Clonidine as Adjuvant to Local Anesthetic During Intravenous Regional Anesthesia: Evaluation of Analgesic Efficacy

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Abstract
The present study was designed to evaluate the analgesic efficacy and safety of clonidine used as adjuvant to local anesthesia during intravenous regional anesthesia (IVRA). The study comprised 40 patients assigned to undergo minor hand and forearm operative procedures under IVRA (0.5% xylocaine; 35 ml) in addition to either saline (Placebo group) or clonidine 1 μg/kg (Clonidine group). The degree of both surgical site and tourniquet pain was evaluated using 4-point verbal analogue scale (VAS) every 10 min during the operative procedure and after deflation of tourniquet, postoperative pain was assessed every 20 min for 3 postoperative hours, using visual analogue scale (VAS). Throughout the first 3 postoperative hours, if VAS was ≥4, IM declophenac sodium was provided. The duration of postoperative analgesia was estimated starting at time of tourniquet deflation till patient requested for rescue analgesia. Intra and postoperative sedation, hypotension, or bradycardia were recorded. Both groups reported a rapid onset of action and no patient complained of severe tourniquet pain throughout the intraoperative period. The analgesic effect extended till deflation of tourniquet in patients received clonidine where 7 patients reported no pain at time of deflation. Comparison of pain intensity throughout operation revealed a significant decrease of pain scores in clonidine compared to placebo group. As regards operative site pain, patients reported mild pain; 2 in placebo and one in clonidine groups, near end of surgery. Throughout the first postoperative 3-hr, the total pain score records showed a significant decrease in clonidine compared to placebo group, with a significantly prolonged duration of postoperative analgesia. There was a significant reduction in favor of clonidine group as regards the number of patients required analgesia and the dose of requested analgesia in comparison to placebo group. Only one patient had transient hypotension that required intravenous fluid therapy. It could be concluded that the use of clonidine as adjuvant to local anesthetic for IVRA could delay onset of tourniquet pain and ameliorate its intensity, reduces surgical site pain with extended postoperative analgesia and is well tolerated in the used dosage.

Introduction
Intravenous Regional Anesthesia (IVRA) has been first described in 1908 by the German surgeon August KG Bier, (1). IVRA is simple to administer, reliable and cost-effective, (2). It is ideal for short operative procedures on the extremities performed on an ambulatory basis. Disadvantages include concerns about local anesthetic toxicity, slow onset, poor muscle relaxation and minimal postoperative pain relief, (3).

Tourniquet pain often limits the use of IVRA, it can occur 45–60 minutes after tourniquet inflation. Patients undergoing surgery under IVRA initially experience a dull ache in the exsanguinated limb after about 30 minutes of tourniquet application. This may occur even
when a second cuff is inflated on an anaesthetized section of limb. As the pain worsens, patients may become restless and eventually the pain may become unbearable despite the presence of an otherwise satisfactory block.\(^4\)

The pain may be transmitted through C fibers (slow, persistent, poorly localized pain), which are more resistant to local anesthetic than A\(\delta\) fibers (sharp, fast pricking pain). At the onset of neural blockade, when the concentration of local anesthetic is high, both are inhibited. As the local anesthetic is metabolized, the concentration becomes insufficient to block C fibers despite continuing to anaesthetize A\(\delta\) fibers. This theory is supported by the observations that longer-acting local anesthetic agents reduce the incidence of tourniquet pain and that its onset is delayed if a larger dose of local anesthetic is used.\(^5\)

Once tourniquet pain has developed it is difficult to treat, other than by releasing the tourniquet. General anesthesia may need to be used if the surgery is continuing. Opiates alone are disappointing and tend to cause side-effects from excessive dose once the tourniquet is released and the afferent stimulus ceases.\(^6\) The ideal IVRA solution should have the following features: rapid onset, reduced dose of local anesthetic, reduced tourniquet pain and prolonged post-deflation analgesia. At present, this may only be achieved by the addition of adjuncts to local anesthetic.\(^7\)

The \(\alpha_2\)-adrenoceptors are located on primary afferent terminals (both at peripheral and spinal endings), on neurons in the superficial laminae of the spinal cord and within several brainstem nuclei implicated in analgesia. The mechanism by which clonidine, an agonist at these receptors, produces analgesia is not fully understood but is likely to be by a number of mechanisms.\(^8\) Peripherally, reduced release of noradrenaline may contribute to analgesia,\(^9\) and there is an inhibitory effect on nerve-fiber action potentials that is not mediated by the \(\alpha_2\)-receptor.\(^10\)

The present study was designed to evaluate the analgesic efficacy and safety of clonidine, used as adjuvant to local anesthesia during IVRA, as regards tourniquet, surgical site and postoperative pain.

**Patients & Methods**

This prospective, randomized study comprised 40 patients assigned to undergo minor hand and forearm operative procedures under IVRA, (Table 1). Patients with known allergies to local anesthetics were excluded from the study. Patients included in the study had mean age of 39.5±12.4,
range 19-63 years. There were 23 male (57.5%) and 17 female (42.5%) patients.

Two intravenous cannula were applied, one in the operative extremity for administration of the study solution and the other in the contralateral extremity for administration of necessary medications or fluids when indicated. After application of routine monitors, the operative extremity was exsangunated by maintained elevation and intermittent squeezing for few minutes and the forearm was wrapped with Esmarch bandage. Then, a double tourniquet was positioned on the upper operative arm, inflated to 250 torr and Esmarch bandage was removed. Circulatory isolation of the operative forearm was confirmed by inspection of the hand and absence of radial pulse.

Patients received IVRA in form of 35 ml of 0.5% xylocaine and were randomly allocated into two equal groups according to adjuvant used: control group received 5 ml saline (placebo) and study group received clonidine 1 μg/kg. No analgesics or opiates were given intraoperatively.

Four point verbal analogue scale (VbAS): none (=0), mild (=1), moderate (=2), and severe (=3), was used to evaluate the degree of both surgical site and tourniquet pain every 10 min during the operative procedure. After deflation of tourniquet, postoperative pain was assessed every 20 min for 3 postoperative hours, using visual analogue scale (a 10 cm-scale, with "0" indicating no pain and "10" indicating worst pain ever). Throughout the first 3 postoperative hours, if VAS was ≥4, IM declophenac sodium (75 mg/ml; 3 ml ampoule) was provided and repeated if necessary. The duration of postoperative analgesia was estimated starting at time of tourniquet deflation till patient requested for rescue analgesia.

Patients were monitored non-invasively during and after surgery for heart rate and mean blood pressure. Postoperative sedation, hypotension, or bradycardia were recorded.

Data were analyzed using t test and Chi-square test. Statistical analysis was conducted using SPSS (Version 10, 2002) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

Patients' demographic and surgical data were presented in Table (1) and showed a non-significant (P>0.05) difference between both groups. There was a non-significant difference between both groups as regards hemodynamic changes, (Table 2). Only one patient had transient hypotension that required intravenous fluid therapy.
Both groups reported a rapid onset of action and no patient complained of severe tourniquet pain throughout the intraoperative observation period. The analgesic effect extended till deflation of tourniquet in patients received clonidine where 7 patients reported no pain at time of deflation. Comparison of pain intensity throughout operation revealed a significant decrease of pain scores in clonidine compared to placebo group, \((X^2=5.14, P<0.05)\); furthermore, number of patients reported intraoperative moderate tourniquet pain was significantly less in patients received clonidine compared to placebo group, \((X^2=4.13, P<0.05)\), (Table 3, Fig. 1). As regards surgical site pain, 3 patients reported mild pain; 2 in placebo and one in clonidine groups, near end of surgical procedure.

Mean postoperative pain scores showed a progressive increase in both groups. However, total pain score showed a significant \((P<0.05)\) decrease in patients received clonidine \((0.99\pm0.95)\) compared to controls, \((1.52\pm1.3\) min) throughout the first postoperative 3-hr, (Fig. 2). Moreover, patients received clonidine had significantly \((P<0.05)\) lower pain scores throughout the first postoperative hour compared to those received placebo but non-significantly \((P>0.05)\) lower thereafter, (Table 4, Fig. 3).

Only 2 patients in placebo group requested postoperative analgesia through the first postoperative hour. Patients received clonidine request rescue analgesia after a mean duration of \(235\pm32.2\) min since release of tourniquet, whereas those received placebo required rescue analgesia after a mean period of \(148.5\pm56.1\) min; with significantly \((P<0.05)\) prolonged duration of postoperative analgesia in clonidine group compared to placebo group, (Table 5, Fig. 4).

Throughout the 24 hours follow-up period, all patient had required analgesia; 5 (25%) and 11 patients (55%) in placebo and clonidine groups, respectively, required postoperative IM declophenac once, whereas 11 patients (55%) in placebo and 7 patients (35%) in clonidine groups required injection twice and the other patients required it trice. There was a significant difference in favor of clonidine group as regards the number of patients required analgesia in comparison to placebo group, \((X^2=4.12, P<0.05)\), (Table 6, Fig. 5).

**Discussion**

Tourniquet pain may arise from ischemia of peripheral neurons or nociceptors distal to tourniquet, or from nerve fiber activation directly under it, again because ischemia. Furthermore, mechanical trauma and tissue
ischemia under or distal to tourniquet lead to release of inflammatory mediators and thus initiate, and/or aggravate tourniquet pain.\textsuperscript{(11)}

The $\alpha_2$-adrenoceptor agonists have several beneficial actions during the perioperative period. They exert a central sympatholytic action, improving hemodynamic stability in response to surgical stress, reducing the anesthetic and opioid requirements and causing sedation, anxiolysis and analgesia. Furthermore, $\alpha_2$-adrenoceptor agonists have an analgesic action at several sites of the peripheral and central nervous system as well as the prolongation of epidurally or intrathecally administered local anesthetics and opioids.\textsuperscript{(12)}

Through the present study, patients assigned to undergo minor surgical procedures under IVRA received clonidine as adjuvant to xylocaine to evaluate its analgesic effect and safety for managing tourniquet, surgical site and postoperative pain.

Only 3 patients reported mild sensation at surgical site near end of surgery; one in clonidine group versus 2 patients in placebo group, this result signified that minimal reduction of the dose and dilution of local anesthetic did not interfere with completion of surgery and illustrated the additive analgesic effect of clonidine. This result goes in hand with results obtained by \textit{Choyce & Peng},\textsuperscript{(13)} who reviewed the use of adjuncts to IVRA for surgical procedures in terms of efficacy of block with reduction of local anesthetic dose and reported no difference on comparison to the use of full dose.

The analgesic effect extended till deflation of tourniquet in patients received clonidine where 7 patients reported no pain at time of deflation with a significantly decreased pain scores compared to placebo group. These results illustrate the additive analgesia provided by using clonidine as adjuvant to local anesthetic. These results agreed with the observation of \textit{Choyce & Peng},\textsuperscript{(13)} who reported that clonidine as adjuvant in dose of 1 $\mu$g/kg prolongs tourniquet tolerance. Also, agreed with \textit{Gentili et al.},\textsuperscript{(14)} and \textit{Lurie et al.},\textsuperscript{(15)} who reported prolongation of tourniquet tolerance in volunteers received local anesthetic and clonidine.

In support of the additive analgesic effect of clonidine, the total VAS records showed a significant (P<0.05) decrease in patients received clonidine compared to controls throughout the first postoperative 3-hr with a significantly (P<0.05) prolonged duration of postoperative analgesia. These results go in hand with \textit{Alayurt et al.},\textsuperscript{(7)} who evaluated the effect of sufentanil, tramadol or clonidine added to
lignocaine for intravenous regional anesthesia and reported that the quality of anesthesia in patients received additive drugs was better than in patients received only local anesthetic with delayed the onset time of the tourniquet pain and reduced the intraoperative consumption of opioid.

There was a significant reduction in favor of clonidine group as regards the number of patients required analgesia and the dose of requested analgesia in comparison to placebo group. These results agreed with Reuben & Duprat, (16), who evaluated the postoperative benefit of clonidine and demonstrated improved postoperative analgesia for two hours and reduced analgesic intake for 24 hr. Only one patient received clonidine developed hypotension that required supplemental intravenous fluid therapy, this goes in hand with Choyce & Peng, (13), who documented that clonidine given in dose of 1 μg/kg is well tolerated and with Brill & Plaza, (17), who evaluated the trials for administration of various non-narcotic adjuvants to local anesthetic and reported that clonidine has shown considerable analgesic effect, with minimal adverse effects and was found to increase duration and quality of postoperative analgesia.

It could be concluded that the use of clonidine as adjuvant to local anesthetic for IVRA could delay onset of tourniquet pain and ameliorate its intensity, reduce surgical site pain with extended postoperative analgesia and is well tolerated in the used dosage.

References
Care Medicine, Medicine Publishing Co.; 77-9.


Table (1): Patients' demographic data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo group</th>
<th>Clonidine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.5±12.6</td>
<td>41.5±12.1</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>11:9</td>
<td>12:8</td>
</tr>
<tr>
<td>Operative procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carpal T</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Tenolysis</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Ganglion</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Plastic</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>30.6±4.1</td>
<td>32.4±3.2</td>
</tr>
<tr>
<td>Tourniquet time (min)</td>
<td>34±3.9</td>
<td>36.3±3.6</td>
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</tbody>
</table>

Data are presented as mean±SD, ratios & numbers

Table (2): Mean (±SD) MAP and HR changes occurring throughout the study period in both groups

<table>
<thead>
<tr>
<th></th>
<th>Placebo group</th>
<th>Clonidine group</th>
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<tbody>
<tr>
<td></td>
<td>MAP</td>
<td>HR</td>
</tr>
<tr>
<td>Baseline</td>
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<td>73±9</td>
</tr>
<tr>
<td>10 min</td>
<td>98±10</td>
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<tr>
<td>20 min</td>
<td>99±10</td>
<td>73±10</td>
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<tr>
<td>30 min</td>
<td>97±12</td>
<td>73±9</td>
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<tr>
<td>40 min</td>
<td>99±16</td>
<td>75±8</td>
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<tr>
<td>60 min</td>
<td>95±23</td>
<td>74±11</td>
</tr>
<tr>
<td>120 min</td>
<td>96±13</td>
<td>76±16</td>
</tr>
<tr>
<td>180 min</td>
<td>97±18</td>
<td>72±12</td>
</tr>
</tbody>
</table>

Table (3): Patients' distribution according intraoperative verbal analogue scale for tourniquet pain

<table>
<thead>
<tr>
<th>Group</th>
<th>Time</th>
<th>10 min</th>
<th>20 min</th>
<th>30 min</th>
<th>At deflation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>17</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>2</td>
<td>14</td>
<td>12</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td></td>
<td>19</td>
<td>12</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Mild</td>
<td>1</td>
<td>8</td>
<td>11</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
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</table>
Table (4): Mean (±SD) postoperative pain scores

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo group</th>
<th>Clonidine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 min</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40 min</td>
<td>0.4±0.5</td>
<td>0.2±0.4*</td>
</tr>
<tr>
<td>60 min</td>
<td>1.8±1</td>
<td>0.85±0.8*</td>
</tr>
<tr>
<td>90 min</td>
<td>1.55±1.1</td>
<td>1.1±0.79</td>
</tr>
<tr>
<td>120 min</td>
<td>1.85±1.3</td>
<td>1.2±0.83</td>
</tr>
<tr>
<td>180 min</td>
<td>2.15±1.5</td>
<td>1.6±1.5</td>
</tr>
<tr>
<td>Total score</td>
<td>1.52±1.3</td>
<td>0.99±0.95*</td>
</tr>
</tbody>
</table>

*: Significant (P<0.05) versus control group

Table (5): Mean (±SD) duration of postoperative analgesia

<table>
<thead>
<tr>
<th>Group</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo group</td>
<td>148.5±56.1</td>
</tr>
<tr>
<td>Clonidine group</td>
<td>235±32.2*</td>
</tr>
</tbody>
</table>

*: Significant (P<0.05) versus control group

Table (6): Patients' distribution according to number of rescue analgesia requests

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo group</th>
<th>Clonidine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Once</td>
<td>5 (25%)</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Twice</td>
<td>11 (55%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Trice</td>
<td>4 (20%)</td>
<td>2 (10%)</td>
</tr>
</tbody>
</table>

Fig. (1): Patients' distribution among each group according to degree of tourniquet pain
Fig. (2): Mean total postoperative pain score in clonidine group compared to placebo group.

Fig. (3): Mean pain score recorded throughout the first postoperative 3-hr in clonidine versus placebo.
Fig. (4): Mean duration of postoperative analgesia in patients received clonidine versus those received placebo.

Fig. (5): Patients' distribution among each group according to times of request of rescue analgesia.