Use of Methadone in Pediatric Posterior Spinal Fusion: A Randomized, Controlled Trial

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Background/Introduction: Patients undergoing major spine surgery experience severe pain postoperatively, require large amounts of opioids, and frequently have adverse respiratory events. Methadone is a μ-opioid agonist with slow elimination, resulting in prolonged effects, and may significantly diminish the need for postoperative analgesics. It has no active metabolites or pro-drug forms, and is metabolized by cytochrome P450 2B6. We previously demonstrated that methadone (0.1-0.3 mg/kg) follows linear pharmacokinetics in adolescents. In this follow up study, we aimed to assess a) if a single dose of intraoperative methadone, when used as the sole intraoperative opioid, can lead to a reduction in opioid consumption; and b) assess the pharmacokinetics of a dose of 0.4 mg/kg of methadone in pediatric patients.

Methods: After IRB approval, patients were consented on the day of surgery. Based on the results of our previous study, subjects were randomized 1:2 to either control (intraoperative opioid per anesthesiologist discretion) or methadone HCl (0.4 mg/kg ideal body weight). After unexpectedly observing sedation in the subjects receiving 0.4 mg/kg methadone, a decision was made to reevaluate the effects of the 0.3 mg/kg dose. Subjects in this cohort were randomized 1:2 to receive either control or 0.3 mg/kg methadone. Anesthesia and surgical care was not altered for the purpose of this investigation. To examine pharmacokinetics, blood samples were drawn at 0, 5, 30, 60, 90, 120, 180, 240, 360, 480, 600, and 720 minutes following methadone administration, and every morning for up to six days post-operatively, or until hospital discharge. We compared total opioid consumption in morphine equivalents, pharmacokinetic data, postoperative pain scores, and adverse events between the groups.

Results: Patients were between 11 to 18 years old. Twenty patients received 0.3 mg/kg methadone, 13 received 0.4 mg/kg, and 15 did not receive methadone. Total hospital stay opioid consumption in IV morphine equivalents was compared between the three groups. One-way, between subjects ANOVA demonstrated a significant difference between the groups [$F(2, 45) = 3.88$, $p = 0.0279$]. Post hoc comparisons using Tukey's test demonstrated a significant difference between the control group (3.34 ± 0.93 mg/kg) and the 0.3 mg/kg methadone group (2.51 ± 0.84 mg/kg). There was no difference between the 0.4 mg/kg methadone group (2.77 ± 0.90 mg/kg) and either the control or the 0.3 mg/kg methadone groups. There was no significant difference in average daily pain scores between the groups. Patients administered 0.4 mg/kg methadone had peak plasma concentration of 176 ± 104 and 231 ± 132 ng/ml R- and S-

methadone respectively. Peak plasma R- and S methadone was respectively 99 ± 37 and 129 ± 44 ng/ml in patients given 0.3 mg/kg methadone. Preliminary analysis of adverse events (e.g. respiratory depression, excessive sedation, decreased oxygen saturation, reintubation, or altered mental status) suggest similar frequencies of these events between the three groups.

Conclusions: The use of a single dose of intraoperative methadone is associated with a significant decrease in overall opioid consumption without a change in average daily pain scores following posterior spinal fusion surgery in adolescents. Retrospective examination of this study and our previous study suggest the unexpected sedation seen with the 0.4 mg/kg methadone dose may be due to the institution of a post-operative pain treatment protocol that includes gabapentin and methocarbamol.

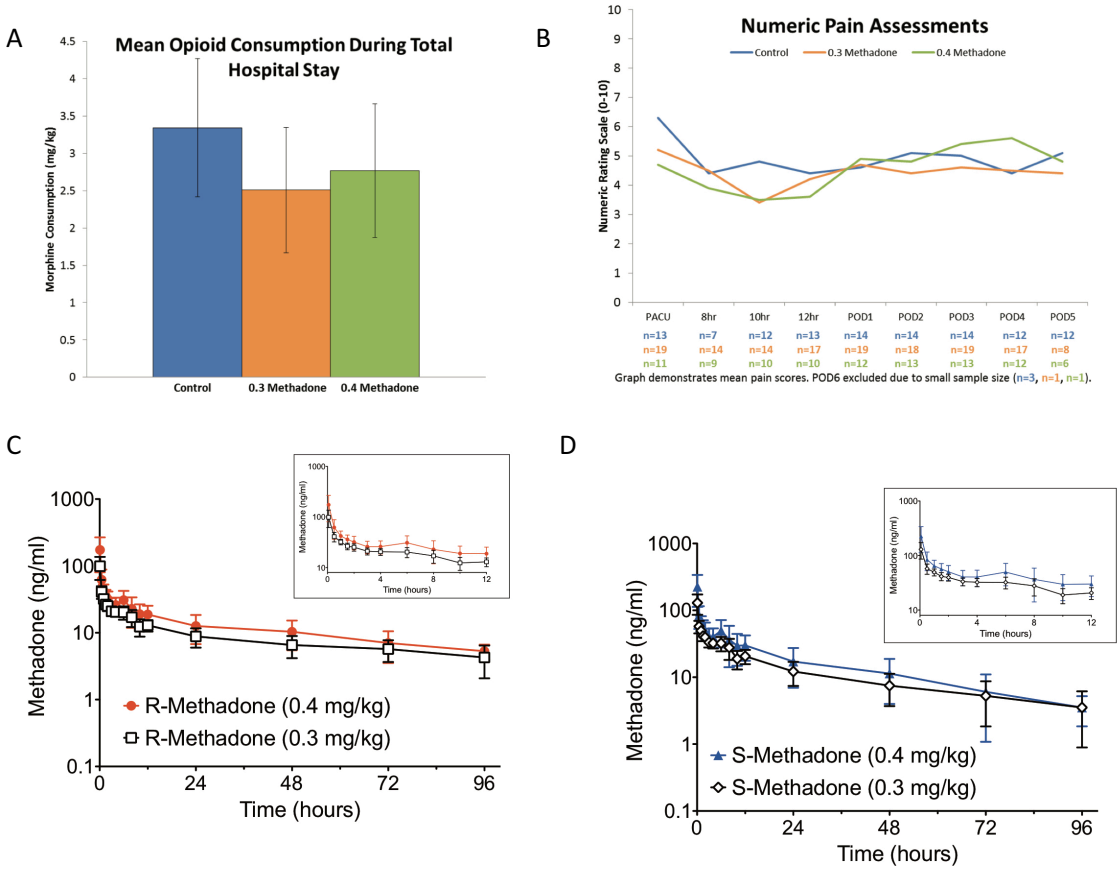

Figure Legend: a) Total hospital stay opioid consumption in IV morphine equivalents; b) PACU, 8, 10, 12 hours postoperative, and average daily pain scores; c) and d) R- and S-methadone pharmacokinetics over 96 hours with 0 to 12 hours post IV bolus dosing presented as insets.