I-104 Population PK/PD modeling of levobupivacaine and ropivacaine for motor block in spinal anesthesia

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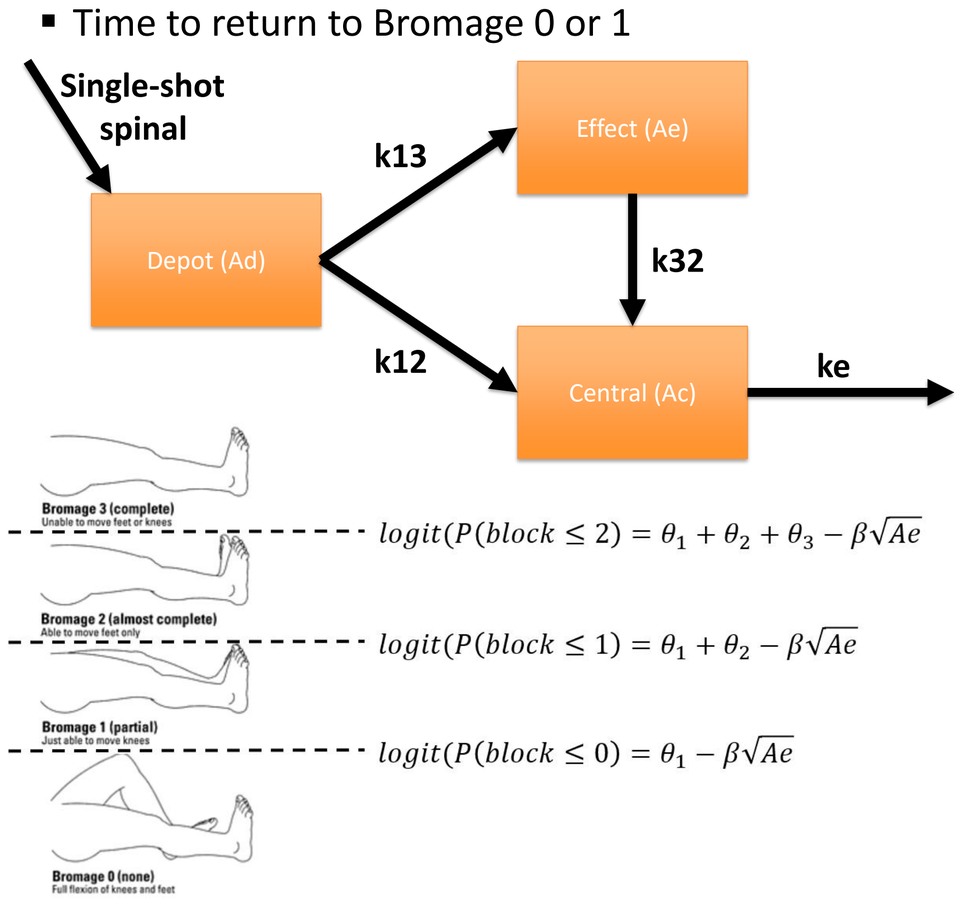
INTRODUCTION

- **Clinical context:** Spinal anesthesia with long-acting local anesthetics remains the gold standard for lower abdominal and lower extremity surgery.
- **Agents of interest:** To mitigate racemic bupivacaine's cardiotoxic risk, the S-enantiomer levobupivacaine and the structurally related ropivacaine are now preferred.
- **Knowledge gap:** Although both drugs reliably produce motor block (graded by the Bromage scale 0–3), existing studies report only discrete PD milestones (e.g., time to Bromage 3), neglecting the full time-course and underlying PK contributions.
- **Rationale for PK/PD modeling:** Integrating population pharmacokinetics with continuous pharmacodynamic profiling can elucidate how systemic exposure drives the onset, intensity, and recovery of motor block.
- **Hypothesis:** When dosed for equipotent effect, levobupivacaine and ropivacaine will exhibit similar PD profiles for onset and duration.
- **Study aim: Fit a PK/PD model to observed data, verify dose equivalence between and benchmark against traditional motor block secondary endpoints**

MATERIALS AND METHODS

- Study Design
  - Open-label, prospective, monocenter, randomized trial
  - No pre-block vascular loading; standard cardio-respiratory monitoring
  - Intrathecal injection (N=60 patients)
  - Randomization to ropivacaine (15/20/25 mg) or levobupivacaine (10/12.5/15 mg)
- PK & PD Sampling
  - PK: Blood draws at 0, 5, 15, 30, 60, 120, 240, 480, and 1 440 min post-dose
  - PD: Motor block scored via Bromage
    - Assessment frequency: q2.5 min (0–30 min), q5 min (30–60 min), q15 min (60–330 min)
- PK & PD Modeling
  - MonolixSuite v2024R1®
  - Joint estimation of PK and PD parameters
  - PD: ordered categorical outcome via a cumulative logit link
  - Covariate assessment: age, BMI, sex, anesthetic type
  - Model Validation: RSE, GoF plots, residuals, BICc, bootstrap
  - Simulation: EBE at 1-minute resolution
- Secondary endpoints
  - Area under the block curve (AUC)
  - Time to reach maximal block
  - Maximal block duration
  - Time to return to Bromage 0 or 1



RESULTS

- PK/PD Modeling
  - Reliable results based on bootstrap.
  - Impact of BMI on ke, Age on k23 and treatment on β

Parameter	REFERENCE	MEAN	S.E.	R.S.E.(%)	P2.5	MEDIAN	P97.5	Bias(%)
Fixed Effects								
k12_pop	0.013	0.013	0.0016	12.47	0.0098	0.013	0.016	-3.03
V_pop	170.65	168.52	11	6.53	149.01	168.36	190.74	-1.24
ke_pop	0.0025	0.0025	0.00015	6.06	0.0022	0.0025	0.0028	1.92
logtIMC on ke	-1.26	-1.37	0.31	22.82	-2.01	-1.37	-0.77	9.12
k13_pop	0.022	0.02	0.0038	18.71	0.013	0.02	0.028	-6.5
k32_pop	0.015	0.016	0.0017	10.66	0.013	0.016	0.02	7.02
logtAge on k32	-0.4	-0.42	0.16	37.23	-0.8	-0.4	-0.18	5.08
th1_pop	14.14	13.15	1.09	8.31	11.19	13.07	15.44	-6.98
th2_pop	3.95	3.85	0.45	11.71	3.03	3.82	4.79	-2.51
th3_pop	6.16	5.9	0.64	10.87	4.76	5.89	7.21	-4.18
β_pop	0.56	0.54	0.043	7.88	0.47	0.54	0.63	-3.34
Treatment (Ropivacaine) on β	-0.31	-0.29	0.067	23.16	-0.42	-0.29	-0.16	-7.02
Standard Deviation of the Random Effects								
omega_k12	0.74	0.72	0.12	17.24	0.47	0.72	0.97	-2.58
omega_V	0.41	0.4	0.052	12.97	0.31	0.4	0.51	-2.09
omega_k	0.35	0.34	0.047	13.76	0.24	0.34	0.42	-2.99
omega_k13	0.43	0.4	0.062	15.44	0.28	0.4	0.51	-7.47
omega_k32	0.33	0.31	0.088	28.15	0.18	0.29	0.52	-5.64
omega_th1	0.066	0.06	0.023	37.7	0.025	0.057	0.11	-9.37
omega_th2	0.68	0.65	0.084	12.97	0.49	0.64	0.82	-4.66
omega_th3	0.63	0.62	0.082	13.18	0.47	0.62	0.79	-1.92
omega_beta	0.084	0.066	0.029	43.78	0.023	0.062	0.13	-21.22
Error Model Parameters								
a1	1.14	1.2	0.24	20.31	0.79	1.17	1.73	5.84
b1	0.2	0.2	0.018	8.81	0.17	0.2	0.23	-0.38

Table 1: Model parameters

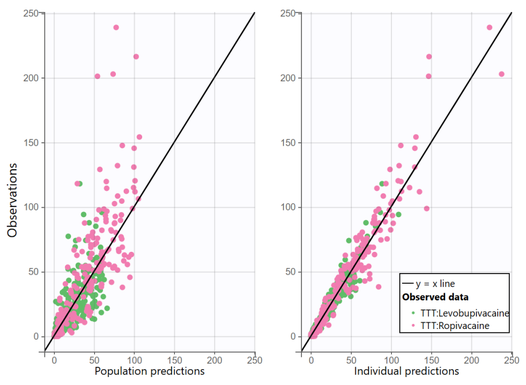


Figure 1: Observations vs. Predictions

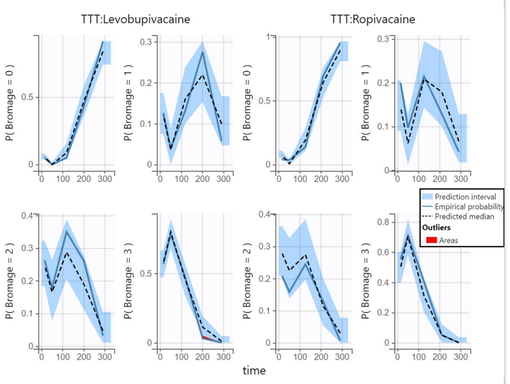


Figure 2: PD Visual Predictive Check

- Dose equivalence for motor block is well supported

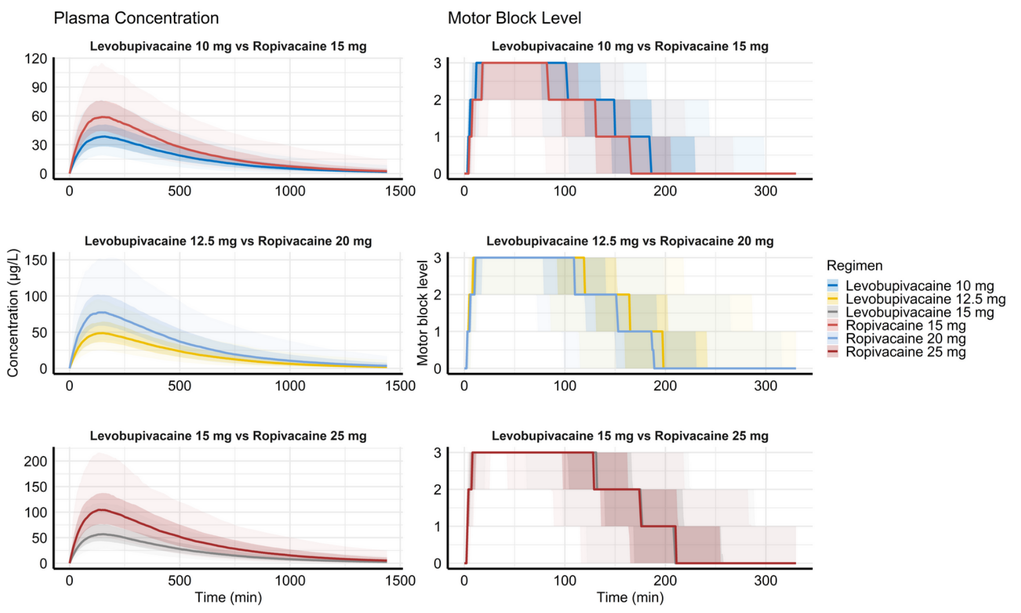


Figure 3: PK /PD of a typical individual with 25th-75th and 5th-95th percentiles

- Secondary endpoints
  - Effect of BMI, sex, age, treatment and dose

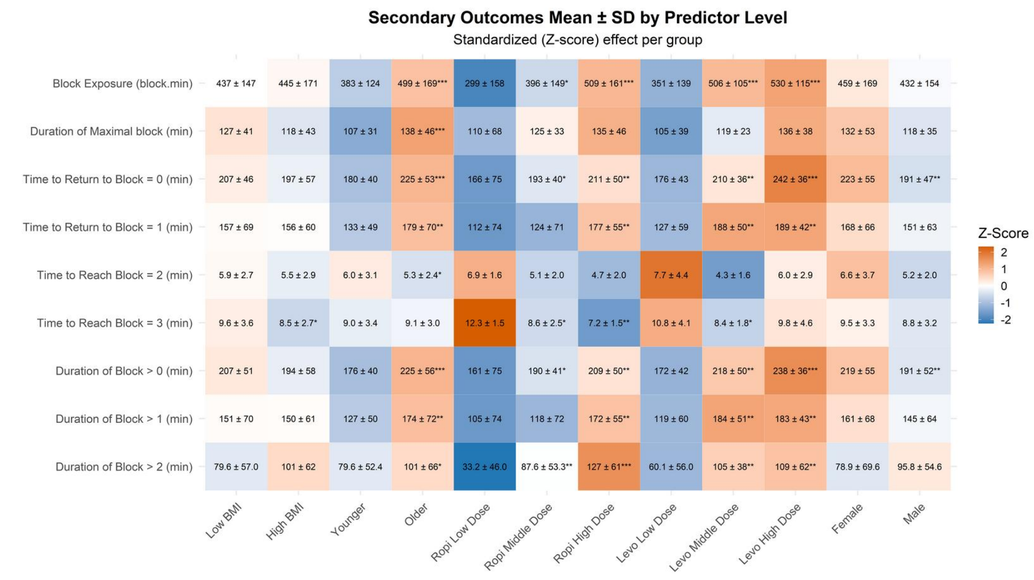


Figure 4: Heatmap of secondary outcomes by predictor

DISCUSSION / CONCLUSION

- Robust parameter estimates supporting the stability of the joint PK/PD model
- Excellent predictive performance
- Adequate PD model validation
- BMI, sex and age exert moderate but consistent effects on secondary outcomes
- Together, these results support tailoring spinal anesthetic dose to individual patient characteristics to balance block efficacy against recovery time.