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"Impact of Intra-operative Acetaminophen Administration on Post-operative Opioid Consumption in Patients Undergoing Hip or Knee Replacement"

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1.) Why do you think the authors selected opioid requirements as the primary endpoint?

Opioid requirements as a primary endpoint in this study was used as a surrogate measure of pain control. Ideally, pain scores at given time points over a 24-hour period would have been useful in a prospective analysis, but since this study design was a retrospective cohort, the timing of collection for individual patient pain scores would not have been consistent amongst the cohort. The authors also noted that the use opioid requirements as a primary endpoint has been previously been cited reduction in opioid consumption during the post-operative period as a justification for intravenous acetaminophen utilization.

What are the concerns with increased opioid utilization in the perioperative setting?

Some of the concerns associated with increased opioid utilization during the perioperative setting include a myriad of gastrointestinal (nausea, vomiting, constipation) and central nervous system (somnolence, dizziness, oversedation) adverse effects. Side effects may range in severity from pruritus to respiratory depression. As mentioned in the article, there are multiple reports linking increased opioid utilization to an increased likelihood of suffering opioid-related adverse events. Patients suffering from opioid-related adverse events may end up with an increased length of hospitalization, which increases costs to the institution for post-operative patient care.

2.) This study utilized 24-hour opioid requirements as its primary endpoint. What are some outcomes that can be evaluated in this patient population that may justify utilization of this agent?

Some alternative outcomes that may be evaluated in this patient population include post-operative pain scores over a given time frame (24 or 48 hours), time to ambulation after procedure completion, and overall length of hospitalization.

3.) What are some patient-specific factors in hip or knee replacement candidates that may impact their opioid requirements in the perioperative setting?

Patient-specific factors influencing opioid requirements in the perioperative setting include age, weight, previous history of opioid use, extent of prior opioid use, and type of surgery performed.

4.) If this study had used percentage of patients rating their post-operative pain control as "adequate," what statistical test could the authors have used? What about pain scores from 0 (no pain) to 10 (worst pain possible) at 4 hours post-procedure? What about length of stay in hours?

For this sample size, a chi-square test would be utilized to compare percentage of patients in each group rating post-operative pain control as "adequate," since this is nominal level data comparing independent samples. For a single pain score from 0-10, this is ordinal level data; because the samples are independent, a Wilcoxon rank sum or Mann-Whitney U test may be utilized. If length of stay in hours (a continuous variable) was being evaluated, and the data were normally distributed, an unpaired *t* test would be appropriate. If the data were not normally distributed, then the Wilcoxon rank sum or Mann-Whitney U test could be used for this variable.

5.) Are there any other non-opioid analgesics that have been recently evaluated in the intra-operative setting? What were they compared against? What did the results show?

The main non-opioid analgesics for use in the intra-operative setting that have recently been approved include liposomal bupivacaine, intravenous ibuprofen, and intravenous diclofenac. The prescribing information for liposomal bupivacaine includes studies evaluating the agent against placebo in patients undergoing hemorrhoidectomy or bunionectomy. Liposomal bupivacaine patients experienced significantly less post-operative pain and required less opioids than placebo patients. Smaller studies have

also evaluated the agent (compared to bupivacaine hydrochloride) in orthopedic surgery and in patients undergoing open colectomy. Intravenous diclofenac (*Dyloject*) is an injectable nonsteroidal anti-inflammatory drug (NSAID) that was just FDA approved in December. It has been evaluated against IV ketorolac and placebo in 2 studies: one in patients undergoing elective orthopedic surgery, and the other in patients undergoing abdominal or pelvic surgery. In the study with patients undergoing orthopedic surgery, diclofenac was associated with improved pain scores, faster onset of analgesic efficacy, and reduced opioid requirements versus ketorolac and placebo. In the study evaluating patients undergoing abdominal or pelvic surgery, both ketorolac and diclofenac provided superior analgesic efficacy compared with placebo. There is one phase III study that compared intravenous ibuprofen to placebo in patients who underwent orthopedic or abdominal single-site surgery. Intravenous ibuprofen was associated with a significant decrease in opioid requirement, pain at rest, and pain at movement compared to placebo.

6.) What are some of the benefits and drawbacks of utilizing these newer non-opioid agents in perioperative analgesia?

Some of the benefits to utilizing these newer non-opioid agents for perioperative analgesia include a potential decrease in opioid utilization, which may result in a limitation in opioid-related side effects. A multi-modal analgesia regimen is also recommended by the most recent guidelines for pain management from the American Society of Anesthesiologists (ASA).

One drawback to these new agents (intravenous acetaminophen, ibuprofen, and diclofenac; liposomal bupivacaine) is their cost when compared with opioids, ketorolac, and bupivacaine hydrochloride. There are also a paucity of data supporting the assumptions that these agents actually reduce opioid-related adverse events or contribute to outcomes such as time to discharge from the hospital.

7.) What are some limitations to the study that may have influenced the results?

There were several limitations to the study that potentially influenced results; most of them derived from the study design being a retrospective cohort analysis. Patients may have not received the same perioperative analgesic regimen (depending on prescriber preference), which could have impacted overall opioid utilization. Although there was not a statistically significant difference in the number of hip patients and number of knee patients, there were more hip patients in the intravenous acetaminophen group and vice versa. Although opioid utilization is a surrogate marker for pain control,

important outcomes such as patient pain scores, time to ambulation, and length of stay were not evaluated. These 3 outcomes may influence (indirectly or directly) costs to the institution. Finally, the impact of the intravenous administration of acetaminophen during the intra-operative period may have been lessened due to the 24-hour time frame evaluated, given the pharmacokinetics of the drug.

8.) How do you think the results of this study would impact practice or drug utilization within your institution?

This question is open for discussion between preceptor and student/resident. Topics for discussion may include formulary status of the drug within a specific facility, whether the use is restricted to specific populations at an individual institution, and potential medication use evaluation (MUE) ideas based on past institutional usage.

9.) You are interested in evaluating the impact of this agent in your institution. What patient populations would you focus on and how would you design your study?

This question should be used to generate discussion between the preceptor and student/resident. Patient populations will vary between individual institutions as a result of different restrictions or formulary status for the drug.

10.) Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey results are a recent area of emphasis for hospital and health-system administrators. How would perioperative care for these patients impact survey results?

There are 2 questions in the HCAHPS survey that would mostly likely be influenced by pharmacologic perioperative pain management. Question 13 on the survey states: “During this hospital stay, how often was your pain well controlled?” The second question is: “During this hospital stay, how often did the hospital staff do everything they could to help you with your pain?” These are the survey questions that most directly assess pain management during the hospital stay.