Intravenous Regional Anaesthesia With Lignocaine, Fentanyl And Pancuronium – Prospective Randomised Controlled Double Blind Study.
A Puttappa, G Patkar

Citation
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Abstract
Intravenous Regional Anaesthesia (IVRA) is a simple and effective technique for upper limb distal surgery. However, a relatively large dose of LA is required to induce motor and sensory blockade. Lignocaine 3mg/kg as a 0.5% solution is needed to ensure adequate analgesia. Systemic toxic reactions (convulsions, coma, cardiac arrest) can occur when the tourniquet deflates unexpectedly during the procedure or when it deflated intentionally at the end of short surgery. Therefore we conducted this prospective randomized double blind study to compare and evaluate the effects of addition of fentanyl and pancuronium to reduced dose of LA against the standard practice of 0.5% lignocaine. In this study, 75 patients of both sexes in the age group more than 18 years belonging to ASA 1 and 2 undergoing both elective and emergency surgeries of the forearm and hand were divided randomly into group L, group P and group F with 25 patients in each group. In patients belonging to group L, 40 cc of 3mg/kg of 0.5% lignocaine diluted in normal saline was used for administering IVRA, and in patients of group F 40 cc of 1.5mg/kg of 0.25% lignocaine combined with fentanyl 1mg/kg, and in patients of group P 1.5mg/kg of 0.25% lignocaine combined with fentanyl 1mg/kg and pancuronium 0.5mg was used. The time for onset of sensory blockade in group L was 11.76±3.08 minutes, group F was 12.96±3.06 minutes, and group P was 10.20±3.52 minutes which was clinically comparable in all the groups. However the time for onset of motor blockade was significantly delayed in group F (21.1±2.7 minutes) as compared to other two groups: group L (12.5±2.6 minutes) and group P (11.36±3.5 minutes). The patients in group P were showing significantly excellent muscle relaxation and excellent intraoperative analgesia as compared to other two groups. Post operative analgesia in group P (56.4±2.6 minutes) was significantly longer as compared to group F (46.8±4.9 minutes) and group L (39±8 minutes). Our results showed that hemodynamic parameters like pulse rate, blood pressure, respiratory rate were well maintained throughout the intra and post operative period in all the patients of all the groups. There were no major untoward side effects were noticed. Thus from the present study, we conclude that the addition of fentanyl 1mg/kg and pancuronium 0.5mg to 0.25% of lignocaine enhances lignocaine action and results in Adequate sensory and motor block.-Excellent intraoperative analgesia.-Excellent intraoperative muscle relaxation. Thus, using this combination the dose of lignocaine for IVRA can be reduced to a non toxic level for the same quality of analgesia and at the same time not offer any post analgesic benefit as all study patients were required supplement of analgesics post operatively after about 50-60 minutes.

INTRODUCTION
Intravenous regional anesthesia was first described by August Gustav Bier in 1908. This technique is a simple, easy to administer, effective and reliable method for anesthesia. It involves intravenous injection of local anesthetics into the limb on which surgery is to be performed after the limb is exsanguinated and a tourniquet has been applied proximally. It is the surest way of obtaining a block with a very minimal failure rate, and has gained immense popularity more so for upper limb surgeries. Besides it is extremely useful for emergency surgeries. Being a regional technique it avoids all the complication of general anesthesia, more so in patients coming for emergency surgery as well as patients belonging to ASA class 3 and 4.

However the dose of local anesthetic agent required to induce motor and sensory blockade has the potential to cause systemic local anesthetic toxicity. Therefore various methods have been tried to reduce the dose of Local anesthetic used in Intravenous regional anesthesia such as alkalization of the local anaesthetic solution, addition of an opioid, muscle relaxant, non steroidal anti-inflammatory drugs, potassium, and Ketamine with various results.

We conducted this prospective randomized double blind
study to know the effect of combining fentanyl 1/µg/kg alone and fentanyl 1/µg/kg plus pancuronium 0.5mg with reduced dose of lignocaine (0.25%) for Intravenous regional anesthesia.

AIMS & OBJECTIVES
To study the effect of IVRA with lignocaine 0.5% with lignocaine 0.25% plus fentanyl 1/µg/kg and lignocaine 0.25% plus fentanyl 1/µg/kg plus pancuronium 0.5mg with respect to:

- Time of onset of sensory block.
- Time of onset of motor block
- The degree of muscle relaxation
- Intraoperative analgesia.
- Hemodynamic studies
- Post operative analgesia.

OBJECTIVE
To lower the dosage of lignocaine, with addition of fentanyl and pancuronium in IVRA thereby reducing the systemic side effects of LA but at the same time giving an adequate sensory and motor blockade, good operative condition and intraoperative analgesia.

MATERIALS AND METHODS
INCLUSION CRITERIA
- Patients with age >18 years.
- Adult patients belonging to ASA grade 1 and 2 patients.

EXCLUSION CRITERIA
- All patients with age <18 years
- Hypersensitivity to either Lignocaine or Fentanyl or Pancuronium.
- ASA grade 3/4/5
- History of Coagulation disorders
- History of Severe renal dysfunction
- Severe cardiac disease, with low cardiac output where the pharmacokinetics of lignocaine might be affected.
- Severe hepatic dysfunction where metabolism of the drug may be greatly altered.
- Sickle cell disease.
- The above study was approved by the departmental review board.
- After ascertaining the selection criteria, informed, valid, written consent was obtained from each of the seventy five patients for participation in the trial.

CONDUCT OF STUDY
The study was a prospective, randomized double blind controlled study The chosen patients were randomly assigned to 3 groups to receive study solutions as follows.

Figure 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug Combination injected IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>Preservative free Lignocaine 0.5% in 40 cc of normal saline (3mg/kg)</td>
</tr>
<tr>
<td>F</td>
<td>Preservative free Lignocaine 0.25%(1.5mg/kg) + Fentanyl 1 microgram/kg in 40cc of normal saline</td>
</tr>
<tr>
<td>P</td>
<td>Preservative free Lignocaine 0.25% (1.5mg/kg)+Fentanyl 1microgram/kg + Pancuronium 0.5mg in 40cc of normal saline</td>
</tr>
</tbody>
</table>

* Xylocard, Astra Zeneca Pharma India limited.
* Trofentanyl, Troika pharmaceuticals limited.
* Pancuronium, Troika pharmaceuticals limited.

ANESTHETIC PROCEDURE
With all standard monitors attached to the patient, an intravenous access was obtained for intravenous fluids on the hand opposite to be operated. A 22g intravenous cannula was inserted in to a vein on the dorsum of the hand to be operated as distal as possible. Two pneumatic tourniquet were securely placed on this arm, one proximal to the other. The limb to be operated was exsanguinated by Esmarch bandage. In case of painful limb, where exsanguinations could not be carried out, limb elevation was given for five minutes. The proximal tourniquet was inflated to a pressure...
100-120 mmHg above the systolic pressure before removal of Esmarch bandage. 0.4 ml of study solution was injected intravenously at a rate of 20 ml/min in the operative limb. The drug combination was prepared by another anesthesiologist not involved in the study and the one performing the block and later monitoring the patient was blinded to the nature of the drug combination being injected. When patients complained of tourniquet pain, the distal cuff inflated and proximal one released to minimize discomfort of the tourniquet.

The following parameters were studied:

Time for onset of sensory blockade (minutes) i.e. The time interval after completion of injection of solution to the loss of pin prick sensation using 23G hypodermic needle. It was checked at all the six separate areas of the hand selected to represent the innervation of the ulnar, median and radial nerves.

Time to motor Block (Minutes) the complete motor block was recorded when the patient could not induce any movement of the fingers following Injection of study solution.

3) Intraoperative Analgesia:

This was evaluated using Objective Pain Scoring System.

4) Intraoperative Degree of muscle relaxation this was assessed using the following grading:

**Figure 2**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Muscle relaxation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>Complete Limp limb</td>
</tr>
<tr>
<td>Good</td>
<td>Minor movements of digits possible</td>
</tr>
<tr>
<td>Fair</td>
<td>Weak grip possible</td>
</tr>
<tr>
<td>Poor</td>
<td>No obvious relaxation</td>
</tr>
</tbody>
</table>

5) The duration of post operative analgesia was described as the time to the first request for analgesics after completion of surgery.

Vital parameters monitors like RR, HR, and BP were monitored every five minutes for first 30 min & then every 15 min till the end of the surgery.

7) Adverse effects: patients were observed clinically for signs of adverse or unpleasant sequelae noted and were treated symptomatically.

For short surgical procedures, a minimum time of 45 minutes was allowed to elapse before deflation of the tourniquet. The tourniquet was deflated by cycled deflation technique i.e. the tourniquet was deflated for 5 seconds, reinflated for 1 minute, deflated for another 5 seconds, reinflated for another minute, then deflated totally at the conclusion of surgery.

**STATISTICAL ANALYSIS**

Analysis of variance (Anova) technique for comparison between the three groups for parametric data. Paired t test was used for comparison within the group.

Least significance test (LSD) was used for comparison between two groups.

Chi-square test was used for non parametric data.

P value <0.05 was considered to be significant

**OBSERVATIONS AND RESULTS**

Patients were randomly divided into three groups of 25 patients each

Drug combinations injected intravenously.

**Figure 3**

<table>
<thead>
<tr>
<th>Group</th>
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</tr>
</thead>
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<tr>
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</tr>
<tr>
<td>F</td>
<td>Preservative free Lignocaine 0.25% (1.5mg/kg) + Fentanyl 1mg/kg in 40cc of normal saline</td>
</tr>
<tr>
<td>P</td>
<td>Preservative free Lignocaine 0.25% (1.5mg/kg) + Fentanyl 1mg/kg + Pancuronium 0.5mg in 40cc of normal saline</td>
</tr>
</tbody>
</table>

Demographic characteristics of patients
Intravenous Regional Anaesthesia With Lignocaine, Fentanyl And Pancuronium – Prospective Randomised Controlled Double Blind Study.

Figure 4

<table>
<thead>
<tr>
<th></th>
<th>Group L (n=25)</th>
<th>Group F (n=25)</th>
<th>Group P (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patient</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>0.303</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>27.5±11.3</td>
<td>26.3±10.1</td>
<td>30.1±11.7</td>
<td>0.097</td>
</tr>
<tr>
<td>ASA Status(1/2)</td>
<td>20/5</td>
<td>21/4</td>
<td>19/6</td>
<td>0.007</td>
</tr>
<tr>
<td>Mean weight(kg)</td>
<td>60.3±6</td>
<td>62.1±5</td>
<td>61.5±6</td>
<td>0.507</td>
</tr>
<tr>
<td>Duration of surgery(min)</td>
<td>64.7±8.5</td>
<td>60.8±5.7</td>
<td>66.9±13</td>
<td>0.010</td>
</tr>
<tr>
<td>Sex(M/F)</td>
<td>21/4</td>
<td>18/7</td>
<td>23/2</td>
<td>0.171</td>
</tr>
</tbody>
</table>

P >0.05 not significant Annova(analysis of variance) LSD(least significance) test between two groups. Above table shows that all the demographic variables are comparable in all three groups.

Onset of Sensory Block

Figure 5

<table>
<thead>
<tr>
<th></th>
<th>Group L (n=25)</th>
<th>Group F (n=25)</th>
<th>Group P (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory Onset</td>
<td>11.76±3.06</td>
<td>12.96±3.062*</td>
<td>10.20±3.52</td>
</tr>
</tbody>
</table>

* P = .032 significant difference(p<0.05 by anova test)

The above table shows that the onset of sensory block in group P is faster in comparing to group F. The time for sensory onset between group P and group L, and group L and group F are comparable.

Onset of Motor Block

Figure 6

<table>
<thead>
<tr>
<th></th>
<th>Group L (n=25)</th>
<th>Group F (n=25)</th>
<th>Group P (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor Block (mean ± S.D) in min</td>
<td>12.52±2.06</td>
<td>21.16±2.76*</td>
<td>11.36±3.51</td>
</tr>
</tbody>
</table>

P=.01 significant difference (p<0.05 by anova test) from group p and group L

The above table shows that the time for onset of motor block in group F is significantly more as compared to group P and group L. However the time for motor onset is comparable between group L and group P.

Figure 7

Table 5: Intra-operative analgesia score.

* P=.003 significant difference (p<0.05 by Chi-Square test)
Totally 48% of patients (36 patients) under study has excellent intraoperative analgesia and 49.3% (37 patients) had good analgesia. Only 2 patients had incomplete analgesia and required complete general anesthesia. The above table also shows that 84% of patients in group P had excellent intraoperative analgesia which was significant (p=0.03 Chi-Square test as compared to group L and group F).

**Figure 8**
Table 6: Muscle Relaxation

<table>
<thead>
<tr>
<th>Muscle Relaxation Score</th>
<th>Group L (n = 25)</th>
<th>Group F (n = 25)</th>
<th>Group P (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>17 (68%)*</td>
<td>2 (8%)</td>
<td>23 (92%)*</td>
</tr>
<tr>
<td>Good</td>
<td>8 (32%)</td>
<td>13 (52%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Fair</td>
<td>Nil</td>
<td>10 (40%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Poor</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

* P=0.01 significant difference (p<0.05 by Chi-Square test) from group F and group L.

# P=0.02 significant difference (p<0.05 by Chi-Square test) from group F. The above table shows that there are 92% (23 patients) showing excellent muscle relaxation in group P which is significantly higher in comparison to group F and group L. However between group L and group F muscle relaxation is significantly better in group P.

**Figure 9**
Table 7: Post Operative Analgesics

<table>
<thead>
<tr>
<th>Post Operative Analgesics</th>
<th>Group L (n = 25)</th>
<th>Group F (n = 25)</th>
<th>Group P (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vicodin 5.0</td>
<td>36.08 ± 8.0</td>
<td>46.84 ± 4.94*</td>
<td>56.4 ± 2.54*</td>
</tr>
</tbody>
</table>

* P=0.012 significant difference (p<0.05 by anova test) from group L and group F. # P=0.01 significant difference (p<0.05 by anova test from group L.

The above table shows that post operative analgesia in group L is significantly less as compared to group P and group F.

There is a significantly increased post operative analgesia in group P as compared to group F. However this is not clinically significant.

**DISCUSSION**

**TIME TO SENSORY BLOCK:**
Onset of sensory block in group P was faster (10.2/3.52 min). This was statistically significant (p=0.032, Anova test) as compared to group F.

Though there is a virtual absence of opiate receptors in the spinal ventral roots and in peripheral nerves, fentanyl is found to reduce the action potential in desheathed peripheral nervous system similar to that produced by LA. This action is not related to opiate receptors as naloxone failed to inhibit this effect. Therefore it is possible that addition of fentanyl to lignocaine enhances the LA action of fentanyl and this synergism allows the reduction of dose of lignocaine in IVRA as seen in our study.

**TIME TO MOTOR BLOCK:**
Onset of motor block in group P was 11.36/3.5 minutes. This was statistically significant as compared to group F where the mean time for onset of sensory block was 21.16/2 minutes. Thus addition of pancuronium to reduced dosage of 0.25% lignocaine in IVRA caused onset of motor block as comparable to conventional 0.5% lignocaine. Muscle relaxants exert an effect on the neuromuscular junction. In IVRA they probably interfere with the muscle spindle activity resulting in loss of muscle tone and spasm. The spindle is the sensory end organ of skeletal muscles, sending information about fibre length to the brain. The resulting loss of tone and spasm may improve both intraoperative pain and operating conditions and at the same time potentiate the effect of lignocaine thus allowing a reduction in the dose of lignocaine in our study.

**INTRAOPERATIVE ANALGESIA:**
Patients rating their intraoperative analgesia as excellent in group P was 84% as compared to group L (36%) and group F (24%). Rest of the patients had good analgesia i.e. group L (60%), group F (72%) and group P (16%). Only two patients one each in group L and group F had incomplete analgesia requiring supplementation with complete general anesthesia. Thus it was observed that addition of fentanyl has shown excellent to good intraoperative analgesia even with low dose lignocaine. Addition of pancuronium to low dose lignocaine and fentanyl improved the quality of analgesia.
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and relaxation in such a way that upper limb surgery could be accomplished with success in all cases.

The peripheral analgesic effect of opioids is still controversial. Although no in vivo studies have demonstrated a measurable local anaesthetic effect of fentanyl, in vitro studies have shown that perineural fentanyl depresses the action potential in nerve fibres of different types. Power L, et al 1988). Recordings of fast conducting A fibres and slow conducting C fibres before and after exposure to 50 and 100µg/ml of fentanyl indicate that a high concentration of fentanyl may partially suppress conduction in peripheral nerve and apparently does not diffuse well through a nerve sheath. Thus it is unlikely that fentanyl per se would cause conduction blockade in vivo in peripheral nerves that are enclosed within a nerve sheath.

Aaron J.G,et al, indicated that the action of opiates is dual i.e. through the opioid receptor in the spinal column and in the peripheral nerve there is a virtual absence of opioid receptors here(site of action of IVRA) they act by reducing conduction in peripheral nervous system similar to that seen with LA. At low concentrations they are effective on unshaved peripheral nerves but at high concentrations they suppress conduction in both sheathed and unshaved peripheral nerves. Opioids are much more effective at blocking dull pain (C fibres) than acute pain (A δ fibres). Thus surgical pain is not completely blocked by opioids alone and therefore in our study fentanyl is synergistic with 0.25% lignocaine in its action during IVRA.

Therefore the primary clinical effect of fentanyl is related to interaction with opiate receptors after epidural or intrathecal administration. Fentanyl at the peripheral nerve may cause some depression of nerve transmission similar to that produced by local anesthetics. Hence fentanyl may possess weak local anaesthetic properties. It is possible that addition of local anesthetics to fentanyl enhances its weak local anaesthetic effect.

In group P 84% of patients rated their intraoperative analgesia as excellent, here addition of pancuronium further enhanced the effect of fentanyl and lignocaine. Probably muscle relaxants interfere with the muscle spindle resulting in loss of muscle tone and control of voluntary movement, with a decrease nervous input into the brain. This in turn makes the surgery easier and blockade of the muscle spindles, induced by the muscle relaxants, may alleviate muscle spasm and reduce pain during and after surgery. Walied Y. Abdulla and Nihal M. Fadhil in 1992 conducted a study to reduce the dose of local anesthetics during IVRA in which group A received 100mg lignocaine, group B received 100mg lignocaine + 0.05mg fentanyl, group C received 100 mg lignocaine + 0.5mg pancuronium and group D received 100mg lignocaine + 0.05mg fentanyl + 0.5mg pancuronium. Their results showed that 60% of patients in group D had excellent intraoperative analgesia. The results in group D of this study (which is similar to our group P) are consistent with the results of our study. MC glone et al in 1988 conducted a study on effect of Atracurium 2 mg in IVRA and reported that the addition significantly improved both intraoperative analgesia and operating conditions for performing closed and open reduction of wrist and hand fractures.

INTRAOPERATIVE MUSCLE RELAXATION

Muscle relaxation after IVRA was excellent in 92% of patients in group P as compared to group F(8%) and group L(68%).Quality of muscle relaxation was good in 32% in group L,52% in group F and 8% in group P.40% of patients in group F had muscle relaxation which could be graded as fair however this did not hamper the surgical procedure.

In a similar study conducted by Sztark F et al in 1994 showed that addition of atracurium to lignocaine for IVRA improved the muscle relaxation. and Mc Glone et in 1988 reported the same finding. Sztark F, et al in 1997 showed that the addition of pancuronium and fentanyl to lignocaine for IVRA showed excellent muscle relaxation and allowed the reduction in the dosage of lignocaine.

Muscle relaxants exert an effect at the neuromuscular junction, muscle relaxants probably interfere with the muscle spindle activity resulting in loss of muscle tone and spasm, and therefore improving muscle relaxation. Thus addition of 0.5mg of pancuronium allowed us to reduce the dose of lignocaine to 1.5 mg/kg.

POSTOPERATIVE ANCALGESIA

Postoperative analgesia in group P was 56.4 ± 2.6minutes as compared to group L (39 ± 8 minutes) and group F (46.8±4.9 minutes).However the post operative analgesia was significantly increased in group F as compared to group L.

In a similar study conducted by Sztark F et al showed that the postoperative analgesia in fentanyl group was 45 ± 21 minutes was significantly prolonged as compared to
conventional 0.5% lignocaine (36 ± 17 minutes)

M.T.Pitkanen et al, conducted the study on effect of addition of 0.1mg (A) or 0.2 mg (B) fentanyl to 40 ml 0.5% prilocaine in IVRA and found out that postopanalgesia in group A and group B was 10.8 minutes and 14.3 minutes and concluded that it is insignificant.

**ADVERSE EFFECTS**

Two patients in group L developed transient drowsiness after release of tourniquet. The patient was carefully monitored and the drowsiness disappeared without any treatment within next 10 to 15 minutes. However the patient’s vital parameters like respiratory rate, heart rate and blood pressure were within normal limits, all the time. One patient in group L experienced hypotension of systolic BP 95mmHg 5 minutes after tourniquet deflation who responded to fluid and become normotensive after 10 minutes. These acute symptoms were similar to those described by Armstrong et al and are typical of symptoms attributed to systemic release of LA. Release of metabolites, including potassium, may be a remote contributory cause of some of the toxic effects associated with the release of lignocaine into the general circulation.³²

Three patients in group P and 5 patients in group F experienced nausea who responded to Inj ondansetron 0.1mg/kg. This side effect probably due entirely to the effect of fentanyl ³³

**CONCLUSION**

From the present study, we conclude that the addition of fentanyl 1μg/kg and pancuronium 0.5mg to 0.25% of lignocaine enhanced lignocaine action and results in

- Adequate sensory and motor block.
- Excellent intraoperative analgesia.
- Excellent intraoperative muscle relaxation.

Thus, using this combination the dose of lignocaine for IVRA can be reduced to a non toxic level for the same quality of analgesia and at the same time not offer any post analgesic benefit as all study patients were required supplement of analgesics post operatively after about 50-60 minutes

**References**

8. McKeown D W and D.B.Scott. “ Influence of the addition of Potassium to 0.5% Prilocaine Solution During I.V. Regional Anaesthesia”, British Journal of Anaesthesia 1984; 56; 1167 – 70.
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