Comparison of Analgesic Efficacy of Single Dose of Ketorolac with Single Dose of Pregabalin with a Combination of Ketorolac and Pregabalin in Patients Undergoing Unilateral Total Knee Replacement

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ABSTRACT

BACKGROUND
Preventing and treating post-operative pain after TKR remains challenging as it plays an important role in early mobility, decreasing hospital stay and decreasing complications like DVT, pulmonary embolism, and nosocomial infections. Pre-emptive analgesia is where analgesia is initiated before surgery. This study was done to compare the pre-emptive efficacy of an NSAID alone and when combined with a GABA analogue and when GABA analogue is used alone with respect to duration of analgesia, reduction in total post-operative requirements of opioids and NSAIDS in acute post-operative period.

METHODS
Ninety patients of either sex in ASA grade I and II were randomly allocated to one of the three groups of thirty each. Patients in Group A were given single dose of pregabalin 150 mg with tab ketorolac 10 mg, whereas patients in Group B were administered only pregabalin 150 mg, and patients in group c were given only tab ketorolac 10 mg one hour prior to administration of spinal anaesthesia. Time from spinal anaesthesia to the first dose of rescue analgesia was noted. Pain was assessed by Visual Analogue Scale at 12 hr and 24 hrs. Total amount of NSAID (paracetamol) and opioid (butorphanol) required was compared between the 3 groups.

RESULTS
Pre-emptive analgesia with the combination of ketorolac and pregabalin are effective in decreasing the acute pain sensation after total knee replacement. Pregabalin alone has no role in acute post-operative period. Ketorolac when used alone has modest analgesic effect in acute post-operative period. We observed that the patients who were prescribed with pregabalin were not anxious while they were shifted to OT. Post operatively only one patient had dizziness. 4 patients in group A had bradycardia which got revived with treatment. No other adverse effects were observed.

CONCLUSIONS
Combined ketorolac and pregabalin when used as preemptive analgesia showed better analgesic adequacy in acute post-operative period. Ketorolac alone showed moderate analgesic adequacy and pregabalin alone has no role as analgesic in the acute post-operative period.

KEYWORDS
Pregabalin, Ketorolac, Spinal Analgesia, Pre-Emptive Analgesia
**BACKGROUND**

Pre-emptive analgesia is analgesia given before the onset of painful stimuli to prevent central sensitization of nervous system to subsequent stimuli that could increase pain. The idea of pain prevention was first introduced into clinical practice by Crile in 1913 and further developed by Wall and Woolf who suggested that 'simple changes in the timing of treatment can have profound effects on postoperative pain'.

In 1983 by Woolf showed evidence for a central component of post injury pain hypersensitivity in experimental studies. Various studies have demonstrated that various anti-nociceptive techniques applied before injury were more effective in reducing the post injury central sensitization phenomena as compared with administration after injury. Multimodal analgesia is the rational approach to pain management since no single analgesia targets all types of pain. Epidural, peripheral nerve blocks, and local articular injections, patient controlled analgesia have been reported to give good results but they are associated with many side-effects such as headache, hypotension, neurologic bladder, and dense motor block.

AIM of the study – GABA analogues like Gabapentin is a structural analogue of gamma amino butyric acid, which was introduced in 1994 as an antiepileptic drug, particularly for partial seizures. These drugs supress the hyper excitability of dorsal horn neurons caused due to tissue damage. They are also known to bind to the alpha 2 – delta subunit of voltage gated calcium channels and they have anxiolytic effect. But these drugs carry side effects like somnolence, dizziness, sedation, vomiting, headache etc. The primary aim of this study was to compare the pre-emptive analgesic efficacy of ketorolac in the acute post-operative period when used alone compared with the analgesic efficacy when used with pregabalin. Pregabalin was selected in our study as it was 6 times more affinity to calcium channels than gabapentin and it has less side effects like gastric sparing.

**METHODS**

Ninety patients scheduled for unilateral total knee replacement ranging from 40-80 years of age in physical status, ASA grade I and II were selected. Clearance from institutional Ethics committee was obtained. They were randomly allocated to one of the three group of thirty each by allocating the patients alternatively to either group. Patients were excluded if they refused for taking drug, history of renal, cardiac disease, peptic ulcer disease, and coagulopathies. Informed consent was obtained from all the patients. Patients in Group A (n=30) were given single dose of pregabalin 150 mg and ketorolac 10 mg whereas in Group B (n=30) were administered only pregabalin 150 mg orally group C was administered only tab ketorolac 10 mg one hour prior to administration of spinal anaesthesia by the ward staff nurse who was blinded. No other premedication was given. Routine monitoring, in the form of NIBP, pulse oximetry and ECG was instituted on arrival of patient in operation theatre. All patients were preloaded with 10 ml/Kg lactated Ringers solution. Spinal anaesthesia was performed under strict aseptic conditions with 25 gauge Quincke needle 3 ml of 0.5% bupivacaine was given. Any episodes of hypotension was treated with fluid replacement and vasopressors and bradycardia was treated with atropine 0.6 mg. Pain was assessed postoperatively by visual analogue score at 12 hour and 24th hour by the staff nurse in ICU who had no idea about the drugs received by the patient. If VAS score of 3 and more than 3 paracetamol 1 gm was given and if VAS score more than 5 butorphanol 1 mg intravenous was given. Time since spinal anaesthesia to first dose of rescue analgesia asked was noted and total dose of analgesia (paracetamol and butorphanol) in first 24 hours was recorded. Any complications like dizziness, somnolence, diplopa, vomiting, confusion, and urinary retention were recorded in first 24 hours post-operative period.

**RESULTS**

<table>
<thead>
<tr>
<th>N</th>
<th>Mean± S.D. (Hours)</th>
<th>Minimum</th>
<th>Maximum</th>
<th>F-Value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>90</td>
<td>9.71±1.795</td>
<td>6</td>
<td>12</td>
<td>101.690**</td>
</tr>
<tr>
<td>Group B</td>
<td>90</td>
<td>4.49±5.33</td>
<td>4</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Group C</td>
<td>90</td>
<td>6.45±1.625</td>
<td>4</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Time to Rescue Analgesia**

**Table 2. VAS Score**

<table>
<thead>
<tr>
<th>N</th>
<th>Mean± S.D.</th>
<th>Minimum</th>
<th>Maximum</th>
<th>F-Value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS12HR</td>
<td>Group A</td>
<td>30</td>
<td>3.63±.809</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Group B</td>
<td>30</td>
<td>4.63±1.048</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Group C</td>
<td>30</td>
<td>4.93±1.311</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>4.40±1.216</td>
<td>2</td>
<td>9</td>
<td></td>
</tr>
</tbody>
</table>

| VAS24HR | Group A | 30 | 3.43±.898 | 1 | 5 | 31.288** | 0.000 |
| | Group B | 30 | 3.53±.629 | 2 | 3 | |
| | Group C | 30 | 5.17±1.234 | 3 | 8 | |
| Total | 90 | 4.04±1.235 | 1 | 8 | |

**Table 2. VAS Score**

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Patients who were given both pregabalin and ketorolac had lesser VAS scores than patients who were given only ketorolac and only pregabalin. Patients prescribed with
kеторолак, как и пьезогеналин, имел наивысшие значения VAS в течение 12 часов и 24 часов.

<table>
<thead>
<tr>
<th>Total Dose Given in 24 Hrs</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Chi-Square</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol (gms.)</td>
<td>1-dose</td>
<td>12 (40.0)</td>
<td>4 (13.3)</td>
<td>12 (40.0)</td>
</tr>
<tr>
<td></td>
<td>2-dose</td>
<td>18 (60.0)</td>
<td>25 (83.3)</td>
<td>18 (60.0)</td>
</tr>
<tr>
<td></td>
<td>3-dose</td>
<td>0 (0.0)</td>
<td>1 (3.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>30 (100.0)</td>
<td>30 (100.0)</td>
<td>30 (100.0)</td>
<td></td>
</tr>
<tr>
<td>OPIOID (mg.)</td>
<td>Nil</td>
<td>22 (73.3)</td>
<td>14 (46.7)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td></td>
<td>1-dose</td>
<td>8 (26.7)</td>
<td>16 (53.3)</td>
<td>22 (73.3)</td>
</tr>
<tr>
<td></td>
<td>2-dose</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>Total</td>
<td>30 (100.0)</td>
<td>30 (100.0)</td>
<td>30 (100.0)</td>
<td></td>
</tr>
</tbody>
</table>

Преемптивная анальгезия с комбинированным кеторолаком и пьезогеналином значительно снизила количество парациетамола и опиоидов в постоперационном периоде.

**DISCUSSION**

Преемптивная анальгезия определяется как лечение, которое начинается перед операцией в целях предотвращения образования централизованного ощущения боли от зон, которые могут быть повреждены в процессе операции. В этом исследовании было показано, что преемптивная анальгезия уменьшает интенсивность послеоперационной боли и предотвращает развитие хронической боли, связанной с изменением в чувствительных нервах.

Кеторолак - это селективный нестероидный противовоспалительный препарат (NSAID). Это эффективное противовоспалительное средство, которое ингибирует синтез простагландинов, но также может блокировать тромбоциты и увеличивать время кровотечения. Он доступен в виде инъекции и обладает биодоступностью 80%. Его действие начинается через 4-6 часов, и он помогает уменьшить послеоперационную боль.

Пьезогеналин - это аналгетик, который действует через связывание с α2-дельта субъединиц. Он может быть полезным в управлении хронической нейропатической болью, как показано в различных исследованиях.

Limitations

В нашем исследовании мы обнаружили, что только одна доза кеторолака в 10 мг и в лечебном плане выбрана. Дополнительные исследования должны быть проведены с более высокими дозами кеторолака для оценки анальгетического эффекта.

**CONCLUSIONS**

Комбинированный кеторолак и пьезогеналин показали лучший анальгетический эффект в постоперационном периоде. Кеторолак, применяемый в качестве преемптивной анальгезии, показал лучший анальгетический эффект, чем пьезогеналин, применяемый самостоятельно.

**REFERENCES**