OFIRMEV…NEXT BEST INTRAOPERATIVE PAIN MANAGEMENT ADJUNCT?

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ABSTRACT

- **Purpose**: Opioid administration in the intraoperative period contributes to respiratory depression, nausea, vomiting, constipation and urinary retention. The purpose of this study was to test whether Ofirmev (IV acetaminophen) would decrease the intraoperative administration of fentanyl. **Methods**: Double blind randomized controlled trial involving 2,500 male subjects > 18 years old undergoing inguinal hernia repair procedures in 10 nationwide university medical centers. 1,250 subjects received Ofirmev prior to surgical incision and 1,250 did not. All subjects were administered fentanyl for additional pain management. Intraoperative fentanyl administration was analyzed with 150 mcg or < defined as "decreased opioid administration," and > 150 mcg of fentanyl as "increased opioid administration." Intraoperative pain was assessed through the established pain parameters: increased heart rate >20% of baseline, increased blood pressure >20% of baseline, and increased respiratory rate >20 breaths/min as defined by the American Society of Anesthesiologists. **Results**: One-tailed test with alpha of .05 and a sample mean of 100 mcg of fentanyl in Ofirmev group, and independent group t-test with $p<0.05$ rejected null hypothesis. Greater than 72% of Ofirmev group demonstrated administration of 150 mcg of fentanyl or less and greater than 92% of control group exhibited greater than 150 mcg of fentanyl administration intraoperatively. **Conclusion**: The administration of Ofirmev prior to surgical incision demonstrated decreased intraoperative fentanyl administration for inguinal hernia repairs in male patients greater than 18 years of age. The addition of Ofirmev contributed to the multi-modal analgesic effect that enabled anesthesia providers to limit intraoperative opioid use.

- Key Words: Ofirmev, inguinal hernia repair, multi-modal analgesia

INTRODUCTION & BACKGROUND

- Intraoperative pain management is an ongoing problem for all anesthesia providers, with opioids as the most common medication administered (Stomberg, Sjostrom, & Haljamde, 2001).
- Although successful for pain management, opioids are not benign. Many common side effects include: respiratory depression, nausea, vomiting, constipation and urinary retention; all of which complicate surgical recovery (Viscusi, Singla, Gonzalez, Saad, & Stepanian, 2012).
- Multi-modal analgesia has become a new mainstay within the past decade in reducing postoperative pain through administration of different analgesics working on different pathways and receptors to lower opioid doses and adverse events.

INTRODUCTION & BACKGROUND

- Ofirmev, IV acetaminophen, is a new drug that has contributed to the multi-modal approach through a central analgesic effect. The most recent evidence has postulated that acetaminophen is a TRPV-1 agonist that mediates the response to pain (Viscusi et al., 2012). The huge advantage of acetaminophen is it's safety and tolerability profile such as lack of respiratory depression, ileus, sedation, substance abuse and misuse (Babiash, 2012).
- IV acetaminophen results in a rapid elevation in plasma concentrations and higher peak levels (70 %) with sustained pharmacokinetics (1 hour peak lasting for 4 to 6 hours with onset of 5 to 15 minutes), as compared to the oral alternative with a 45 to 75 minute onset, or rectal route with a 3 to 4 hour onset (Viscusi et al., 2012). This higher peak concentration is also well below the concentration threshold for hepatotoxicity at 150 mcg/ml at 4 hours after administration (Viscusi et al., 2012).

PURPOSE & OBJECTIVE

- To prove that a multi-modal analgesic approach using Ofirmev in the intraoperative period can result in less opioid use by the anesthesia provider with better pain relief for the patient.
- **Hypothesis**: Ofirmev decreases intraoperative opioid administration.
- **Null Hypothesis**: Ofirmev has *no effect* on intraoperative opioid administration.

DESIGN

- Double blind randomized controlled trial involving an experimental group and a control group
- Design chosen to blind the anesthesia provider and the patient to eliminate provider bias and subject contamination through the “Hawthorne effect”

SAMPLING

- Simple random probability sampling involving:
  - 2, 500 adult male subjects > 18-years-old undergoing inguinal hernia repairs at 10 nationwide university medical centers over 1 year
  - Control group: Does not receive 1000 mg Ofirmev intraoperatively
  - Experimental group: Received 1000 mg Ofirmev intraoperatively prior to incision

- All subjects received general anesthesia with a laryngeal mask airway (LMA) for airway protection to allow for spontaneous breathing with Sevoflurane as the chosen volatile agent to establish reliability in the intervention
- Exclusion criteria: subjects taking metoprolol which could blunt the increased heart rate to establish a pain response, surgeon preference of using muscle relaxation which eliminates the use of an LMA, subjects not tolerating an LMA and need the conversion to an endotracheal tube, patients with either acute or chronic liver disease established by AST >40 units/L and ALT >56 units/L, medication allergy to acetaminophen, complicated hernia repairs involving the use of muscle relaxants, Ofirmev not delivered in specified timeframe, chronic kidney disease with GFR <60 ml/min and subject refusal

SAMPLING CONTINUED

- Subjects were presented with this study by 1 of 2 different researchers
- Provided with brochures and consented for ethical implications
- Randomized into either group by being assigned a number (1-2,500) by the assigned researcher, inhibiting blinding of the researchers
- The website www.randomizer.org used to enter the number into the tool to assign a subject to a group
- Blinding of the anesthesia provider was essential to eliminate bias, permitting the provider to rely on the established pain parameters
- Subjects blind to provide a valid tool for assessing postoperative pain

MEASUREMENT STRATEGY

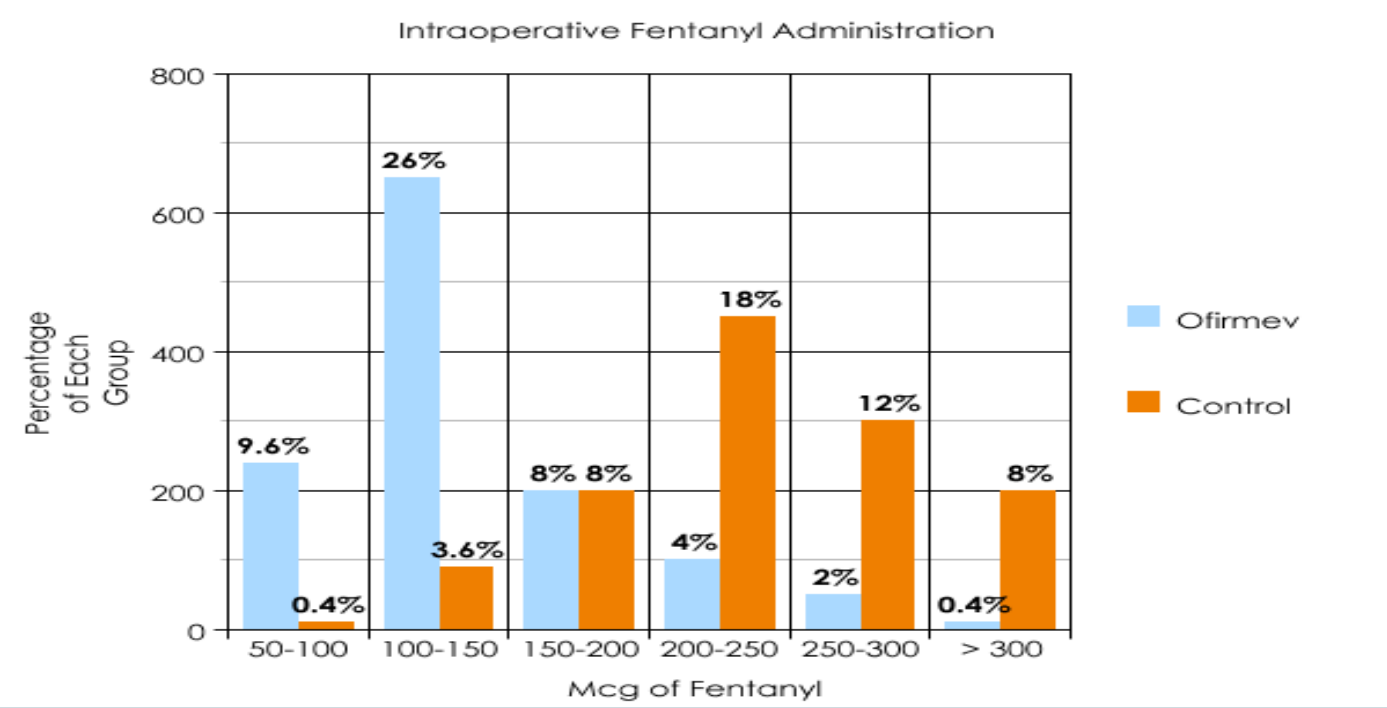
- **Dependent variable**: Intraoperative opioid administration
- **Independent variable**: Administration of Ofirmev
- Intraoperative pain parameters established: increased HR >20% of baseline, increased BP >20% of baseline, and increased respiratory rate >20 breaths/min as defined by the American Society of Anesthesiologists
- All subjects received fentanyl IV for pain management intraoperatively to maintain consistency and reliability of the measurement tool
- The anesthesia provider was blinded by receiving a standard 500 ml glass bottle without a label containing a clear solution (control containing just 0.9% normal saline) for all patients and instructed to give it prior to incision and after induction of general anesthesia
- Effectiveness of the intervention was measured by the amount of fentanyl the subject received intraoperatively:
  - 150 mcg fentanyl or less = decreased opioid administration
  - > 150 mcg of fentanyl = increased opioid administration and support of null hypothesis

DATA ANALYSIS & STATISTICAL PLAN

- One-tailed test to prove that the experimental group would benefit from receiving Ofirmev resulting in less opioid use and less side effects
- Alpha .05 with a sample mean of 100 mcg and a standard deviation of 50 mcg of fentanyl in experimental group would result in rejection of null hypothesis
- Independent group t-test comparing experimental group to control group
- $p<0.05$ statistically significant, rejecting null hypothesis

RESULTS

- n= 2,500 subjects 1, 250 Ofirmev 1, 250 Control
- Greater than 72% of the **experimental group** met the definition of "decreased opioid administration," (150 mcg or < of fentanyl)
- Greater than 92% of the **control group** met the definition of "increased opioid administration," (> 150 mcg of fentanyl)



DISCUSSION

- As evidenced by this study, it is proven that Ofirmev can decrease the administration of opioids intraoperatively. Greater than 72% (of the 1, 250 subjects) of the Ofirmev group demonstrated decreased fentanyl use (150 mcg or <) and greater than 92% of the control population demonstrated increased fentanyl use (150 mcg or >). These results clearly demonstrate that IV acetaminophen can reduce opioid use in a traditionally painful surgery. Despite the positive results, several limitations to this study exist. Since the subject population chosen was very specific (male, ages 18 years or older receiving inguinal hernia repairs) it is hard to generalize these results for all surgeries and subject populations. Even though the procedure chosen is traditionally very painful, it is impossible to compare it to other painful procedures. Gender could play a large role as well. If females were included, would the results have been different? These are questions that remain to be answered and could set the foundation for future prospective studies. The last limitation involves the assessment of pain. As defined by the ASA, intraoperative pain measurements include: increased HR >20% of baseline, increased BP >20% of baseline, and increased respiratory rate >20 breaths/min; however, patients could be in pain without demonstrating these vital signs. Pain is best assessed through a patient's report of pain, but since the subjects were under general anesthesia, it is difficult to distinguish actual pain from other stimulating effects of the surgery. Anesthesia providers all differ in their care and thresholds for treating pain, which also could skew the results. These are all legitimate limitations that could decrease the credibility of the results; however, this study demonstrates a positive result for multi-modal analgesia that should not be ignored.

IMPLICATIONS FOR PRACTICE & CONCLUSION

- Through the confirmation of the hypothesis and rejection of the null hypothesis, this study permits enough credibility to be implemented into anesthesia practice. It is clearly demonstrated that IV acetaminophen decreases opioid administration intraoperatively despite the identified limitations. If IV acetaminophen is available and appropriate for the patient then it should be used because the benefit outweighs the risk. Not only does this study outline the positive effect of IV acetaminophen, it calls for attention to the practice of multi-modal analgesia. With all of the side effects and negative outcomes with opioid administration, it is important for anesthesia providers to learn multi-modal analgesia and implement it into practice. With the identified limitations to this study, additional strong evidence through more experimental trials and prospective studies supporting IV acetaminophen would grant attention from the anesthesia community. If studies included females and involved other painful procedures with positive results, then the administration of Ofirmev could not be ignored and more patients would experience better pain relief.

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