A Comparative Study of Two Different Doses of Epidural Clonidine as an Adjuvant for Post Operative Analgesia After Lower Limb Surgeries

KEYWORDS

clonidine, Morphine, bupivacaine, lower limb surgeries, post operative analgesia.

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ABSTRACT

Background: Severe pain is common after surgeries like TKR (Total Knee Replacement) and can delay early commencement of physiotherapy which is the most important determinant of successful postoperative knee rehabilitation. Attainment of adequate postoperative analgesia in patients who undergo lower limb surgeries is often a challenging task. The current and the most common approach in post operative pain management is multimodal analgesia. Various combinations of epidural clonidine, opioids and local anaesthetics have improved post operative analgesia after lower limb surgeries. This study is done to determine the optimal epidural bolus dose of clonidine, which provides the best analgesia and least side effects.

Aim of the study: This study was designed to evaluate the effects of the addition of two different doses of clonidine to epidural morphine and bupivacaine on duration and efficacy of post operative analgesia and side effects after lower limb surgeries

Materials and methods: The study included 60 patients, ASA I and II scheduled for lower limb surgeries at ASRAM Medical College and Hospital, Eluru. These patients were randomly allocated into three groups, 20 patients in each group. Group A where patients received 2-mg morphine + 12.5mg Bupivacaine, Group B where patients were given 2-mg morphine + 12.5mg Bupivacaine+75µg of clonidine while patients in Group C received 2-mg morphine + 12.5mgBupivacaine + 100µg of clonidine. Postoperative pain was assessed using Visual Analog Scale (VAS). Demographics, time intervals, and continuous variables (SBP, DBP, heart rate, VAS) were analyzed using the one-way analysis of variance (ANOVA) test. Categorical data (ASA, sex) were analyzed using chi-square test. In all cases, \( P < 0.001 \) was considered statistically significant.

Results: Demographic characteristics as well as intraoperative SBP, heart rate and were similar among groups. Epidural administration of combinations of local anesthetic bupivacaine(1mg/ml), opioid morphine(0.2mg/ml), and clonidine(7.5µg/ml in group B and 100µg/ml in group C) resulted in significant improvement of analgesia after lower limb surgeries. The total amount of drug consumed in clonidine groups was significantly lower compared with control group (group-A) \( p<0.001 \). The clonidine groups (group-B, group-C) compared with control group (group-A) had significantly less pain at 4hr, 12hr and 16hrs as \( p<0.001 \). Systolic blood pressure and diastolic blood pressure were low for the clonidine groups (group-B, group-C) compared to control group (group-A) at all sampling intervals. Relative hypotension in group-C who received higher dose of clonidine (435µg over 24 hr period) for diastolic blood pressure were recorded which were statistically significant at 16hr, 20hr and 24hrs though did not require any therapeutic intervention. In this study 10 patients in group-C and 5 patients in group-B have higher (score 2) sedation scores at 4hr and 16hr, scores were statistically significant between clonidine groups and control group at 4hr.

Conclusion: When added to lumbar epidural mixture of bupivacaine, morphine and clonidine augmented analgesia both in quality and duration after lower limb surgeries in comparison with patients who received bupivacaine and morphine drug combination only.

Group with lower concentration of clonidine group-B (7.5µg/ml) produced significant analgesia compared to control group ( group-A with bupivacaine(0.125%) and morphine 0.2mg/ml only) and experienced significantly less side effects of clonidine compared to group-C (with 10µg/ml of clonidine) .

Introduction

Pain is one of the most unpleasant experiences for mankind. International association for the study of pain defines the term pain thus: “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such pain.”

Surgical pain is a kind of acute pain, which is always a challenge to the anaesthesiologist. However, the patients’ problems of pain do not end with the surgical procedure. Pain during post-operative period is also of concern to the anaesthesiologist.

Post-operative pain control is generally best managed by anaesthesiologist, because they offer regional techniques of anesthesia as well as pharmacological expertise in analgesics. Adequate postoperative analgesia after total knee Replacement (TKR) is often a challenging task. Pain is rated as severe in the majority of patients who undergo TKR. This can easily hinder early physical therapy, which is the most important factor for successful postoperative knee rehabilitation. Postoperative pain control is complicated by rehabilitation and the recovery goal of continuous movement of the joint.

The current trend in postoperative pain management is multimodal analgesia.

Effective postoperative analgesia can be provided by neuraxially applied local anesthetics or opioids, which may be accompanied by unwanted side effects, such as motor block, hypotension, or respiratory depression.
The analgesic neuraxial effect of the alpha-2-adrenergic agonist clonidine is well described.1-10

The alpha-2-adrenergic agonist clonidine produces analgesia by a different mechanism that mimics the effect of endogenously released norpinephrine to stimulate post-synaptic alpha-2 receptors in the spinal cord. Intrathecal (IT) and epidural clonidine provide effective analgesia in volunteers11, in patients in labor12, and in those with post-operative pain13, without inducing respiratory depression or motor block.14

intrathecal morphine is a well described modality for providing prolonged postoperative analgesia. Unfortunately, both drugs are limited by their unique side effect profiles.15-16

First, we hypothesized that the combined administration of epidural morphine and clonidine would provide superior postoperative analgesia in patients undergoing lower limb surgeries with comparison of two doses of clonidine. Second in addition taking advantage of the potential synergy between neuraxial morphine and clonidine, we hypothesized that the doses of these drugs could be reduced, therefore minimizing their side effect profiles.

Aim and objectives:
To evaluate the effects of the addition of two different doses of clonidine to epidural morphine and bupivacaine on duration and efficacy of post operative analgesia and side effects after lower limb surgeries.

Review of literature
From time to time man has resorted to many means in his search for relief of pain. Painless surgery and painless post operative period is probably the greatest achievement that has been granted to the patients. There are various methods used, each one carrying its own merits and demerits.

During the past two decades, epidural and intrathecal administration of drugs have been increasingly used for relief of pain.

Motsch J, Graber, Ludwig et al in 1990 compared the analgesic effect of the combination of epidural morphine and clonidine versus epidural morphine alone in patients with postoperative pain. They reported pain scores were lower in clonidine and morphine group compared to epidural morphine only group.17

Mogensen T, Eliasen K, Ejlersen et al in 1992 compared the value of adding clonidine to a low-dose epidural regimen for postoperative pain by a randomized, double-blind, placebo-controlled trial. They concluded that a continuous low-dose epidural clonidine infusion enhances analgesia from a combined low-dose epidural bupivacaine and morphine regimen after hysterectomy.18

Marjan Jahangiri, J W P Bradley, Dark et al in 1994 studied combined efficiency of epidural infusion containing diamorphine, bupivacaine and clonidine in preventing phantom limb pain in a prospective controlled study undergoing lower limb amputation. They concluded that perioperative epidural infusion of diamorphine, clonidine and bupivacaine is safe and effective in reducing the incidence of phantom pain after amputation.19

Michael J. Paech, J. G. Pavy, E. P. Orlikowski, et al in 1997 studied the effect of adding clonidine in different doses to epidural Bupivacaine and fentanyl infusion on postoperative analgesia in patients undergoing abdominal gynecological surgeries. The study was randomized and double blinded. They also studied to determine an effective dose rate that would minimize the sedative and hemodynamic effects. They concluded that high-quality analgesia after abdominal surgery produced by postoperative epidural bupivacaine and fentanyl was further enhanced by the addition of epidural clonidine.20

Brian D. Sites, Michael Beach, Russell Biggs et al in 2003 compared the effect of intrathecal Clonidine with morphine versus morphine in a prospective, randomized placebo-controlled study on postoperative analgesia after total knee arthroplasty. They concluded that intrathecal morphine, the combined administration of clonidine and morphine reduces postoperative IV morphine use and improves the VAS score at 24 hours. There was an increase in relative hypotension which did necessitate intervention.21

Marjan Jahangiri, C H Dark, A P Jayatunga et al studied the effect of adding clonidine to epidural bupivacaine and diamorphine on post operative analgesia in patients undergoing lower limb amputation. They concluded that perioperative epidural infusion of diamorphine, clonidine and bupivacaine is safe and effective in reducing the incidence of phantom pain after amputation.22

B.S.Sethy, Mary Samuel, Deepak et al in 2007 studied the effect on post operative analgesia provided by low dose intrathecal clonidine admixed with bupivacaine as compared to bupivacaine alone. They concluded that addition of clonidine to bupivacaine in the dose 1µg/kg intrathecally significantly increased the duration of analgesia compared to bupivacaine alone without significant side effects.23

Yuan-Shiou Huang, Liu-Chi Lin, Billy K et al in 2007 studied the effect of adding clonidine to epidural ropivacaine and morphine on post operative analgesia in patients undergoing Total knee Arthroplasty. In that double blind study they also sought to determine the optimal epidural bolus dose of clonidine which provides the best analgesia and fewest side effects. They concluded that by adding clonidine to lumbar epidural mixture of ropivacaine and morphine augmented analgesia after TKA surgery without significant adverse effects in lower concentrations of clonidine. They concluded that by adding clonidine to a lumbar epidural mixture of ropivacaine.24

Materials and methods
This randomized study after approval from ethical committee was conducted in 60 patients. Informed consent was obtained from each patient under study.

Inclusion Criteria
- Age group 40 – 80 years.
- Both sexes.
- ASA grade I and II.

Exclusion Criteria
- H/O allergic reaction and CI to any of the study drugs.
- CI to epidural catheter placement.
- CI to use of opioids, NSAIDS, corticosteroids.
- Inability to understand VAS (visual analogue scale).
- DBP > 100 mm of Hg

After the pre anaesthetic checkup patients were recruited for the study as per the inclusion and exclusion criteria.
Patients were familiarized with visual analogue scale at the time of pre anaesthetic checkup.

60 patients undergoing lower limb surgeries were randomly divided into 3 groups of 20 patients each to receive:

- **Group A**: 2 mg morphine + 12.5 mg (2.5 ml of 0.5%) Bupivacaine and Normal saline to make 10 ml.
- **Group B**: 2 mg morphine + 75 µg Clonidine + 12.5 mg (2.5 ml of 0.5%) Bupivacaine and Normal saline to make 10 ml.
- **Group C**: 2 mg morphine + 100 µg Clonidine + 12.5 mg (2.5 ml of 0.5%) Bupivacaine and Normal saline to make 10 ml.

**Pre Medication:**

All the patients were premedicated the night before and on the day of surgery with Tab. Omeprazole-20 mg, Tab. Alprazolam- 0.5 mg. Inj. Tramadol-1 mg/kg was given IM one hour before surgery.

Pre operatively lumbar epidural space was identified between L2-L3/L3-L4 and catheter inserted and cephalically advanced up to 3-4 cm in the epidural space.

Epidural catheter will be activated at the end of the surgery by injecting the epidural analgesic mixture of volume 10 ml.

Top up dose was given whenever VAS > 4.

Top up dose of 10 ml mixture consist of 2 mg of morphine+0.125% bupivacaine.

Visual analogue scale, Heart rate, Systolic blood pressure, Diastolic blood pressure, Sedation score were measured every 4 hr up to 24 hrs post operatively.

Duration between activation of epidural catheter (first epidural analgesic dose) and first top up dose and total number of top up doses given up to 24 hrs in each group were recorded.

**Pain evaluation:** A 0 – 10 scale VAS with end points labeled no pain and worst possible pain

Pain intensity was measured every two hours up to 24 hrs post operatively

**Sedation:** Score noted every two hours up to 24 hrs post operatively as per the following scale.

**Scale:**

1. Awake and alert
2. Awake but drowsy responsive to verbal stimulus
3. Drowsy but arousable responsive to physical stimulus
4. Unarousable not responsive to physical stimulus

**Sensory level:** Assessed by pinprick

**Data analysis:**

The collected data was summarized by calculating the mean and standard deviation and presented in the form of table and diagrams. Paired “t” test and analysis of variance for repeated measures were used for the analysis of significance. Chi Square test was used to obtain other possible associations.

**Observation and Results**

Demographic data like age, sex and ASA physical status are presented as mean ± SD where appropriate. There were twenty patients in each study group, and the groups were demographically similar.

**TABLE-I: AGE DISTRIBUTION (MEAN±SD):**

<table>
<thead>
<tr>
<th></th>
<th>GROUP-A</th>
<th>GROUP-B</th>
<th>GROUP-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEAN±SD</td>
<td>61.8 ± 4.3</td>
<td>61.8 ± 5.88</td>
<td>60.7 ± 6.86</td>
</tr>
</tbody>
</table>

**Table-I and graph-I shows age distribution of the three Groups. Group A is the bupivacaine 0.125% + morphine 2 mg group, Group B is the bupivacaine 0.125% + morphine 2 mg + clonidine 75 µg group and group C is the bupivacaine 0.125% + morphine 2 mg + clonidine 100 µg group. The range of age is comparable in all the groups’ i.e Group A 61.8 ± 4.3, Group B 61.8 ± 5.88 and Group C 60.7 ± 6.86.**

**TABLE II: SEX DISTRIBUTION (MEAN±SD):**

<table>
<thead>
<tr>
<th>SEX</th>
<th>GROUP-A</th>
<th>GROUP-B</th>
<th>GROUP-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>11</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

p = NS (chi-square)
The three Groups had comparable patients in terms of male and female distribution. Group-A (bupivacaine 0.125% + morphine 2mg) had 9 male and 11 female patients. Group-B (bupivacaine 0.125% + morphine 2mg + clonidine 75µg) had 7 male and 13 female patients. Group-C (bupivacaine 0.125% + morphine 2mg + clonidine 100µg) had 8 male and 12 female patients.

**TABLE III: ASA PHYSICAL STATUS (MEAN±SD):**

<table>
<thead>
<tr>
<th>ASA STATUS</th>
<th>ASA-1</th>
<th>ASA-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A</td>
<td>6</td>
<td>14</td>
</tr>
<tr>
<td>Group-B</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Group-C</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

P = NS (chi-square)

All the patients in our study belonged to ASA physical status I and II and the distribution of these patients randomly into the three study groups were comparable.

**ANALGESIC EFFECTS AND TOTAL DRUG CONSUMPTION**

Means for demographic variables did not differ significantly among the three groups (Table 1, 2 and 3). No patients required rescue analgesic (inj. Tramadol). No patients were excluded from the study. Patients in the clonidine groups experienced significantly less pain than those in the control group during the 24 hr period after the surgery.

**Table-IV -Visual analog scale (VAS) pain scores (means)**

<table>
<thead>
<tr>
<th>VAS</th>
<th>0hr</th>
<th>4hr</th>
<th>8hr</th>
<th>12hr</th>
<th>16hr</th>
<th>20hr</th>
<th>24hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3.4</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Group-B</td>
<td>4</td>
<td>1.6</td>
<td>4</td>
<td>1.55</td>
<td>4</td>
<td>3.8</td>
<td>4</td>
</tr>
<tr>
<td>Group-C</td>
<td>4</td>
<td>1.4</td>
<td>4</td>
<td>1.6</td>
<td>4</td>
<td>2.7</td>
<td></td>
</tr>
</tbody>
</table>

Visual analog scale (VAS) pain scores for the control Group (Group-A) were significantly higher at 4hr, 12hr and 16hr than those for the 2 clonidine Groups (Group-B, Group-C).

Visual analog scale (VAS) pain scores for the Group-B with lower dose of clonidine (75µg) were higher at 4hr, 16hr and 24hr. VAS score was lower at 12 hr.

The total volumes of analgesic solution consumed by the different Groups during the study period were Group-A 67 ± 4.58ml; Group-B 50 ± 4.47ml; Group-C 43.5 ± 4.769ml.
ANALYSIS

Source of variation | Sum of squares | DF | Mean square
--- | --- | --- | ---
Between Groups (influence factor) | 5890.0000 | 2 | 2945.0000
Within Groups (other fluctuations) | 1275.0000 | 57 | 22.3684
Total | 7165.0000 | 59 |  
F-ratio | 131.659 |  
Significance level | P < 0.001 |  

Student-Newman-Keuls test for all pair wise comparisons

<table>
<thead>
<tr>
<th>Factor</th>
<th>n</th>
<th>Mean</th>
<th>Different (P&lt;0.05) from factor nr</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 100C</td>
<td>20</td>
<td>43.5000</td>
<td>(2)(3)</td>
</tr>
<tr>
<td>(2) 75C</td>
<td>20</td>
<td>50.0000</td>
<td>(1)(3)</td>
</tr>
<tr>
<td>(3) P</td>
<td>20</td>
<td>67.0000</td>
<td>(1)(2)</td>
</tr>
</tbody>
</table>

Group-C used a significantly lower volume of analgesic solution (p<0.001) than the other Groups during first 24hrs after surgery.

Groups with clonidine (Group-B and Group-C) used a significantly lower volume of analgesic solution (p<0.001) than the control Group (Group-A)

HEMODYNAMIC EFFECTS

Table V - SYSTOLIC BLOOD PRESSURE (MEAN)

<table>
<thead>
<tr>
<th>SBP</th>
<th>0HR</th>
<th>4HR</th>
<th>8HR</th>
<th>12HR</th>
<th>16HR</th>
<th>20HR</th>
<th>24HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A</td>
<td>134.8</td>
<td>109.8</td>
<td>126</td>
<td>129.7</td>
<td>130.5</td>
<td>133.1</td>
<td>132.7</td>
</tr>
<tr>
<td>Group-B</td>
<td>134.4</td>
<td>108.7</td>
<td>122.4</td>
<td>129.6</td>
<td>130.25</td>
<td>132.2</td>
<td>129.65</td>
</tr>
<tr>
<td>Group-C</td>
<td>135.8</td>
<td>108.3</td>
<td>122.1</td>
<td>129.2</td>
<td>129.3</td>
<td>131.8</td>
<td>128.7</td>
</tr>
</tbody>
</table>

The systolic blood pressures were lower in clonidine Groups (Group-B, Group-C) than in the control Group (Group-A) but the difference was not statistically significant.

Table VI - DIASTOLIC BLOOD PRESSURE

<table>
<thead>
<tr>
<th>DBP</th>
<th>0HR</th>
<th>4HR</th>
<th>8HR</th>
<th>12HR</th>
<th>16HR</th>
<th>20HR</th>
<th>24HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A</td>
<td>71.4</td>
<td>61.5</td>
<td>69.2</td>
<td>69.75</td>
<td>70.15</td>
<td>82.1</td>
<td>81.6</td>
</tr>
<tr>
<td>Group-B</td>
<td>78.1</td>
<td>59.4</td>
<td>69.15</td>
<td>69.1</td>
<td>67.7</td>
<td>69.2</td>
<td>66.1</td>
</tr>
<tr>
<td>Group-C</td>
<td>74</td>
<td>58.6</td>
<td>68.2</td>
<td>68.9</td>
<td>61.5</td>
<td>68.7</td>
<td>65.7</td>
</tr>
</tbody>
</table>

Group-C used a significantly lower volume of analgesic solution (p<0.001) than the other Groups during first 24hrs after surgery.

Graph-6: Comparison of systolic blood pressures between the Groups

Graph-7: Comparison of diastolic blood pressures between the Groups
The diastolic blood pressure in clonidine Groups (Group-B, Group-C) were lower compared to control Group (Group-A) at all sampling intervals during post operative period. The difference was statistically significant at 16hr, 20hr and 24hrs.

The difference of diastolic blood pressure between clonidine Groups (Group-B and Group-C) were not statistically significant.

**TABLE – VII - HEART RATE**

<table>
<thead>
<tr>
<th>HR</th>
<th>0hr</th>
<th>4hr</th>
<th>8hr</th>
<th>12hr</th>
<th>16hr</th>
<th>20hr</th>
<th>24hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A</td>
<td>77.25</td>
<td>65</td>
<td>75.5</td>
<td>77.65</td>
<td>77.9</td>
<td>78.1</td>
<td>78</td>
</tr>
<tr>
<td>Group-B</td>
<td>77.45</td>
<td>65.3</td>
<td>75.2</td>
<td>77.3</td>
<td>75.5</td>
<td>77.6</td>
<td>76.45</td>
</tr>
<tr>
<td>Group-C</td>
<td>77.2</td>
<td>65.25</td>
<td>75</td>
<td>77.55</td>
<td>72.4</td>
<td>74.7</td>
<td>74.9</td>
</tr>
</tbody>
</table>

The heart rate in clonidine Groups (Group-B, Group-C) were lower compared to control Group (Group-A) at all sampling intervals during post operative period. The difference was statistically significant at 16hr, 20hr and 24hrs.

The difference of diastolic blood pressure between clonidine Groups (Group-B and Group-C) were not statistically significant.

**Graph-8:- comparison of heart rates between the Groups**

The heart rate in clonidine Groups (Group-B, Group-C) were lower compared to control Group (Group-A) at all sampling intervals during post operative period. The difference was statistically significant at 16hr, 20hr and 24hrs.

The difference of diastolic blood pressure between clonidine Groups (Group-B and Group-C) were not statistically significant.

**SEDATION**

**Table- VIII (mean of sedation scores)**

<table>
<thead>
<tr>
<th>SS</th>
<th>0hr</th>
<th>4hr</th>
<th>8hr</th>
<th>12hr</th>
<th>16hr</th>
<th>20hr</th>
<th>24hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Group-B</td>
<td>1.25</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Group-C</td>
<td>1.5</td>
<td>1</td>
<td>1</td>
<td>1.55</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**Graph-9:- comparison of sedation scores between the Groups**

10 patients in Group-C and 5 patients in Group-B have higher (score 2) sedation scores at 4hr and 16hr, but the sedation scores were not statistically significant between clonidine groups. Scores were statistically significant between clonidine groups and control group at 4hr. Group-C experienced a higher incidence of clonidine related side effects than groups A & B (p<0.05).

**ANOVA (one way analysis of variance) for SEDATION at 4hr**

**Source of Variation**

<table>
<thead>
<tr>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>P-value</th>
<th>F crit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Groups</td>
<td>2.5</td>
<td>2</td>
<td>1.25</td>
<td>8.142857</td>
<td>0.000775</td>
</tr>
<tr>
<td>Within Groups</td>
<td>8.75</td>
<td>57</td>
<td>0.153509</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11.25</td>
<td>59</td>
<td>0.058039</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions:-**

All the three groups A, B and C were comparable with respect to age, sex, weight and ASA physical status.

Base line pulse rate, systolic blood pressure and diastolic blood pressure were comparable in all the three groups.

Intraoperative and postoperative hemodynamics in clonidine groups (groups B and C) are more stable when compared to group A.

Visual analog scale (VAS) pain scores for the group A were significantly higher at 4 hr, 12 hr and 16 hr than those for
References
23. B.S.Sethy, Mary Samuel, Deepak . Efficacy of analgesic effects of low dose intrathecal clonidine as adjuvant to bupivacaine. Indian journal of anaesthesia 2007;51(S):415-419
50. Telford RJ and Holway TE: Observations on deliberate dural puncture.


