

A novel perioperative multi-dose methadone-based multi-modal analgesic strategy achieves safe blood methadone levels, enabling opioid sparing sustained analgesia with no respiratory depression in children undergoing spine fusions

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BACKGROUND

- Methadone is being increasingly used for perioperative analgesia
- The optimal dosing strategy for methadone in children is unknown
- Conventionally, centers use single large intraoperative dose (0.2-0.3 mg/kg), with the associated safety concerns of a large dose
- We demonstrated the safety of multiple small doses (0.1 mg/kg; Q12H)
- Traditionally described blood level of methadone for RD is 100 ng/mL
- We have described the PK, efficacy and safety profile of multiple small doses of methadone

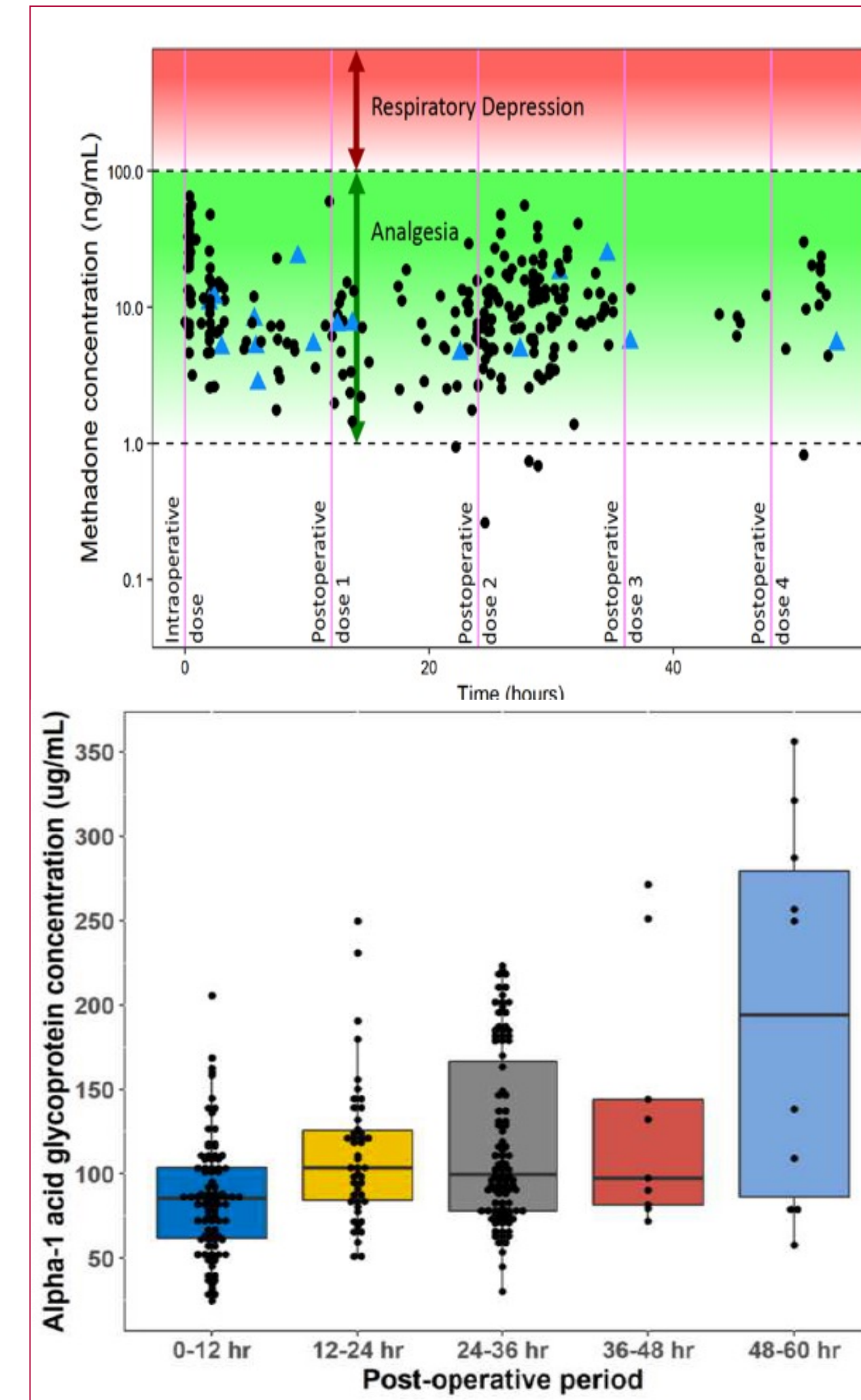
MATERIALS and METHODS

- Adolescents undergoing posterior spinal fusion (PSF) for idiopathic scoliosis or pectus excavatum (PE) repair were included after IRB approval and consent
- Subjects received methadone intraoperatively (0.1 mg/kg, maximum 5 mg) and postoperatively every 12 h for 3-5 doses in a multimodal analgesic protocol.
- Blood samples were collected up to 72 hours post-operatively and analyzed for R- and S-methadone, 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) metabolites, and alpha-1 acid glycoprotein (AAG), the primary methadone-binding protein.

- Peak and trough concentrations of enantiomers, total methadone, and AAG levels were correlated with clinical outcomes including pain scores, postoperative nausea and vomiting (PONV), respiratory depression, and QT interval prolongation.

RESULTS

- The study population included 38 children (10.8 – 17.9 years), 25 PSF and 13 PE patients.
- Total methadone peak plasma concentration was 24.7 (19.2-40.8) ng/mL and trough was 4.09 (2.74-6.4) ng/mL.
- AAG concentration almost doubled at 48 hours after surgery (Median 193.9 IQR 86.3 to 279.5 ug/mL) from intraoperative levels (Median 87.4 IQR 70.6 to 115.8 ug/mL, $P < 0.001$), and correlated with R-EDDP ($P < 0.001$), S-EDDP ($P < 0.001$) levels, and pain scores ($P = 0.008$).
- Median opioid usage was minimal, 0.66 (IQR 0.59-0.75) mg/kg morphine equivalents/day.
- No respiratory depression or significant QT prolongation occurred.
- PONV occurred in 12 patients and was correlated with rescue opioid dose ($P = 0.005$).



Summary & Conclusion

- Novel multiple small perioperative methadone doses resulted in safe and lower blood methadone levels, <100 ng/ml, a threshold previously associated with respiratory depression.
- This methadone dosing in a multimodal regimen resulted in lower analgesic concentrations of methadone, than the historically described minimum analgesic concentrations of methadone from an era prior to multimodal postoperative analgesia (30 ng/ml; 58 ng/ml).
- We had no postoperative respiratory depression or prolonged QTc.
- Median morphine equivalent dose 0-72 hour (mg) was about 50% less with this multidose methadone regimen compared to pediatric adolescent PSF historical cohorts (that used PCA for analgesia).
- Larger studies are needed to further study the safety and efficacy of this dosing strategy of methadone in different surgical cohorts.

References

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