Pregablin in preventing chronic pain post total knee arthroplasty

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Chronic pain

• Despite advances in surgical technology and perioperative anesthetic management
  – the incidence of chronic neuropathic pain after TKA surgery has not decreased
  – and is as high as 12.7% at 6 mo postoperatively

Incidence

• In fact, up to 15% of patients evaluated 5 to 8 years after TKA have significant pain and functional limitation

Perioperative Oral Pregabalin Reduces Chronic Pain After Total Knee Arthroplasty: A Prospective, Randomized, Controlled Trial

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The Primary Objective

• To evaluate whether pregabalin given
  – before and
  – for 14 days after TKA
• Will reduce the incidence of neuropathic pain assessed at 6 mo postoperatively
Secondary Outcomes

• Assessed include
  – knee range of motion (ROM)
  – Acute postoperative opioid requirements
  – Time until hospital discharge criteria is achieved
Inclusion Criteria

- Scheduled to undergo a primary TKA
- With a diagnosis of osteoarthritis of the operative knee
- Had the ability to understand and read English
Exclusion Criteria

- If they were younger than 21 yr or older than 80 yr
- Had an ASA physical status of IV
- Had prior use of gabapentin (or pregabalin) or NSAIDs within 2 wk before surgery
- Had a history of neuropathic pain or any other chronic pain condition, other than osteoarthritis pain
- Were pregnant
- Had a sulfa allergy
- Were currently enrolled in another investigational study
Treatment Protocol

• Patients were randomly assigned to receive either the study medication or placebo

• Patients randomized to the experimental arm of the study received pregabalin
  – 300 mg orally 1–2 h before surgery
  – 150 mg twice daily for the first 10 postoperative days
  – 75 mg twice daily on Days 11 and 12
  – 50 mg twice daily on Days 13 and 14
Control patients

- Received po matched placebo tablets, at identical time points
- Both pregabalin and placebo capsules provided by Pfizer (New York, NY)
- After discharge, patients were provided with diaries in which they recorded the exact times at which they took pregabalin/placebo each day
- They were asked to return any unused drug, along with the diaries, at their 1-mo visit to the surgeon’s office
• The physicians and nurses managing the patient perioperatively
• The personnel involved with postoperative pain assessments and management of the epidural infusion
• Physical therapists, and the study patients were
  
  Blinded to group assignments
Anesthesia

• Combined spinal-epidural anesthetic was used for the operation
• After obtaining clear CSF, 1.5 mL of 0.75% hyperbaric bupivacaine with 25 mcg of Fentanyl was injected.
• An Epidural catheter was inserted
• Patients were sedated with IV propofol for the duration of the surgery
Outcome Measures and Results
Adverse Events

• Assessed daily during hospitalization
  – Sedation
  – confusion
  – dizziness
  – headache
  – dry mouth
  – peripheral edema
  – diplopia

• Postoperative nausea and vomiting and pruritus

• Adverse events data after hospitalization were supplemented by the surgeon’s clinical records up to the 6-mo patient visit
Adverse Events

• Sedation, confusion, and dry mouth occurred more frequently in the pregabalin group than in the placebo group on the day of surgery and the first postoperative day

• By postoperative day 2, no adverse event reached statistical significance
Table 2. Incidence of Adverse Events on Day of Surgery (Day 0), Postoperative Days 1 and 2

<table>
<thead>
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<th></th>
<th>Pregabalin</th>
<th>Placebo</th>
<th>Day 1</th>
<th>Pregabalin</th>
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<td><em>n = 106</em></td>
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<tr>
<td>Sedation</td>
<td>16 (13%)</td>
<td>4 (3%)</td>
<td>28 (26%)</td>
<td>15 (14%)</td>
<td>0.019*</td>
<td>15 (15%)</td>
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<td>Confusion</td>
<td>6 (5%)</td>
<td>0 (0%)</td>
<td>14 (13%)</td>
<td>4 (4%)</td>
<td>0.011*</td>
<td>9 (9%)</td>
<td>4 (4%)</td>
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<td>Dizziness</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>18 (17%)</td>
<td>12 (11%)</td>
<td>0.197</td>
<td>10 (10%)</td>
<td>8 (8%)</td>
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<tr>
<td>Headache</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>0.076</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
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<tr>
<td>Dry mouth</td>
<td>3 (3%)</td>
<td>0 (0%)</td>
<td>7 (7%)</td>
<td>1 (1%)</td>
<td>0.027*</td>
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<td>Nausea</td>
<td>9 (8%)</td>
<td>10 (8%)</td>
<td>13 (12%)</td>
<td>16 (15%)</td>
<td>0.642</td>
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<td>Vomiting</td>
<td>3 (3%)</td>
<td>3 (3%)</td>
<td>4 (4%)</td>
<td>6 (6%)</td>
<td>0.479</td>
<td>1 (1%)</td>
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<td>Pruritus</td>
<td>1 (1%)</td>
<td>6 (5%)</td>
<td>4 (4%)</td>
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<td>Peripheral edema</td>
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<td>0 (0%)</td>
<td>0 (0%)</td>
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<td>0.316</td>
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<td>0 (0%)</td>
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<tr>
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<td>Diplopia</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0.323</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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* There was a statistically significant difference (P < 0.05) between groups.
Lower Extremity Chronic Neuropathic Pain

• Patients were evaluated in a blinded fashion at 3 and 6 mo after TKA using the self-report version of the Leeds Assessment of Neuropathic Symptoms and Signs pain scale (SLANSS)

• The 3- to 6-mo time points are often used to define when acute postsurgical pain becomes chronic pain

The LANSS Pain Scale

• Would you describe your pain as strange unpleasant sensations in your skin? (e.g. pricking, tingling, pins and needles) – Yes/No

• Does the skin in the painful areas look different to normal? (e.g. mottled, more red/pink than usual) – Yes/No

• Is the skin in the affected area abnormally sensitive to touch? (e.g. unpleasant sensations if lightly stroked, painful to wear tight clothes) – Yes/No

• Does your pain come on suddenly in bursts for no apparent reason when you are still? (e.g. like electric shocks, 'bursting' or 'jumping' sensations) – Yes/No
The LANSS Pain Scale

• Do you feel that skin temperature in the painful area has changed (e.g. hot, burning) – Yes/No

• Does stroking the affected area of skin with a piece of cotton wool produce an unpleasant painful sensation? – Yes/No

• Does touching the affected area of skin with a sharp needle feel sharper or duller when compared to an area of normal skin? – Yes/No
Lower Extremity Chronic Neuropathic Pain

• Patients with an S-LANSS score of 12 or more at 6 mo came to the physician’s office for a standardized physical examination

• The incidence of neuropathic pain at 3 and 6 mo postsurgery was less frequent in the pregabalin group compared with the placebo group
At 3 Months

• The incidence of neuropathic pain after TKA was 0% (0 of 113 patients) in the pregabalin group compared with 8.7% (10 of 115) in the placebo group ($P \ 0.001$)

• The incidence of allodynia in the operated leg was also lower ($P \ 0.002$) for the pregabalin group (2%, 2 of 113) than for the placebo group (12%, 14 of 115)

• The incidence of hyperalgesia in the operated leg was lower ($P \ 0.009$) for the pregabalin group (8%, 8 of 113) than for the placebo group (20%, 23 of 115)
At 6 Months

• The incidence of neuropathic pain was 0% (0 of 113) in the pregabalin group and 5.2% (6 of 115) in the placebo group (P 0.014)

• The incidence of allodynia in the operated leg was also lower (P 0.002) for the pregabalin group (0%, 0 of 113) than for the placebo group (8%, 9 of 115)

• The incidence of hyperalgesia in the operated leg was lower (P 0.006) for the pregabalin group (2%, 2 of 113) than for the placebo group (11%, 12 of 115)
Lower Extremity Chronic Neuropathic Pain

• The neuropathic pain in all 6 patients with an S-LANSS score of 12 or more at 6 mo was confirmed by physical examination by the physician

• All 6 patients had allodynia and hyperalgesia to touch, and 5 of 6 had abnormal response to pin prick
Range of Motion

• Patients in the pregabalin group had greater active flexion of the operated knee during postoperative days 1–30 compared with placebo patients
• Passive ROM during postoperative days 1–3 was also improved in the pregabalin group compared with the placebo group
Active range of motion (ROM) of operated knee over postoperative days 1–30
Epidural Drug Use

• In the immediate postoperative period, was less in the pregabalin group (5.77 ± 1.31 mL/h) than in the placebo group (6.40 ± 1.26 mL/h; *P* 0.003)

• *In addition, the number of epidural PCEA* boluses delivered was less in the pregabalin group (0.36/h [0.21–0.55]), than in the placebo group (0.63/h [0.30–0.98]) (*P* 0.009)
Postoperative Pain Assessment

• The NRS values tended to be lower with pregabalin than with placebo at the discharge physical therapy session, during both
  – active ROM (5.2 ± 2.4 vs 6.1 ± 2.4; \( P < 0.059 \)) and
  – passive ROM (6.0 ± 2.3 vs 7.0 ± 2.2; \( P < 0.032 \))
• There was no difference in use of NSAIDs, opioids, or acetaminophen/tramadol between the pregabalin and placebo groups in the 6-mo postsurgery period.

• Placebo group patients were prescribed more gabapentin or pregabalin during this postoperative period than the pregabalin group
Time to Meeting Hospital Discharge Criteria

• Pregabalin group met hospital discharge criteria faster than patients in the control group (mean 60.2 ± 15.8 h compared with 69.0 ± 16.0 h, respectively; \( P \ 0.001 \))

• The actual hospital discharge time, however, was not different between the 2 groups
Discussion

• The study was designed with the intent to prevent spinal cord sensitization by preoperatively administering a recommended upper limit dose (300 mg) of pregabalin that was continued for 14 days after surgery
Discussion

• The first dose at 1–2 h before surgery was not intended to be “preemptive analgesia.”

• Instead, it was to provide coverage immediately after surgery, when it would have been difficult to administer this oral medication
Discussion

- Although they chose a 14-day postoperative regimen, the minimum duration or the dose required to prevent the long-term sequelae of spinal cord sensitization after a major surgery such as TKA cannot be determined from this study.
Discussion

• The 300-mg dose of pregabalin given before surgery produced higher sedation scores at 90 and 120 min after elective ambulatory and short-stay surgery compared with placebo.

Discussion

• Therefore, lower pregabalin doses should be considered in future studies to minimize such side effects, and hopefully, maintaining therapeutic efficacy

• One of the limitations of this study is the absence of dose response data
Hypothesis/Research Question

- Our intent is to answer the question:
  - In adults undergoing a total knee replacement
  - Does taking a low or high dose of perioperative pregabalin
  - Have any benefits on reducing the incidence of chronic pain
  - When compared to patients not taking pregabalin
Objective

- Our objective is to address the gap in current literature where taking low dose perioperative pregabalin may still have the benefits of reducing chronic pain while minimizing the risk of postoperative confusion and sedation.
Focused objective

• Will be to compare the effects of high dose pregabalin (300mg/day) for 2 weeks beginning 1-2 hours before surgery with low dose pregabalin (150mg/day) and placebo.
Methodology

- Prospective, RCT with three treatment groups

- **Inclusion Criteria:**
  - Patients between the ages of 18 - 90
  - Elective total knee arthroplasty
  - Ability to understand and read English
  - Stable and eligible for femoral nerve block with either a spinal anesthetic or general anesthetic
  - Informed consent

- **Exclusion Criteria:**
  - Patients with a history of neuropathic or chronic pain other than osteoarthritis
  - Compromised renal function (CrCl < 30)
  - Prior use of pregabalin or gabapentin
  - Sulfa allergy
  - Pregnant
Methodology

• Sample Size = N patients randomized to following groups

  – Group 1: Placebo

  – Group 2: 300mg oral pregabalin 1-2 hr before surgery, then 150mg BID on POD 1-10, then 75mg BID on POD 11-12, then 50mg BID on POD 13-14.

  – Group 3: 150mg oral pregabalin 1-2 hr before surgery, then 75mg BID on POD 1-10, then 50 mg BID on POD 10-14.
Methodology

• Data Collection:
  - Primary outcome will be measured using the Leeds Assessment of Neuropathic Symptoms and Signs scale at 3 and 6 months postoperatively
  - Secondary outcomes will include hospital standard scales for measuring postoperative sedation, confusion, sleep disturbance, nausea and vomiting, pain, opioid requirements, time to ambulation, time to discharge.

• Data Analysis:
  - All data will be entered in SPSS and analysed using various statistical analytical tools.
Expected Results/Outcomes

• We hope that our data will further support the use of perioperative pregabalin in adults undergoing total knee arthroplasty as a way to reduce the incidence of chronic pain

• Identify whether lower doses of the drug offers similar benefits while minimizing postoperative sedation and confusion
Expected Conclusions

- The research project will have answered the research question if data collected shows a significant reduction in chronic pain 3 and 6 months after a total knee replacement
  - In low and high dose pregabalin
  - When compared to our placebo group
- We hope that with this data, we will know whether low dose pregabalin can retain benefits while reducing the risk of postoperative confusion and sedation
Expected Conclusions

• It is expected that our research project will enhance the use of perioperative pregabalin to reduce chronic post-operative pain.
References

Thank You