Population Pharmacokinetics of Intraperitoneal Bupivacaine Using Manual Bolus Atomization versus Micropump Nebulization and Opioid Requirements in Young Children

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Introduction: Intraperitoneal (IP) administration of local anesthetics is used in adults[1] and children[2] for perioperative analgesia during elective laparoscopic surgery. We previously demonstrated reduced opioid requirements after IP bupivacaine in children.[3] The population pharmacokinetics (PK) of IP bupivacaine has not been characterized in children. The objectives were (1) to develop a population PK model to compare the PK of bupivacaine and (2) assess opioid requirements following IP manual bolus atomization versus micropump nebulization.[4]

Methods: After IRB approval and written informed parental consent, we prospectively enrolled 67 children (44 males, 23 females) ages 6 months to 6 years (median 30 months), undergoing robot-assisted laparoscopic urologic surgery to receive IP bupivacaine after creation of the pressurized pneumoperitoneum. Group 1 received 1.25 mg/kg bupivacaine in 30mL NS via mucosal atomization (Fig. 1A) as a bolus over 30sec. Group 2 received 1.25mg/kg of undiluted bupivacaine 0.5% via a micropump nebulizer (Fig.1B) into the CO_2 insufflation tubing over 15-30min. Venous blood samples were obtained at 4 time intervals between 1-120min. Nonlinear regression modeling was used to estimate PK parameters for each technique with 95% confidence intervals.

Results: Baseline characteristics of the 2 groups were comparable. No clinical signs of neuro-or cardio-toxicity were observed. Highest plasma concentration was 2.44µg/mL for the atomizer vs 0.97µg/mL for the nebulizer technique (Fig.2). IP bupivacaine PK was described as 1-compartment model with significant group differences in all PK parameters except half-life and mean residence time (Table 1). The nebulizer had a significantly lower Cmax and shorter Tmax (P<0.001). Lower plasma concentrations with less variability (95% CI) were observed (Fig.2) and predicted by the PK model (Fig.3) for the nebulizer than the atomizer (P<0.001). Adjusting for age as a covariate, Cmax and AUC were significantly lower with the nebulizer (P<0.001, Wald test). Regardless of the application technique IV morphine requirements were low at all time points (Table2) and there were no differences in cumulative postop IV/oral morphine requirements through 24h (0.14 vs 0.17mg/kg, p=0.85).

References: 1) Boddy AP, Anesth Analg 2006; 2) Hamill JK et al Eur J Pediatr Surg 2016; 3) Freilich DA et al J Ped Urol 2008; 4) Meier PM et al SPA/AAP 2013

Figure 1 A: Manual bolus atomization

Figure 1B: Micropump nebulization

Figure 2: Comparison of observed Bupivacaine plasma concentrations. The dashed line represents the calculated concentration profile using a spline function to describe the trend of the concentrations.

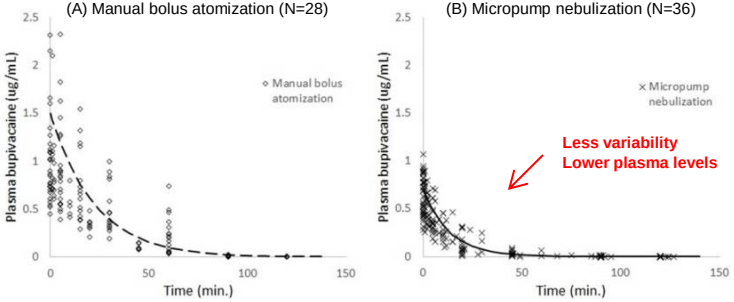

Table 1: Comparison of PK parameters for manual bolus atomization and micropump nebulization techniques

	Manual Bolus Atomization		Micropump Nebulization		*P* - values	
PK Parameters	**1Cpt**	**NCA**	**1Cpt**	**NCA**	**1Cpt**	**NCA**
Cmax (mg/mL)	1.05 (0.73 - 1.37)	1.17 (0.97 - 1.37)	0.61 (0.50 - 0.72)	0.52 (0.45 - 0.59)	**<0.001**	**<0.001**
Tmax (min)	2.55 (0.45 - 4.65)	8.93 (4.15 - 13.7)	1.12 (0.17 - 2.07)	3.33 (2.17 - 4.50)	**<0.001**	**0.03**
$AUC_{0\rightarrow\infty}$ (mg.min/mL)	53.6 (19.2 - 90.5)	56.2 (36.7 - 75.6)	10.0 (6.17 - 13.8)	11.2 (8.01 - 14.4)	**0.03**	**<0.001**
MRT (min)	61.8 (27.2 - 96.5)	54.9 (34.9 - 74.8)	54.8 (52.9 - 56.6)	47.9 (45.9 - 56.8)	0.33	0.27
T1/2 (min)	42.9 (3.91 - 81.9)	38.0 (18.1 - 57.9)	35.1 (4.1 - 66.1)	33.2 (6.21 - 60.2)	0.28	0.18
V/F (mL/kg)	941 (325 - 1599)	1152 (919 - 1386)	2309 (1884 - 2734)	2521 (2120 - 2922)	**<0.01**	**<0.001**
CL/F (mL/min/kg)	38.4 (8.59 - 70.4)	49.4 (33.9 - 64.8)	282 (110 - 454)	241 (105 - 377)	**<0.01**	**<0.01**

All PK parameters were estimated using nonlinear regression modeling with administration techniques compared using Student's t-test. Values represent mean (95% CI)
1Cpt = One compartment model with first order elimination; NCA = Noncompartmental analysis

Discussion / Conclusion: This is the first population PK study of IP bupivacaine administration in children. Delivery by micropump nebulization resulted in lower plasma concentrations, less patient variability, reduced toxicity risk, and equal analgesic efficacy compared to manual bolus atomization. Some limitations include:
(1) micropump nebulization technique required longer delivery time;
(2) blood sampling was not extended to PACU; (3) the design of the study did not include the assessment of pain scores. We recommend the use of the micropump nebulization technique based on the more desirable PK characteristics with comparable efficacy.

Table 2: Postoperative IV Morphine requirements

Postop. IV morphine equivalent, mg/kg	Manual Bolus Atomization (n = 29)	Micropump Nebulization (n = 34)	*P* value
0 - 2 hrs			
No. of patients	22 (76%)	23 (68%)	0.58
Median (IQR)	0.04 (0.03-0.06)	0.05 (0.03-0.06)	0.86
2 - 6 hrs			
No. of patients	5 (17%)	5 (15%)	0.99
Median (IQR)	0.10 (0.06-0.10)	0.07 (0.04-0.10)	0.31
6 - 12 hrs			
No. of patients	3 (10%)	3 (9%)	0.99
Median (IQR)	0.10 (0.06-0.10)	0.10 (0.10-0.10)	0.70
12 - 24 hrs			
No. of patients	3 (10%)	0	0.09
Median (IQR)	0.10 (0.05-0.1)		

Figure 3: Plasma concentration-time curves with 95% CI for the two techniques based on PK modeling