagram showing the flow of participants through each stage of a randomized trial.

2.5. Statistical analysis

The data were analyzed via the IBM SPSS 22.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics methods were used for data description, while the one-way analysis of variance was applied to compare three groups regarding quantitative variables. A repeated measurement test was used to compare the within-group differences and the complication occurrence and opioid consumption in patients in different groups compared by *Chi-square* tests.

3. Results

This randomized clinical trial was conducted on 177 subjects with forearm surgery selected from Valiasr Hospital, Arak, Iran. Participants' age range was 20-56 years with a mean of (34.19 ± 7.24) years and the mean of their body mass index was 21.88 ± 1.87 . Most of them were male (57.6%; $n=102$). No significant differences were observed among the studied groups respecting participants' age, sex, arterial oxygen saturation, heart rate, and blood pressure ($P>0.05$) (Table 1).

The groups significantly differed from each other respecting the time to sensory block onset and the time to motor block onset ($P=0.001$). In the nitroglycerin and the rocuronium groups, the duration of sensory block onset was significantly lower and the duration of sensory block was significantly higher than the control group ($P<0.05$). Moreover, the interval to sensory block onset in the nitroglycerin group was lower than the rocuronium group ($P=0.001$), while no significant difference was observed among the three groups respecting the time of sensory block ($P=0.941$) (Table 2). In addition, the three groups significantly differed from each other respecting the time to motor block onset and the time of motor block ($P=0.001$). In the nitroglycerin and the rocuronium groups, the time to motor block onset was significantly lower and the duration of motor block was significantly higher than the control group ($P<0.05$). Moreover, the time to motor block onset in the nitroglycerin group was shorter than the rocuronium group while the duration of motor block in the rocuronium group was significantly longer than the nitroglycerin group ($P<0.05$).

Table 1. Participant characteristics.

Parameters	Nitroglycerin group ($n=59$)	Rocuronium group ($n=59$)	Control group ($n=59$)
Age, years	34.2 ± 7.1	34.2 ± 7.3	34.2 ± 7.5
Body mass index, kg/m^2	21.8 ± 1.9	21.9 ± 1.9	21.4 ± 1.9
Baseline blood pressure	95.8 ± 7.0	96.0 ± 6.0	95.8 ± 7.0
Baseline heart rate	92.3 ± 7.2	92.7 ± 6.6	92.5 ± 7.2

Data are expressed as mean $\pm$ SD. Body mass index (BMI) is calculated as weight in kilograms divided by height in meters squared.

Three groups were similar statistically concerning the mean score of pain at all measurement time points ($P<0.05$), while for six and eight hours after tourniquet deflation ($P>0.05$). The pain score in the nitroglycerin and the rocuronium groups was significantly lower than the control group ($P<0.05$), while the mean score of pain in nitroglycerin and rocuronium groups was not statistically different ($P>0.05$) (Table 3).

A postoperative opioid administration was significantly different among the groups respecting ($P=0.001$). Postoperative opioid administration in the nitroglycerin and the rocuronium groups was similar and was significantly lower in the control group ($P=0.001$) (Table 4). Moreover, study groups significantly differed from each other respecting the prevalence of the side effects of the medications used in the study ($P=0.009$). The side effects occurrence in the nitroglycerin group were significantly more prevalent in the control group and the rocuronium groups with seven cases of headache, while there were only three cases of dizziness in the rocuronium group. No side effects were reported in participants of dizziness in the control group (Table 4).

4. Discussion

The current double-blind randomized clinical trial was carried out on patients with forearm surgery to compare the combination effects of rocuronium and ropivacaine versus nitroglycerin and ropivacaine for IVRA on pain and hemodynamic parameters status. Findings showed that nitroglycerin significantly reduced the duration of sensory and motor block onset, while the duration of motor block in the rocuronium group was significantly longer. Moreover, nitroglycerin and rocuronium groups were similar regarding to mean score of pain, while the side effects incidence in the nitroglycerin group was more than the rocuronium group. These findings imply that both nitroglycerin and rocuronium are recommended with caution as adjuvant to local anesthetics in IVRA. Of course, the final choice varies according to patients' conditions and anesthesiologists' judgment.

In agreement with our findings, Moshiri *et al.* compared the combination effects of dexmedetomidine, granisetron, and nitroglycerin with ropivacaine for IVRA in forearm surgeries. Their findings showed that dexmedetomidine significantly decreased the time to sensory and motor block onset, prolonged the duration of sensory and motor blocks, reduced pain, and reduced the need for opioid analgesics during the 24 hours after surgery. They also found that nitroglycerin significantly reduced pain and the need for opioid analgesics, but the effects of dexmedetomidine were greater than nitroglycerin[11]. Similarly, our findings indicated that nitroglycerin significantly reduced the duration of sensory and motor block onset, while the motor block onset duration was calculated greater in the

rocuronium group. The mean score of pain did not show a significant difference in the nitroglycerin and rocuronium groups, but the side effects occurrence was more prevalent in the nitroglycerin group.

Rahimzade *et al.* assessed the effectiveness of intravenous nitroglycerin infusion on postoperative pain score among patients with lower limb orthopedic surgeries and concluded that low-dose nitroglycerin can be used for the control of postoperative pain among patients without any underlying disease as an adjuvant drug[13]. Barazandeh *et al.* also assessed the effects of a combination effect of nitroglycerin and lidocaine for IVRA on pain score and

hemodynamic parameters among patients with upper limb surgeries. They concluded that nitroglycerin improves the effects of anesthetic medications without significantly increasing the prevalence of complications, particularly hemodynamic complications[18]. Moreover, Lapisatepun *et al.* study to assess the effects of rocuronium added to lidocaine for upper limb IVRA and found that it decreased the time to motor block onset and increased the anesthesia quality without causing any serious complications[16].

Goodman *et al* study compared the degree of pulpal anesthesia acquired by lidocaine plus epinephrine combination with lidocaine

Table 2. Group comparison respecting the means of sensory block and motor block onset and duration.

Parameters	Nitroglycerin group (n=59)	Rocuronium group (n=59)	Control group (n=59)	F	P
Sensory block time to block onset, minutes	5.2±0.8	6.0±0.7	7.7±0.8	172.4	0.001
Sensory block duration of block, minutes	121.2±5.1	121.1±4.8	117.6±6.5	8.0	0.001
Motor block time to block onset, minutes	1.2±0.5	1.7±0.6	1.4±0.5	217.6	0.001
Motor block duration of block, minutes	111.2±6.6	121.0±7.4	107.2±6.5	82.2	0.001

Data are expressed as mean±SD; One-way analysis of variance is used.

Table 3. Group comparison respecting the mean score of pain.

Parameters	Nitroglycerin group (n=59)	Rocuronium group (n=59)	Control group (n=59)	F	P
After tourniquet inflation	1.2±0.5	1.4±0.5	1.7±0.6	10.6	0.001
15 minutes after surgery onset	1.2±0.4	1.3±0.4	1.5±0.5	5.1	0.007
30 minutes after surgery onset	1.2±0.4	1.3±0.4	1.4±0.5	4.9	0.009
45 minutes after surgery onset	1.1±0.3	1.2±0.4	1.4±0.5	7.9	0.001
Immediately after tourniquet deflation	1.7±0.5	1.6±0.5	1.9±0.5	6.3	0.002
30 minutes after tourniquet deflation	1.8±0.4	1.8±0.5	2.1±0.6	7.1	0.001
60 minutes after tourniquet deflation	2.1±0.1	2.0±0.1	2.4±0.5	27.5	0.001
90 minutes after tourniquet deflation	2.2±0.4	2.2±0.4	2.6±0.5	15.7	0.001
120 minutes after tourniquet deflation	2.6±0.5	2.6±0.5	3.1±0.3	23.6	0.001
4 hours after tourniquet deflation	3.2±0.4	3.2±0.4	3.7±0.6	19.8	0.001
6 hours after tourniquet deflation	4.2±0.6	4.2±0.6	4.3±0.6	0.6	0.550
8 hours after tourniquet deflation	4.3±0.4	4.3±0.4	4.4±0.5	1.3	0.278
10 hours after tourniquet deflation	4.3±0.5	4.3±0.5	4.1±0.3	5.6	0.004
12 hours after tourniquet deflation	4.1±0.3	4.1±0.3	4.3±0.5	7.3	0.001

Data are expressed as mean±SD; One-way analysis of variance is used.

Table 4. Group comparison respecting the prevalence of opioid analgesic use.

Parameters		Nitroglycerin group (n=59)	Rocuronium group (n=59)	Control group (n=59)	F	P
Opioid use, n (%)	Not applied	3 (5.1)	3 (5.1)	0 (0.0)	14.3	0.001
	25 milligrams	54 (91.5)	54 (91.5)	48 (81.4)		
	50 milligrams	2 (3.4)	2 (3.4)	11 (18.6)		
Side effects, n (%)	No side effect	51 (86.4)	56 (94.9)	59 (100.0)	18.1	0.009
	Headache	7 (11.9)	56 (94.9)	59 (100.0)		
	Dizziness	1 (1.7)	3 (5.1)	0 (0.0)		

Chi-square test is used.

plus epinephrine plus meperidine and epinephrine in IAN blocks. They concluded that adding meperidine to a standard lidocaine solution is not effective for inferior alveolar nerve block[19]. Furthermore, Abbasivash *et al.* examined the combination effects of nitroglycerin and lidocaine in IVRA and reported that it shortened the time to sensory and motor block onset and reduced tourniquet pain and postoperative pain without increasing the risk of complications[10]. Sen *et al.* study assessed the analgesic effects of nitroglycerin added to lidocaine for IVRA and found that it significantly improved sensory and motor block and reduced pain while no serious complication was reported[9].

Nitroglycerin is metabolized in the liver to nitric oxide. Nitric oxide rises the intracellular concentration of cyclic guanosine monophosphate and thereby, causes the dilation and relaxation of the smooth muscles of the vessels and moderates pain in the peripheral and central nervous systems[8,13,20,21]. Nitrates also block nociception and the neural components of inflammatory edema and thereby, exert analgesic and anti-inflammatory effects. Moreover, they may directly stimulate peripheral fibers through imitating the actions of acetylcholine[22,23]. Rocuronium is a non-depolarizing neuromuscular blocker and is used to treat musculoskeletal paralysis, facilitate endotracheal intubation, and improve surgical conditions during general anesthesia[24,25]. Although its exact mechanism of action is still unknown, its possible mechanisms of action include the stimulation of nociceptors through changing osmolality or pH and the stimulation of the statement of indigenous inflammatory intermediaries such as histamine and kinin[2,15,16].

This study was exposed to some limitations. The recruitment of patients with eligibility criteria was the most important limitation of this study and it taken time for authors. In addition, we did not follow the patients for assessment of long time complications.

Therefore, authors suggest that future studies for evaluation the long time effect and complications of these combinations.

In conclusion, Nitroglycerin shortens the duration of sensory and motor block onset in IVRA, while rocuronium has a longer motor block. Their analgesic effects are similar, while the side effects of nitroglycerin are more than rocuronium. Therefore, both nitroglycerin and rocuronium can be used as adjuvant for IVRA, though the final choice depends on patients' conditions and anesthesiologists' judgment.

Conflict of interest statement

The authors report no conflict of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding authors upon request.

Authors' contributions

All authors worked in manuscript drifting and final approval. SA: Work in data collection and data analysis. HM: Work in

study concept and design, management, data collection. EM: Work in study concept and design, management, data collection. AK: Analysis and interpretation of data, critical revision of the manuscript for important intellectual content. SYS: Statistical analysis and interpretation of data.

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