COMPARISON OF THREE METHODS OF PREVENTING ROCURONIUM INDUCED PAIN ON INJECTION USING VENOUS OCCLUSION TECHNIQUE

- A Randomized Prospective Double Blind Controlled Study –

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Abstract

Background: Intravenous administration of rocuronium bromide causes pain at the site of injection in most patients. The mechanism that leads to this side effect is still unknown and multiple drugs' pretreatments were used to prevent its occurrence with varying success rates.

Purpose: The study aimed to evaluate the effects of the pretreatment with lidocaine, fentanyl, and remifentanil using a venous occlusion technique in preventing pain caused by intravenous injection of rocuronium during induction of general anesthesia.

Method: Two hundred patients, ASA I-II, requiring various types of surgical procedures under general anesthesia with muscle relaxation and mechanical ventilation, were enrolled. Patients were pre-educated to report pain severity on rocuronium injection on a 4-point severity scale. Patients were allocated randomly using sealed envelopes method into one of four pretreatment groups: (Xylocaine group, 50), Remifentanyl group 50), (Fentanyl group, 50), and (Normal saline group, 50). After venous occlusion, study drugs were injected and the venous occlusion was maintained for one minute. Rocuronium was then administered and patients were asked to report their pain score.

Results: Compared to control group, all pretreatment drugs were effective in reducing pain on rocuronium injection. Xylocaine was the most effective (Mean difference-1.42, $P < 0.001$), followed by Remifentanil (Mean difference-1.32, $P < 0.001$) and Fentanyl (Mean difference-0.50, $P < 0.001$) in reducing pain on rocuronium injection. Remifentanil was statistically comparable to Xylocaine ($P = 0.820$) and both drugs were superior to Fentanyl in reducing pain on rocuronium injection.

Conclusion: Remifentanyl is a better choice of opioid in preventing pain on rocuronium injection using venous occlusion technique than fentanyl, with efficacy comparable to Xylocaine.

Keywords: Fentanyl; Lidocaine; Pain; Remifentanil; Rocuronium Bromide.

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Introduction

Pain on intravenous injection of rocuronium bromide during induction of general anesthesia is common and occurs in 50-80% of patients[1-4]. Unfortunately, the mechanism of this pain is not fully understood yet. Different modalities for the prevention of pain on injection of rocuronium have been tried with different rates of success; including the use of local anesthesthetic drugs[5,6], opioids[6], ondansterone[6], magnesium[7], ketamine[8], and ketorolac[9]. Dilution of rocuronium solution and slow injection rate were also suggested as effective techniques[10]. However the best modality to control pain on rocuronium injection is still controversial.

The aim of our study is to evaluate and compare the effect of pretreatments with Lidocaine, Fentanyl, or Remifentanil in preventing pain caused by intravenous rocuronium injection in patients during induction of general anesthesia using a 60-second venous occlusion technique.

Methods

This study was conducted at University of Jordan Hospital, Amman, Jordan, between September, 2008 and October, 2009. Ethical approval was provided by the Research and Ethics Committee at the Faculty of Medicine-University of Jordan (Institutional Approval Number 11/2006-2007). Verbal consent was considered adequate by the committee. Participation was voluntary and anonymity and confidentiality of patients were ensured. Adult patients scheduled for surgery under general anaesthesia and requiring muscle relaxation were considered for enrolment. A 4-point Likert scale of pain assessment was used to classify reported pain on Rocuronium injection as follows: 0 when there is no pain, 1 if the pain is mild, 2 for moderate pain, and 3 if their pain is severe. Two hundred patients, ASA I-II, were enrolled in the current study. Patients were allocated randomly using sealed envelopes method into one of four groups: the first group (n = 50) was given Remifentanil 1mcg/kg, the second group (n = 50) was given Fentanyl 1mcg/kg and the third group (n = 50) was given 2 ml of Lidocaine 2% (40 mg). All study drugs' solutions were prepared in normal saline in a total volume of 5 ml. The fourth (control) group (n = 50) was given normal saline 5 ml. Exclusion criteria included patients who were not cooperative, those with history of allergy to study drugs, patients having chronic pain, those who received analgesics in the pre-operative period, and patients with difficult intravenous access.

At the end of the preoperative assessment visit, volunteering for enrollment in the study was suggested to each patient after detailed explanation of its aims and procedural aspects. Consenting patients were educated and instructed in the following manner: the patients were told that after insertion of an intravenous cannula at the dorsum of the hand in the operating theatre, an inflatable tourniquet will be applied 5 cm proximal to the intravenous cannula and its pressure will be gradually increased until cessation of flow of the crystalloid solution. After that they will be given anesthetic drugs, and one of these drugs might cause discomfort or even pain at the site of injection. They were taught to quantify the severity of any pain they might feel according to the mentioned 4-point likert scale.

After arrival to the operating theatre and before induction of anesthesia, patients instructions were reviewed a second time. After establishment of monitoring an 18G Venflon® intravenous cannula (BD, Haryana, India) was inserted in one of the large veins at the dorsum of the hand or forearm. A Lactated Ringer's crystalloid solution was mounted and free flow through the venous catheter was ensured. The tourniquet was then applied as mentioned above. The study drug solutions were pre-prepared in 5-ml syringes and kept at room temperature. The drug solutions were unknown to the administering anesthetist who was instructed to inject the prepared drug over 5 seconds. Venous occlusion was released after 60 seconds. The room anesthetist was then asked to administer a 0.6 mg/kg dose of Rocuronium at rate of 0.5 ml per second. Immediately and while the patient is awake, the prime investigator asked the patient whether he/she suffered any pain on Rocuronium injection and to quantify it if any. Pain score was then registered and the anesthesthetic in charge of the patient was asked to proceed with the induction of anesthesia.

Table 1

Summary of Demographic characteristics of study sample

Pretreatment group	Age	Sex (M/F)	BMI
Remifentanyl	41.8 (16.55)	19/31	26.92 (5.41)
Fentanyl	46.4 (14.31)	20/30	26.88 (5.48)
Xylocaine	40.6 (14.65)	14/36	27.03 (4.33)
Normal saline	40.92 (13.20)	15/35	27.48 (4.88)

Values for Age and BMI are in mean (SD)

Statistical Analysis

An effect size of 0.3 reduction in pain score was considered clinically significant. At a study power (β) of 0.8 and statistical significance level (α) of 0.05, a sample size of 150 was found to be the minimum number of patients needed for the study[11]. Statistical analysis was performed using SPSS software (version 19.0.0; SPSS Inc., Chicago, Illinois, USA). Data were analyzed using descriptive statistics to summarize demographic characteristics of study participants using frequencies for categorical variables and mean ± *SD* for continuous ones. The occurrence of pain among different study groups was summarized using frequencies in terms of counts and within-group percentages and Pearson Chi-square test was used to test the differences between study groups. Analysis of variances with post hoc multiple group analysis was used to test the differences of mean pain scores between different pretreatment groups.

Results

Two hundred patients aged 18-70 years (132 females) were enrolled in the study. Study groups were comparable in their demographic characteristics Table 1. Summary of the distribution of study results is cross-tabulated in Table 2 based on ultimate occurrence of pain sensation. In total, 144 patients reported pain on Rocuronium injection: 30 in the Remifentanil group, 42 in the Fentanyl group, 23 in the Xylocaine group, and 49 in the saline group.

Results of specific pain scores in different drug groups are shown in Table 3. Freedom from pain on injection was highest in the Xylocaine group (54%)

Table 2

Summary count distribution of ultimate pain sensation frequencies based on drug group, gender and age group

	Age Group																
Drug Group	**18-40 yr**				**41-60 yr**				**>60 yr**				**Subtotals**				**Total**
	Pain		**No Pain**		**Pain**		**No Pain**		**Pain**		**No Pain**		**Pain**		**No Pain**		
	M	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	*M*	*F*	
Remifentanyl	7	8	2	9	4	5	1	3	2	4	3	2	13	17	6	14	50
Fentanyl	5	10	0	1	5	13	2	3	5	4	2	0	15	27	4	4	50
Xylocaine	2	8	3	15	2	8	1	3	3	0	4	1	7	16	8	19	50
Normal Saline	15	5	2	1	3	18	1	0	1	1	3	0	19	24	6	1	50
Total	29	31	7	26	14	44	5	9	11	9	12	3	54	84	24	38	200

Table 3
*Distribution of pain scores in different treatment groups**

		DRUG GROUP				Total
		Remifentanyl	Fentanyl	Xylocaine	Saline	
Pain Score	No Pain	20 (40%)	8 (16%)	27 (54%)	1 (2%)	56
	Mild Pain	21 (42%)	17 (34%)	13 (26%)	13 (26%)	64
	Moderate Pain	8 (16%)	11 (22%)	8 (16%)	15 (30%)	42
	Severe Pain	1 (2%)	14 (28%)	2 (4%)	21 (42%)	38
	Total	50	50	50	50	200

* Frequencies are within-group counts and percentages.

followed by Remifentanil group (40%), Fentanyl group (16%), and normal saline group (2%). Analysis of variance of pain scores among different drug groups shows that all drug groups were effective in reducing the incidence of pain on injection of rocuronium when compared to Normal saline (P <0.001) (Table 4). Xylocaine and Remifentanil were both superior to Fentanyl in reducing pain on rocuronium injection with a slightly greater effect of Xylocaine (Mean difference -0.92, P <0.001) than Remifentanyl (Mean difference -0.82, P <0.001). Xylocaine was not significantly different than Remifentanyl in reducing pain (Mean difference 0.1, P = 0.582). Patients in the Fentanyl group had the highest frequency of severe pain (28%) and lowest frequency of mild pain (16%) (Table 3).

Among different age groups, the incidence of pain on injection of rocuronium was highest in the middle age group (81%), followed by young (68%) and then old age group (66%) (Table 2). Despite this order of pain frequency, chi square test analysis showed the differences to be statistically non-significant (P = 0.126). When comparisons were made across different drug groups the P value continued to reflect statistical non-significance and was lowest in the Xylocaine group (P = 0.079).

There was no statistically significant difference

Table 4
*Analysis of variance of pain scores among different drug groups**

(I) DRUG GROUP	(J) DRUG GROUP	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
REMMIIFENTNYL	FENTANYL	-.820	.182	<.001	-1.18	-.46
	XYLOCAINE	.100	.182	.582	-.26	.46
	SALINE	-1.320	.182	<.001	-1.68	-.96
FENTANYL	REMMIIFENTNYL	.820	.182	<.001	.46	1.18
	XYLOCAINE	.920	.182	<.001	.56	1.28
	SALINE	-.500	.182	<.001	-.86	-.14
XYLOCAINE	REMMIIFENTNYL	-.100	.182	.582	-.46	.26
	FENTANYL	-.920	.182	<.001	-1.28	-.56
	SALINE	-1.420	.182	<.001	-1.78	-1.06
SALINE	REMMIIFENTNYL	1.320	.182	<.001	.96	1.68
	FENTANYL	.500	.182	.006	.14	.86
	XYLOCAINE	1.420	.182	<.001	1.06	1.78

* Values <0.05 are statistically significant.

between male and female genders in terms of pain sensation (P = 0.882). This statistical non-significance was still valid when the two genders were compared across all drug groups.

No patient suffered from any local or systemic drug reaction and all patients were hemodynamically stable throughout their operations.

Discussion

There are several theories about the cause of pain on injection of some anesthetic drugs. A common perception in all is that activation of polymodal nociceptors leads to the release of endogenous mediators such as kinin, histamine, and bradikinin that mediate the pain response. The stimulation of the pain receptors is proposed to be caused by the unphysiological osmolality or pH of these drugs solutions[5,12-14]. Although rocuronium preparation is isotonic it has a pH of 4 which may explain its association with pain on intravenous injection[12].

Techniques of administration of pretreatment drugs used to prevent pain on rocuronium injection included direct intravenous injection[7,8,15,16], or intravenous injection that was preceded by venous occlusion for one minute or so[6,17]. None of the studies that adopted the venous occlusion technique included remifentanil as a study drug. Thus our study may be to our knowledge the first that tests remifentanil as a possible pretreatment drug of rocuronium induced pain on injection using the venous occlusion technique.

By limiting central spread of drugs, the venous occlusion technique will retain them in the target vein and make any observed effects exclusively local. Our results agree with previous studies using this technique in showing local anesthetic effect of opioid drugs. Opioid receptors are distributed throughout the body including vascular epithelium[18]. However, the mechanism of local anesthetic action of opioids can be either receptor mediated or possibly through nonspecific membrane conduction blocking effects that are shared by many other compounds[19,20]. This second mechanism is supported by the fact that the local anesthetic actions of opioid drugs are not revered by naloxone[21].

The difference in the effectiveness between remifentanil and fentanyl in our study in favor of remifentanil can be explained by the one-minute venous occlusion technique we used. Remifentanil has an onset of action time of around 1 minute compared to fentanyl (3-5 minutes). This time limit was unfavorable for fentanyl to establish its local effect. At physiologic pH, remifentanil (pKa 8.4) is 90% non-ionized compared to 33% for fentanyl (pKa 7.09) which explains remifentanil's faster onset. Xylocaine use for prevention of pain on injection of some anesthetic drugs is well established in literature[5]. It has an onset time of action that is comparable to remifentanil (45-90 seconds), and so the venous occlusion technique is not expected to delay the onset of its action. It is anticipated that venous occlusion will limit the drug dilution by stopping venous blood flow and providing transient stagnancy of the administered doses thus enhancing any local drug effects. Studies comparing remifentanyl and fentanyl administered in the usual way showed inconsistent results about the superiority of remifentanil over fentanyl in controlling pain on rocuronium injection[22,23]. The inconsistency in results is likely to be due to different timing of rocuronium injection after the pretreatment drugs in different studies that affected the onset of their central analgesic effects. The venous occlusion technique adopted in our study tests the peripheral local anesthetic effects of these two opioid drugs within one minute of containment. However, increasing the venous occlusion time longer to accommodate the time for onset of action of Fentanyl may give equal effectiveness of both drugs. This needs to be tested in further studies.

Studies of gender factor in the perception of pain on rocuronium injection had shown that the incidence of this type of pain is significantly higher in females[16]. Our study showed no significant differences between the two genders of patients. The difference between males and females may actually be stemming from central perception of pain, a process that is likely to have been blocked by the local analgesic effect of our study drugs. The same argument can be applied for the lack of significant difference among different age groups in our study. However, these concepts need to be addressed in specially designed studies.

Although propofol is known to be associated

with pain on injection, the venous occlusion technique adopted in our study and the administration of rocuronium and assessment of its associated pain on injection before the administration of propofol excludes any interactive effects from both drugs in causing the pain. Movement of the limb on injection of drugs associated with pain on injection was found to correlate with pain sensation[24]. As our patients were still conscious on administration of rocuronium, we did not include this assessment modality or other surrogate variables (e.g., heart rate and blood pressure) to test pain on rocuronium injection and relied on conscious reporting of pain sensation which we believe provides more objective assessment of pain. Surrogate variables are nonspecific and are also common in stage II anesthesia.

In conclusion, our study showed consistent results with previous studies regarding the effectiveness of xylocaine, fentanyl, and remifentanil in preventing pain on rocuronium injection. We have introduced the possible safe use of remifentanil for this purpose using the venous occlusion technique in a dose of 1mcg/kg with efficacy comparable to xylocaine. Further studies are encouraged to further test the validity of our results.

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