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# THE EFFICACY OF ACETAMINOPHEN ADMINISTRATED INTRAVENOUSLY FOR PREVENTION OF ROCURONIUM ASSOCIATION PAIN WITHDRAWAL RESPONSE

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## ABSTRACT

**Background:** Withdrawal movement during rocuronium injection is a common adverse effect. Rocuronium-associated injection pain/withdrawal response occurred frequently when injection intravenously during anesthesia induction. Many studies had reported that pretreating with antipyretic analgesics (AAs) could reduce the occurrence of RAIPWR, but there was no consensus yet. **Aim of the study:** The aim of this study was to compare the efficacy of IV acetaminophen and IV lidocaine, with tourniquet, for the prevention of withdrawal movement from rocuronium injection. Also examine the incidence and degree of movement after the administration of rocuronium. **Methods:** This randomized Double Blind study enrolled 60 American Society of Anesthesiologists (ASA) I-II patients undergoing general anesthesia and positive pressure ventilation. They were randomly assigned to three treatment groups. After occluding venous drainage using a tourniquet on the upper arm, the saline group received 5 ml of 0.9% sodium chloride solution, the lidocaine group received(5 ml) 40 mg of lidocaine, and the acetaminophen group received (5 ml) 50 mg of acetaminophen. The tourniquet was released after 120 seconds and anesthesia induction was performed using propofol 2 mg/kg followed by rocuronium 0.6 mg/kg. The withdrawal movement was graded on a four-point scale. **Results:** Statistical analysis was done using SPSS shown significant reduction of Rocuronium-associated injection pain/withdrawal response to 40% in acetaminophen group, and to 35% in lidocaine group. The incidence of RAIPWR reach 75% in our study. **Conclusion:** Patients received 40 mg (0.2% lidocaine 5 ml) less withdrawal movement than patents received (acetaminophen) 50 mg (5 ml). in other hand both group (lidocaine, acetaminophen) less withdrawal movement than placebo group. So acetaminophen and lidocaine reduced the incidence of withdrawal movement after rocuronium injection compared with saline.

**KEYWORDS:** Lidocaine, Rocuronium, general anesthesia, acetaminophen, withdrawal response.

## INTRODUCTION

We have observed that, IV injection of rocuronium after the induction of anesthesia is often associated with hand or arm withdrawal or may soon extends to generalized movement[1], which suggests the presence of intense nociception even under anesthesia.[2]

When the drug given intravenously, it causes intense discomfort and pain and withdraw of limbs of the patients. The incidence of this adverse effect has been report ed to be as high as 50-80 % in adults[3] and the estimated incidence in children up to 80 %.[4]

As the pain due to rocuronium injection is early in onset with short duration and no recurrence during repeated injections, it has been suggested that this pain is associated with local irritant effect[1], thus local anesthetic effect of lidocaine (used in this study in comparison with acetaminophen) might be useful for preventing this pain.

Although the mechanism by which rocuronium causes pain is the subject of speculation, the triggering of a local kinin cascade by kininogen released from the vein walls has been implicated in this pain.[5] Prostaglandins may enhance the action of the products of the kinin cascade on nociceptors present in the vasculature[6], include direct activation of nociceptors by the low pH also have been postulated.

Peripheral veins are innervated with polymodal nociceptors[7] which mediate the response to the injection of certain anesthetics that cause pain.

Recently, Blunk et al.[8] concluded that the algogenic effect of amino-steroidal neuromuscular blocking drugs could be attributed to a direct activation of C-nociceptors in the nerve endings.

The mechanism of rocuronium-induced pain remains obscure, although various theories have been postulated. These include direct activation of nociceptors by the low pH or non- physiological osmolality, or activation via the local release of endogenous mediators such as kinin.[9]

However, Borgeat and Kwiatkowski[10] showed that patients, who received normal saline adjusted to pH 4.0, reported no pain. Tuncali et al.[11] showed that undiluted (10 mg/ml) rocuronium caused significant pain on injection compared to diluted rocuronium with 0.9% NaCl to (0.5 mg/ml), although the osmolality of both preparations did not differ significantly. These results render causes associated with pH or osmolality unlikely. Instead, an enzymatic cascade, possibly the local kinin cascade triggered by kininogen, is suspected of being the likely mechanism. According to Borgeat and Kwiatkowski[10] the nature of the pain with rocuronium (e.g. immediate, short-duration pain with a marked decrease in severity with repeated administration) probably reflects a direct irritant effect on the kinin cascade.

## PATIENTS AND METHODS

After approval by the Scientific Committee of the Arabic board of medical specialization in anesthesia and intensive care, and the Committee of Karbala Health Department, a prospective, randomized, double-blinded study of 60 patients were undergoing general elective surgery. The study was done within the period of 5 months from 1st of April 2022 to 31st of August 2022. Patients aged 18-60 years, of ASA physical status I and II.

After through pre- anesthetic evaluation to 60 patients in current study, the procedure was explained to each of them prior to surgery and informed consent was taken. These patients were divided into three groups, each group has 20 patients. No one of these patients has taken premedication before general anesthesia.

### Inclusion criteria

- Age (18 - 69 years).
- Patients ASA physical status I &II.
- Elective surgery under general anesthesia which require muscle relaxant.

The study was approved by local committee of the scientific council of anesthesia & intensive care, data were enrolled using a preconstructed form sheet, a detailed history was taken from each patient, clinical examination was performed & vital signs was measured.

When they reached the operation room, standard monitoring with non-invasive devices such as electrocardiogram, non-invasive arterial pressure, and pulse oximeter. An 20 gauge venous cannula was kept at the largest vein in dorsum of the nondominant hand. After taping the IV catheter, we ensured of the suitable place IV cannula by rapid flow of IV fluid for 5 minutes (Ringer lactated 100 ml).

After 5 minutes, the infusion was stopped and the arm with the I.V. line was elevated for 15 seconds for gravity drainage of venous blood. After occluding venous drainage using a rubber tourniquet on the upper arm, the patients were treated with test drug. The test drug administered within 10 seconds.

All the patients in the three groups received one volume (5ml) as normal saline in group I, 40 mg (0.2% lidocaine), preservative free, in group II and 50mg in of acetaminophen in group III.

After 2 minutes, the rubber tourniquet was released and induction of anesthesia was performed with propofol 2 mg/kg was injected within 10-15 seconds and after that we checked unconsciousness (as assessed by no verbal response and loss of eyelash reflex). After loss of consciousness 0.6mg /kg of rocuronium was injected over 5 seconds. During and after injection of rocuronium, we monitored the patients movement as a result of pain by a study blinded investigator.

Withdrawal movement was graded in to four grades[12]

- Grade 1: without movement.
- Grade 2: movement reported in response to pain as movement in wrist joint.
- Grade 3: movement reported in response to pain as movement in elbow and shoulder joint.
- Grade 4: severe pain (pain reported in response to movement in lower limb or generalized movements, cough or breathing holding.).

The anesthesia continued with an appropriate technique, and 24 hours after the operation, the injection site was checked for pain, edema, wheal, or flare response.

Statistical analyses with (SPSS 13.0 for windows, SPSS) were performed using a statistical package for social sciences.

Data are presented as a mean or number of patients. Demographic data were analyzed using the X2 test and one-way analysis of variance.

## RESULTS

There were 60 patients under go general surgery enrolled in this study assigned into three groups with 20 patients in each one, the demographic criteria of the studied

groups are shown in (Table 1). No statistically significant differences show between both groups in age or ASA classification, (P> 0.05). Furthermore, the mean age was 39.3 ±12.1 (range: 20 – 50) years in the studied group of acetaminophen and it was 36.6 ± 10.7 (range: 20 – 51) years in the lidocaine group. Regarding the gender, females were predominant in both groups.

**Table 1: demographic criteria of the studied groups.**

| | | Group | | | p-Value |
|---|---|---|---|---|---|
| | | **Acetaminophen (No.=20)** | **Lidocaine (No.=20)** | **Placebo (No.=20)** | |
| Age (years) | <29 | 4 (23.5%) | 5 (29.4%) | 8 (47.1%) | 0.6 |
| | 30-39 | 6 (40%) | 5 (33.3%) | 4 (26.7%) | |
| | 40-49 | 5 (26.3%) | 8 (42.1%) | 6 (31.6%) | |
| | >50 | 5 (55.6%) | 2 (22.2%) | 2 (22.2%) | |
| Age (Mean ± SD) | | 39.3 ± 12.1 | 36.6 ± 10.7 | 33.7 ± 10.9 | 0.3 |
| Gender | Male | 7 (28%) | 5 (20%) | 13 (52%) | 0.03 |
| | Female | 13 (37.1%) | 15 (42.9%) | 7 (20%) | |
| ASA | I | 11 (27.5%) | 13 (32.5%) | 16 (40%) | 0.2 |
| | II | 9 (45%) | 7 (35%) | 4 (20%) | |
| Past medical Hx | Negative | 11 (28.2 | 13 (33.3%) | 15 (38.5%) | 0.4 |
| | Positive | 9 (42.9%) | 7 (33.3%) | 5 (23.8%) | |
| BMI (Mean ± SD) | | 28.7 ± 3.2 | 27.6 ± 1.8 | 27.1 ± 2.7 | 0.1 |
| Weight (kg) (Mean ± SD) | | 75.3 ± 10.5 | 69.85 ± 7.2 | 73.45 ± 8.8 | 0.1 |

**Table 2: The Incidence and Characteristics of Withdrawal Movement Associated with Injection of Rocuronium.**

| | **No response** | **Wrist joint** | **Elbow joint** | **Lower limb** | **p-Value** |
|---|---|---|---|---|---|
| Acetaminophen | 12 (60%) | 8 (40%) | 0 | 0 | <0.001 |
| lidocaine | 13 (65%) | 7 (35%) | 0 | 0 | <0.001 |
| placebo | 5 (25%) | 8 (40%) | 5 (25%) | 2 (10%) | 0.072 |

As it shown in (Table 2), 12 patients (60%) in the Acetaminophen group and 13 patients (65 %) in lidocaine group, and 5 patients (25%)in placebo group had grading with no response to rocuronium withdrawal; additionally the 8 patients (40%) in the Acetaminophen group and 7 patients (35 %) in lidocaine group, and 8 patients (40%)in placebo group had grading 2 with wrist joint response to rocuronium pain injection, in both comparison its clearly there is no elbow joint grade three or lower limb grade four in both acetaminophen and lidocaine group but still in placebo group 25% and 10%. (p- value >0.05).

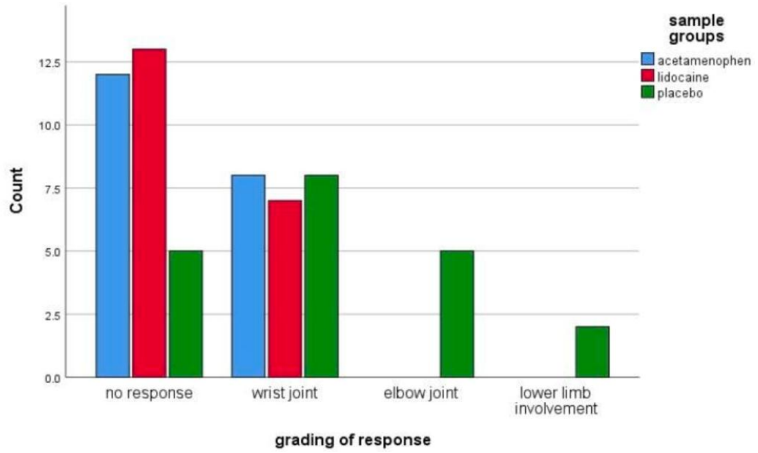


**Figure 1: The Incidence and Characteristics of Withdrawal Movement Associated with Injection of Rocuronium.**

**Table 3: The Incidence and Characteristics of Withdrawal Movement Associated with Injection of Rocuronium (comparison of acetaminophen and placebo groups).**

| | | Group | | p-Value |
|---|---|---|---|---|
| | | **Acetaminophen** | **Placebo** | |
| Grading | I (No Response) | 12 (60%) | 5 (25%) | 0.02 |
| | II (Wrist joint) | 8 (40%) | 8 (40%) | |

| | | | | |
|---|---|---|---|---|
| | III (Elbow joint) | 0 | 5 (25%) | |
| | IV (lower limb) | 0 | 2 (10%) | |

As it shown in (Table 3); none of the patients in acetaminophen group had grading three or four, compared to 5 (25%) 2 (10 %) in placebo patients, and the difference was statistically significant, (P = 0.02).

**Table 4: The Incidence and Characteristics of Withdrawal Movement Associated with Injection of Rocuronium (comparison of acetaminophen and lidocaine groups).**

| | | Group | | p-Value |
|---|---|---|---|---|
| | | Acetaminophen | lidocaine | |
| Grading | I (No Response) | 12 (60%) | 13 (65%) | 0.7 |
| | II (Wrist joint) | 8 (40%) | 7 (35%) | |
| | III (Elbow joint) | 0 | 0 | |
| | IV (lower limb) | 0 | 0 | |

As it shown in (Table 4); the withdrawal movement nearly same frequent among patients in lidocaine group compared to acetaminophen group; 12 patients (60%) in acetaminophen group had grade one compared to 13 patients (65%) in lidocaine group, (P< 0.7). Similarly grade two was reported in 8 patients (40%) in acetaminophen group and 7 (35%) in lidocaine group, (P < 0.7).

## DISCUSSION

It was demonstrated in previous studies that pain associated with I.V. injection of anesthetic agents and withdrawal movements because of this pain led to problems during anesthesia induction. Generalized movements in unconscious patients have caused gastric regurgitation and pulmonary aspiration have been reported.[13] In pediatric patients, the loss of established vascular access and subcutaneous fat tissue thickness require re-cannulation of thin vessels and this can lead to difficulties.[14]

In current study: There is no statistically significant differences had been shown between groups in the age or ASA classification (p>0.05) Regarding the gender; the female were predominant in both groups. In current study none of the patients in acetaminophen and lidocaine groups had grade three or four movement. The difference was statistically significant (p=0.007); so the patients who received acetaminophen or lidocaine were less likely had moderate or severe movement. This supported by a study done by Abbott FV, Hellemans AT 2000 showed the analgesic effect of acetaminophen reflect central and peripheral action, also is supported by a study done at 2013 and another one done at 2010 by Hillstrom C, Jakobsson demonstrated that usage of paracetamol with venous occlusion reduce the incidence of limbs involvements after rocuronium injection.

The Rocuronium-associated injection pain withdrawal Response were significantly less frequent in acetaminophen group & more frequent in placebo groups in more than one grade.

This is supported by a study done at 2015 by Prasai et al who suggested that rocuronium injection causes hand or limb withdrawal or generalized movements in 85% of patients without use of pretreatment drugs, which suggests the presence of intense nociception even under general anesthesia.

Abbott and Hellemans[15] showed the analgesic effect of acetaminophen reflect central &peripheral actions.

25% in placebo group had grade three 0% in Acetaminophen, 10% in placebo group had grade four 0% in Acetaminophen.

There was no statistically significant differences Acetaminophen group and lidocaine in grading of movement.

In this study, acetaminophen pre-treatment with venous occlusion significantly reduced the incidence of rocuronium induced withdrawal movement from 75% in saline group to 40% in acetaminophen group similar to the 35% after lidocaine administration. This suggest that acetaminophen pretreatment also attenuate withdrawal movement during rocuronium injection to the same extent as lidocaine. This is supported by a study done in 2019 by Dr Adim Parasi in Nepal revealed that lidocaine is more effective for reducing the rocuronium associated pain withdrawal movements than acetaminophen.

Different modalities on prevention of pain associated rocuronium injection have been attempted, including the use of local anesthetic drugs, opioids, ondansetron, ketamine, paracetamol, sodium bicarbonate and nitrous oxide.

In current study, we use lidocaine intravenously to prevent this pain. As the pain after rocuronium injection is early in onset and no recurrence during repeated injections, it has been suggested that this pain is associated with local irritant, thus the local effect of lidocaine might be useful for preventing this pain.[16] Cheong et al showed in August 2010 that there was a decrease in pain on rocuronium injection from 77% to 37% and 10% when lidocaine was given before rocuronium at doses of 20 mg & 40 mg respectively.[17]

This study demonstrate that 13 patients (65%) did not experience pain, which is similar to Binarani et al[18] at 2017 and also to study done at 2019 in Nepal MED COLL. By Adim Parasi & Abha Parasi. Who found that 78% of patient who received intravenous lidocaine do not experience pain.

One possible explanation when we give lidocaine to them, the patients will be in much more depth of local anesthesia. As a result they will be less withdrawal movement in lidocaine group. On the other hand the lidocaine has local anesthetic effect on the reduction of the pain at the injection site.

The venous occlusion technique is suitable for studying the peripheral action of pretreatment drugs with local effect such as lidocaine, ondansetron and tramadol[4], but it is not useful drugs that act centrally such as morphine or fentanyl because it prevents the delivery of the drugs to the site where they act. So tourniquet is used to minimize rocuronium injection pain,[16] Shevchenco et al[12] showed pretreatment with lidocaine and venous occlusion decrease the incidence of withdrawal movement to 46%. This study was done by Shevchenco Y at 2010.

Moorthy and Dierdorf[19] stated at 2000 that there will be extreme pain "as burning" if the patient received priming dose of rocuronium (10% of induction dose) before intravenous induction of GA for awaken patient.

The writers reported that the pain can be decreased by giving IV lidocaine to these patients.

Lee et al[5] showed at 2007 that acetaminophen selectively suppresses peripheral PG E2 release and increase COX-2 gene expression in a clinical model of acute inflammation.

Hinz et al showed at 2008 that acetaminophen inhibits COX-2 activity in human blood cells and suppress PG E2 generation in human blood monocytes. Thus, acetaminophen inhibition of PG E2 may influence the intensity of rocuronium injection pain and withdrawal movements.

Memis D & Turkan A[16] showed in 2002 that pretreatment of lidocaine with venous occlusion was more effective than ondansetron, tramadol or fentanyl.

I.V. acetaminophen shows a systemic analgesic effect in 10 minutes, so we used rubber tourniquet. That is easy to use, but it may have inconsistent pressure for different patients, a potential limitation of this study.

Lidocaine, a local anesthetic, reversibly blocks peripheral nerve pathways by blocking excitable membranes and its commonly used to reduced pain and withdrawal movements after injection to 28-40%.[15] It is easily available, cheap and safe to use intravenously and help to decrease the pain. Here lidocaine pretreatment decrease withdrawal movement to 35%. We did not find complications after pretreatment, and pain after I.V. injection of acetaminophen is detected in 2-4% of patients with no any other complications could be mentioned.

In conclusion, pretreatment with acetaminophen (50 mg) reduce the incidence of rocuronium–induced withdrawal movement as much as lidocaine.

## CONCLUSION

Patient received 40 mg (0.2 % lidocaine 5 ml) had shown less withdrawal movement than patents received (acetaminophen) 50 mg (5 ml). in other hand both group (lidocaine, acetaminophen) had less withdrawal movement than placebo group.

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