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The Analgesic Effect of Ondansetron when Added to Lidocaine for Intravenous Regional Anesthesia

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Abstract

Background: *Intravenous regional anesthesia (Bier'sblock) is a simple, reliable, excellent technique for short open surgical procedures and for closed reduction of bony fracture.*
Patients and methods: *Thirty patients were enrolled in this study and randomly divided into two groups , Group A (n=15)received IVRA lidocaine 3 mg/kg 2% diluted with isotonic saline to 0.5% concentration, Group B (n=15) received lidocaine 3mg/kg 2% plus Ondansetron diluted with isotonic saline to 0.5% concentration ,hemodynamic variables and VAS were recorded before and after tourniquet inflation, tourniquet pain, post-operative pain and first analgesic requirement time till 6 hours postoperatively were recorded .*
Results: *No significant difference in demographic data. There was significant decrease of tourniquet pain and post-operative pain in Group B and relatively increase in mean time of first post-operative needing to analgesia by 1.6 hours in Group B relative to Group A.*
Conclusions: *Adding 8 mg of Ondansetron to lidocaine in IVRAdecrease the tourniquet pain, post-operative pain, mean time for need of post-operative analgesia*

Keywords: *Intravenous regional anesthesia, Ondansetron, tourniquet pain, lidocaine, postoperative pain.*

Introduction

Intravenous regional anesthesia (IVRA)

(Bier's block) was first described by German surgeon, August Bier, in 1908. IVRA can provide surgical anesthesia for short surgical procedures about (45-6o min) on an extremity like carpal tunnel release. IVRA is easy, reliable, and cost effective with a success rate of 94-98%[(1)].

Technique

An intravenous catheter is usually inserted in the dorsum of the hand (or foot) and a double pneumatic tourniquet is placed on the arm or thigh, the extremity is elevated and exsanguinated by tightly[(2)].

Wrapping an Esmarch elastic bandage from a distal to proximal direction. The proximal tourniquet is inflated, The Esmarch bandage removed and 0.5% lidocaine (25 ml for forearm 50 ml for an arm and 100ml for a thigh tourniquet) injected over 2-3 min. through the catheter which is subsequently removed.

Anesthesia is usually established after 5-10 min.Tourniquet pain usually developed after 20-30 min. at which time the distal tourniquet is inflated and the proximal tourniquet is subsequently deflated[(3)] .

Disadvantages of this technique include, poor muscle relaxation, delayed onset of action tourniquet pain and lack of postoperative analgesia. Also there may be a certain complications that may occur like accidental or early deflation of the tourniquet or use of excessive doses of local anesthetic can result in toxic reaction, and (rarely); phlebitis (with 2-Chloroprocaine), the development of compartment syndrome and possibility of loss of limb[(4)].

Lidocaine (lignocaine)

Lidocaine is an amide local anesthetic.13 can be used in Epidural, Spinal, local, peripheral nerve block, infiltration, topical, intravenous regional anesthesia[(2)].

That is also used to control ventricular tachyrhythmia, it has class I b anti-arrhythmic action[(5)].

It has a relatively rapid onset of action and intermediate-duration. The cardiotoxic potential of lidocaine at equivalent levels of centrl nervous toxicity is about one –ninth that of pubivacaine[(6)].

Mechanism of action

Local anesthetic action is dependent on blockade of Na channel. Unionized lipid soluble drug passes through the

phospholipid membrane where in the axoplasm it is pronated, in this ionized form it binds to the internal surface of a Na channel, preventing it from leaving the inactive state [5].

Pharmacokinetics

Lidocaineis 70% protein bound to alpha acid glycoprotein[13].Lidocaine is metabolized in the liver by microsomal oxidases and amidases. N-dealkylation followed by by hydrolysis produces ethylglycine, xylidide. And other derivatives that are excreted in the urine[6].

Ondansetron

Ondansetron is a carbazole in structure[6].

Pharmacodynamics

Ondansetron selectively block serotonin 5-Hydroxytryptamine (5HT3) receptor with little or no effect on dopamine receptors[2].

Clinical uses

5-HT3 antagonists are indicated for use in the management of PONV and in the management of nausea and vomiting induced by chemo-radiotherapy. It is ineffective for vomiting induced by motion sickness or dopamine agonists it's licensed for children above 2 years of age. It should be used immediately prior to emergence from anesthesia[7] .

Pharmacokinetics

Ondansetron is well absorbed from gut with an oral bioavailability of about 60% , it is 75% protein –bound and undergoes significant hepatic metabolism by hydroxylation and subsequent glucoronide conjugation to inactive metabolites. It 'shelf life is 3 hours. The dose should be reduced in hepatic impairment[5].

Patients and methods

Thirty Patients scheduled for elective hand and forearm surgery.

Inclusion criteria

- Elective hand and forearm surgery
- (ASA) physical status I and II
- Age of 18 to 60 years

Exclusion criteria

- Patient refusal
- History to allergy to any drug used.
- Pre-existing circulatory difficulties;
  - Homozygous sickle cell disease
  - Peripheral vascular disease
  - In the operating room routine monitoring devices were used and the baseline of (MAP) , the heart rate(HR) , and the peripheral oxygen saturation (spo2) were monitored.

Two intravenous catheters were placed, one in the dorsum vein of the operative hand for injection of local anesthetic drug and the other in the contralateral hand for emergency drugs and intravenous fluid infusion .The patients received no premedication. The operative hand was elevated for 2 minutes and then was exsanguinated with an Esmarch bandage.

A "double" pneumatic tourniquet was placed on the upper arm then the proximal cuff was inflated to 100 mmHg above the systolic arterial pressure or at 250 mmHg .

Confirmation of circulatory isolation of the operative hand was verified by absence of radial pulse, inspection and loss of pulse oximetry tracing in the ipsilateral hand fingers.

IVRA was administered in 3mg /kg 2% Lidocaine diluted with normal saline to 0.5% concentration in the group A (n=15) , and 3 mg/kg 2%Lidocaine plus Ondansetron 8 mg diluted to 0.5% concentration in group B (n=15).

The onset of sensory block (The time elapsed from injection of study drug to sensory block achieved in all dermatomes) was assessed by pinprick with 22 gauge needle at three separate area on the hand represent the innervation of the Ulnar , Radial, Median nerves[16], at 30 seconds interval.

Onset of motor block (the time elapsed from injection of study drug to complete motor block) was assessed by asking the patient to flex and extend his wrist and fingers. The distal cuff was after completion of the sensory and motor block followed by proximal cuff release. The (VAS) visual analog scale score (a scale representing the pain from 0= 'No pain 'to 10= the worst imaginable pain)[9] .

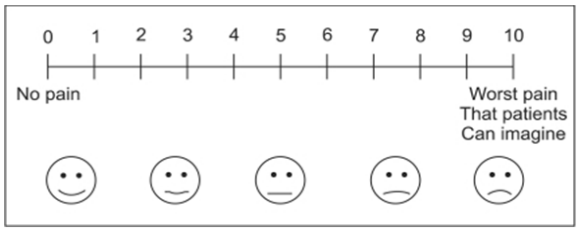

Figure 1 Visual Analog Scale

MAP ,HR, and Spo2 ,were recorded before tourniquet inflation and after injection and at 1 min. , 5 min.,10 min., 15 min.,20 min., 30 min., and 10 min ., 20 min., after tourniquet deflation.

Fentanyl 1 microgram/kg was given if the patient developed tourniquet pain if VAS greater than 3, the first

time of first analgesic administration after tourniquet inflation was recorded, The VAS and hemodynamic parameters were recorded postoperatively at 1, 2, 4 and 6 h.

Diclofenac 75 mg was injected intramuscular to relieve pain postoperatively if the VAS more than 3 and the time of the first postoperative analgesic request was recorded.

Sensory recovery time (the time elapsed after tourniquet deflation up to recovery of pain in all dermatomes), and motor recovery time (the time elapsed after tourniquet deflation up to movement of fingers) were recorded.

The patients were asked and observed for any side effect and signs of toxicity such as numbness, tinnitus, dizziness, lightheadedness, skin rash, gastric discomfort, nausea. No adverse effects have been occurred.

Statistical analysis

- Anderson darling test was done to asses if continuous variables follow normal distribution, if follow normal distribution than mean and standard deviation used.
- Discrete variables presented using there number and percentage used to present the data, chi square test used to analyze the discrete variable or Fisher exact test used to analyze the distribution between 2 groups (used instead of chi square for 2x2 table, if total sample <20 and if 2 or more with expected frequency less than 5).
- Two samples t test used to analyzed the differences in means between two groups (if both follow normal distribution with no significant outlier).

Kaplan–Meier analysis used to estimate median (or mean) time of the cumulative percentage of achieving onset of or recovery of (sensory or motor function) or other surrogate end points, the Logrank test used to calculate the p value and compare the significant between each groups.

Hazard ratio was calculated using Cox proportional hazard regression analysis, to find the tine-dependent association of the model and then calculate the 95% confidence interval, a value less than 1.0 indicate outcome in favor of lidocaine group only and less than 1.0 in favor of combination group (if both was statistically significant).

- SPSS 20.0.0, Minitab 17.1.0, GraphPad Prism 7.0 software package used to make the statistical analysis, p value considered when appropriate to be significant if less than 0.05

Results

Demographic data

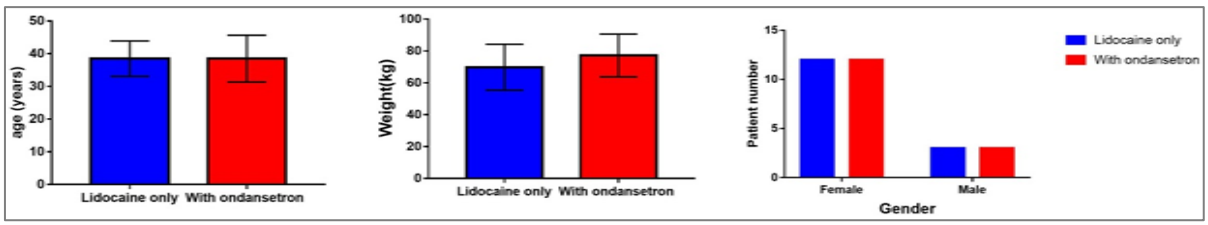

Figure 2: Demographic data

Table 1 Demographic data

		Lidocaine only	With ondansetron	P value
Number		15	15	-
Age yrs.		38.5 ± 5.4	38.5 ± 7.2	1.0
Weight kg		69.8 ± 14.4	77.2 ± 13.4	0.157
Gender	Female	12	12	1.0
		80.0%	80.0%	
	Male	3	3	
		20.0%	20.0%	

Table 2 Various variables and types of anesthesia

		Lidocaine only	With ondansetron	P value
Tourniquet time (minutes)		41.9 ± 5.3	42.0 ± 4.4	0.970
Operation time (minutes)		35.1 ± 4.7	35.5 ± 5.1	0.797
ASA	1 (n=25)	13	12	1.0
		86.7%	80.0%	
	2 (n=5)	2	3	
		13.3%	20.0%	

Age, weight and gender did not differ significantly between both groups, as illustrated in table 1 and figure2.

No significant difference in tourniquet time, operation time and ASA between both groups as illustrated in table2.

VAS score was significantly higher in lidocaine group after 5, 10, and 30 minutes, also 10 and 20 minutes after deflation, as illustrated in table 3 and figure 3 (a).

Table 3 VAS score changes after tourniquet inflation and after tourniquet deflation

VAS score	Lidocaine only	With ondansetron	P value
Before tourniquet inflation	-	-	
1 minutes after	3.3 ± 0.8	2.9 ± 1.1	0.188
5 minutes after	3.9 ± 0.7	2.8 ± 0.9	0.001 [Sig.]
10 minutes after	4.3 ± 1.2	2.7 ± 1.2	0.001 [Sig.]
15 minutes after	3.7 ± 1.0	3.1 ± 1.0	0.163
30 minutes after	4.7 ± 1.5	3.0 ± 0.8	0.001 [Sig.]
10 minutes after deflation	4.6 ± 1.4	2.8 ± 0.9	<0.001 [Sig.]
20 minutes after deflation	3.8 ± 1.1	2.6 ± 0.8	0.003 [Sig.]
P value of interaction = 0.079			

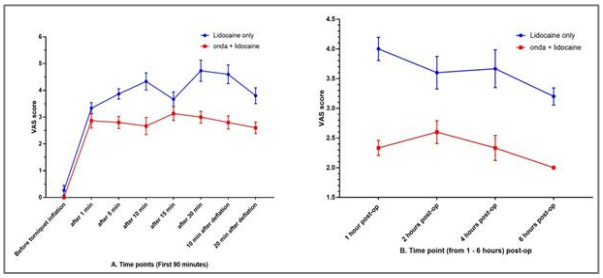

Figure 3: VAS score trend at different time periods (line represent mean and their SEM)

VAS score in the duration from 1 to 6 hours was all significantly higher in lidocaine group as illustrated in table 4 and figure 3 (b).

Table 4 VAS score change from 1 to 6 hours post operation

VAS score	Lidocaine only	With ondansetron	P value
1 hour post-op	4.0 ± 0.8	2.3 ± 0.5	<0.001 [Sig.]
2 hours post-op	3.6 ± 1.1	2.6 ± 0.7	0.005 [Sig.]
4 hours post-op	3.7 ± 1.2	2.3 ± 0.8	0.002 [Sig.]
6 hours post-op	3.2 ± 0.6	2.0 ± 0.0	<0.001 [Sig.]
P value of interaction = 0.281			

No significant difference between both groups in sensory onset time, however in terms of sensory recovery time lidocaine only was faster (with mean time difference of 1.2 minutes) and it was significant ondansetron was slower by almost 3 (the inverse of HR i.e 0.335) folds compared to lidocaine only group.

Both the motor onset time and motor recovery time was slower in lidocaine only group (by approximately 2.7 and 4.4 folds respectively) as illustrated in table 5 and figure 4.

Table 5 Onset and recovery time for sensory and motor nerves

Groups	Mean time	95%CI of mean	HR	95%CI of HR	P value
Sensory onset time (minutes)					
Lidocaine only	4.733	4.377 – 5.089	1.260	0.613 – 2.591	0.530
With ondansetron	4.467	4.143 – 4.791			
Sensory recovery time (minutes)					
Lidocaine only	4.133	3.757 – 4.509	0.335	0.145 – 0.778	0.011
With ondansetron	5.333	4.920 – 5.747			
Motor onset time (minutes)					
Lidocaine only	5.067	4.662 – 5.471	2.685	1.189 – 6.065	0.017
With ondansetron	3.933	3.529 – 4.338			
Motor recovery time (minutes)					
Lidocaine only	5.867	5.445 – 6.289	4.392	1.889 – 10.211	0.001
With ondansetron	3.933	3.486 – 4.381			
Mean time to outcome calculated using Kaplan-Meier analysis, Cox proportional regression used calculate the HR (hazard ratio) P value calculated using Cox proportional regression					

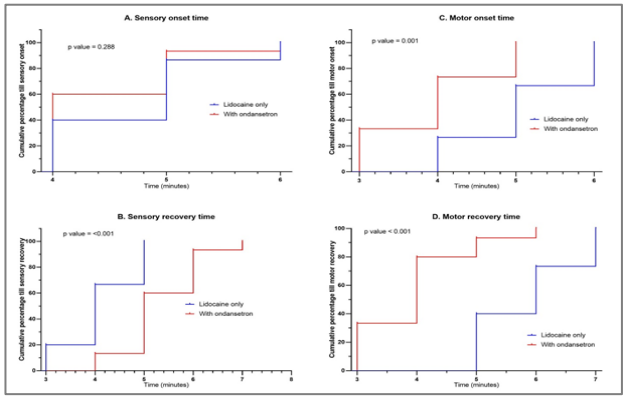

Figure 4: Kaplan-Meier analysis of the cumulative time to reach onset of action and recovery for both sensory and motor nerves

Patients receiving ondansetron in addition to lidocaine need longer mean time (by 1.6 hours) to need first analgesia post operation as illustrate by table 6 and figure 5.

Table 6 Time to first need for analgesia post operation

Groups	Mean time	95%CI of mean	HR	95%CI of HR	P value
Lidocaine only	2.077	1.326-2.828	0.420	0.092 – 1.917	0.263
With ondansetron	3.667	0.819-6.514			

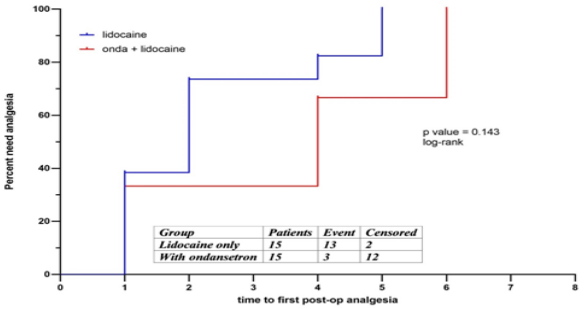

Figure 5: First postoperative use of analgesia

Discussion

Reducing the pain and the analgesic requirement by improving the quality of anesthesia is an important goal in intravenous regional anesthesia, in our study we used 8 mg of Ondansetron as adjunct to assess it`s analgesic effect. The number of patients received analgesia was lower in patients receiving Ondansetron, however the differences were not statistically significant.

A study performed by Farouk et al, showed that the addition of Ondansetron 4 mg to IVRA lessened tourniquet pain, decrease intraoperative and postoperative use of analgesia for first 4 hours after surgery, shortened onset time of sensory and motor block and significantly improved quality of anesthesia[10].

Our study agree with this study in decreasing the tourniquet pain , decrease the post-operative pain, shortened the motor onset time ,prolong sensory recovery time and relatively increase the mean time for need of the first analgesia by 1.6 hours , however it did not reach statistical significance which could be attributed to small sample size which led to underpowered of detection.

In contrast there was no shortened in sensory onset time. Ondansetron has analgesic effect as shown by Ambesh *et al* that pain during injection of propofol can successfully prevented by administration of 4 mg Ondansetron[11] .

Gregory *et al* showed that Ondansetron may be effective in the preventing pain following injection of propofol by binding to the opioid receptors[12].

Ondansetron also has anti-inflammatory effect; Startz and collegues showed that 5 HT_3 receptor antagonists had anti-inflammatory effects and due to this property they could have a role in decreasing pain following surgical incision, they also founded that 5 HT_3 receptor antagonists could acted as supplement replacement for local administration for corticosteroids[13].

As was shown by Ye et al., that Ondansetron could block sodium channels similar to local anesthetics had antinociceptive effect[14].

Conclusions

Adding 8 mg of Ondansetron to lidocaine in intravenous regional anesthesia:

- Decrease tourniquet pain after injection.
- Could prolong the time for need of postoperative analgesia.
- Prolong the sensory block time.

Recommendations

- We recommend to use Ondansetron as adjuvant drug in IVRA to improve the quality of anesthesia and decrease the post-operative pain.
- We recommend to take larger number of patients in study and longer duration of follow up.

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