Published in final edited form as:
Paediatr Anaesth. 2012 July ; 22(7): 676–681. doi:10.1111/j.1460-9592.2012.03806.x.

Geographic differences in perioperative opioid administration in children

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Abstract

Objectives—To investigate whether geographic differences exist in perioperative opioid administration to children.

Aim—To investigate whether perioperative fentanyl use for cleft lip and palate surgery varies between children of three different geographic regions.

Background—Differences have been found in perioperative opioid administration to children of differing ethnicity in the U.S.A. Whether similar differences exist in perioperative opioid administration to children residing in different geographic regions is unknown.

Methods/materials—We retrospectively reviewed the medical records of ASA I children who underwent surgery under standardized general anesthesia between January 2010 and April 2011 during SMILE Network International mission trips to Africa, India and Central and South America. Perioperative administration of fentanyl was compared between these three locations.

Results—We analyzed data from 79 children who underwent surgery in Africa, 76 in India and 153 in Central and South America. Children in Central and South America were given less than 50% of the intraoperative amount of fentanyl (2.0 ± 1.2 mcg/kg) administered to children in Africa (4.1 ± 2.4 mcg/kg; $p<0.001$) and children in India (4.3 ± 2.2 mcg/kg; $p < 0.001$). Postoperatively, fentanyl was administered in equivalent doses to all groups.

Conclusions—Children in Central and South America received less opioid intraoperatively than African and Indian children, under standardized anesthesia for cleft surgeries. Further research is necessary to elucidate the mechanisms underlying these group differences.

Introduction

Understanding of factors affecting pain and opioid requirements in children is needed to manage their perioperative pain appropriately [1]. One such factor that has come to the forefront recently is ethnicity. One retrospective study has examined perioperative opioid use

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Conflict of interest: No Conflict of interest declared

in children of differing ethnicity in the U.S.A. [2], with findings of Latino children receiving 30% less opioid than Caucasian children after tonsillectomy. Psychosocial factors including preoperative anxiety [3] and coping strategies [4, 5] have been shown to influence postoperative pain in children and may play a role in these differences between ethnicities. Since ethnic differences can be found in children living in the same country, it is conceivable that similar, or greater, differences would exist between groups of children who actually live in the geographic areas from where these ethnicities originated. Our primary aim was to investigate whether opioid use for perioperative pain differs by geographic area in children. Secondary aims were to examine overall gender and age differences in opioid administration. We hypothesized that perioperative opioid administration to children undergoing standardized anesthesia for cleft lip and palate surgeries during medical mission trips would differ by geographic area.

Methods

We retrospectively reviewed the perioperative opioid requirements of children who underwent surgery under general anesthesia between January 2010 and April 2011 during SMILE Network International (SNI) missions to Africa, India and Central and South America. Children up to age 18 were included. All children underwent a pre-operative health assessment by SNI physicians to ensure that they had no health comorbidities.

As described in our previous study using data from SNI missions [6], surgeries performed by SNI include cleft lip and palate repairs, revision surgery for these defects, and other minor reconstructive facial surgeries. All children received a similar anesthetic with inhalation induction using 8% sevoflurane, insertion of a peripheral intravenous line, deepening of anesthesia with propofol 1.5 mg/kg and an initial dose of fentanyl 1 to 2 mcg/kg, followed by tracheal intubation. Rectal acetaminophen 30 mg/kg rounded to nearest half suppository size available, dexamethasone 0.5 mg/kg and a prophylactic antibiotic were administered per SNI protocol before incision to all children. Anesthesia was maintained with sevoflurane in air/oxygen mixture and additional fentanyl was titrated as needed, at the discretion of the anesthesia provider. The fentanyl dosing was not standardized. Infiltration with local anesthetic containing epinephrine was performed immediately prior to starting surgery, primarily to decrease perioperative bleeding. No nerve blocks were performed. Postoperative analgesia in the recovery room was limited to intravenous fentanyl given at the discretion of the anesthesia provider; opioids were not administered after the patient left the recovery room. All members of SNI medical staff are fully trained and licensed in the U.S.A. No local providers were used. Anesthesia providers have several years of recent experience in anesthetizing children for surgery and follow the anesthesia practice guidelines of the organization. Patients were under the care of SNI personnel throughout the perioperative period.

All data were obtained in a confidential manner from patient records generated routinely by SNI personnel. The data were collected and managed using REDCap electronic data capture tools hosted at Mayo Clinic [7]. Pre-operative data included mission site, age, gender, weight and oxygen saturation at time of screening. Intraoperative data included type of surgery, anesthetic duration and amount of fentanyl administered. Initial intraoperative fentanyl dose was defined as the first charted dose and subsequent intraoperative fentanyl dose was calculated as the sum of all additional fentanyl administered in the operating room. Postoperative data included total amount of fentanyl administered in the recovery room.

The mission sites were in Kenya and Uganda in Africa, India in Southern Asia, and Mexico, Peru and Ecuador in Central and South America. All children were local to the mission sites and represented the racial groups of the geographic areas. Children undergoing surgery in Cusco, Peru at high altitude were excluded from the study because our previous findings indicated that these children have chronically low oxygen saturations and decreased opioid requirements compared to a similar population at sea level [6].

Statistical analyses

SNI performed approximately 100 surgeries in each geographic region during this time. For our power analysis we set alpha at 0.017 after Bonferroni correction for 3 way analysis and beta at 0.20 for 80% power. We estimated standard deviation for our primary outcome variable (total perioperative fentanyl administration in mcg/kg) from data from our prior study during SNI trips to Peru [6] from the children who underwent surgery at sea level. We calculated that we would have adequate power to detect a difference of 0.86 mcg/kg of total perioperative fentanyl use between groups, which in our previous data corresponded to a 20 % difference.

Data are represented as mean and standard deviation. Fentanyl use was analyzed as mcg/kg. Baseline characteristics and fentanyl use across the three geographic locations were compared using analysis of variance for continuous variables and the chi-squared test for categorical variables. Differences were considered statistically significant if $p < 0.05$. Findings of significant differences across the groups were followed up with individual comparisons between pairs of ethnic groups using Student's two tailed t-test for groups with unequal variance. Using Bonferroni adjustment for multiple analyses, $p < 0.017$ was considered significant for pair wise analyses.

To account for potential differences in patient and procedural characteristics, multivariate analyses were performed using analysis of covariance (ANCOVA) with perioperative fentanyl administration (mcg/kg) as the dependent variable. Explanatory variables included age, anesthetic duration and oxygen saturation modeled as continuous variables and gender, geographic location and surgery type modeled as nominal variables.

Comparison of fentanyl use by gender across the entire group was made using Student's two tailed t-test for groups with unequal variance. Comparison of fentanyl use by age across the groups was made using one-way analysis of variance. For this analysis, patients were divided into three age groups: infants less than 1 year of age, children 1 to 12 years of age and teenagers older than 12 years.

Results

We reviewed the records of 308 ASA I children who underwent surgery during SNI missions during this period. One patient record was missing and was not reviewed. Seventy-nine children underwent surgery in Africa, 76 in India and 153 in Central and South America. There were clinically significant differences in baseline characteristics (Table 1). African children were younger than children undergoing surgery at Indian and Central and South American locations. Anesthetic duration was longer in Central and South America and shorter in India.

The majority of surgeries were cleft lip and palate repairs (Table 2). There were relatively more cleft lip and fewer cleft palate surgeries in African patients. Other procedures included macrostomia repair, frenulectomy and facial scar revision. Eight surgeons filled a total of 13 spots on the 9 mission trips. Fourteen anesthesia providers filled a total of 19 spots on the 9 mission trips. Three anesthesia providers were on more than one trip.

We found significant differences in perioperative fentanyl administration to children from the three geographic regions (Table 3). Children in Central and South America were given less than half the quantity of fentanyl intraoperatively compared to African ($p < 0.001$) and Indian ($p < 0.001$) children. African and Indian children received similar amounts of fentanyl intraoperatively ($p = 0.4$). In contrast, postoperative fentanyl use was equivalent between all three groups. Total perioperative fentanyl use appeared to be lower in all Central and South American locations than in African and Indian locations (Table 4).

Accounting for the duration of surgery, intraoperative fentanyl use was 2.6 ± 1.2 mcg/kg/h for African children, 3.2 ± 1.8 mcg/kg/h for Indian children and 1.2 ± 0.8 mcg/kg/h for children in Central and South America ($p < 0.001$). Thus Indian children received more than twice the intraoperative fentanyl given to children during surgery in Central and South America ($p < 0.001$) and 23 % more than in Africa ($p = 0.01$).

In a follow up multivariable analysis, factors associated with lower perioperative fentanyl administration were surgery occurring in Central and South America ($p < 0.001$ vs. Africa and India), increasing patient age ($p = 0.003$), cleft lip surgery ($p < 0.001$ vs. cleft palate surgery) and shorter anesthetic duration ($p < 0.001$) (Table 5). Differences in perioperative fentanyl administration to children in different geographic locations persisted after adjustment for age, gender, oxygen saturation, anesthetic duration and surgery type ($p < 0.001$).

Across the three locations, boys and girls received similar amounts of perioperative fentanyl (3.6 ± 2.2 mcg/kg vs. 3.9 ± 3.3 mcg/kg, $p = 0.6$). Teenagers received less perioperative fentanyl than infants and children (2.1 ± 1.2 mcg/kg, 4.3 ± 3.4 mcg/kg and 3.9 ± 2.3 mcg/kg respectively; $p < 0.001$ for both comparisons).

Discussion

We found marked geographic differences in opioid administration to children undergoing cleft surgeries under similar anesthetics. Children from Central and South America received statistically significantly less intraoperative opioid than Indian and African children. Indian children received more intraoperative fentanyl than children in both Africa and Central and South America, when taking anesthetic duration into account. Yet postoperative fentanyl administration was similar in all groups. Possible reasons for these differences fall into three categories: 1) The providers' practice of surgery and anesthesia 2) the pharmacology of the drug and 3) the physiological or psychosocial characteristics of the patients.

We cannot completely exclude variation in the anesthesia providers and surgeons as contributing to the group differences but we reject practice variation as a major explanation for our findings. The surgical and anesthetic techniques for the procedures in question are relatively standard and straightforward, and within the context of training of the providers and the protocols that were followed, offered little room for altering practice. The surgeons did infiltrate the surgical site with local anesthetic prior to incision but such infiltration would be expected to achieve poorer analgesia for the palate than the lip surgery. This does not explain why children in Central and South America, where more cleft palate surgeries were performed, received less fentanyl. While intraoperative fentanyl dosing was not standardized, the fact that opioid administration during multiple mission trips to the three locations was highly consistent makes anesthetic management an unlikely reason for the observed results. The fentanyl dispensing and distribution practices during mission trips were the same at all sites and there was an unlimited supply of fentanyl available. English is not the primary language in any of the SNI locations and consequently SNI staff had to rely on vital signs, observations and non-verbal communication to assess level of pain. However, language barriers at the three geographic locations do not explain intraoperative differences in opioid administration since the patient is under anesthesia. Differences in the baseline characteristics and procedure type were adjusted for statistically in our follow-up multivariate analyses.

Alternately, differences in the pharmacokinetics or pharmacodynamics of fentanyl because of genetic differences between children from these three geographic locations could explain our findings. Single nucleotide polymorphisms exist in the mu opioid receptor gene. The distribution of these has been observed to differ among ethnic groups [8, 9]. Single nucleotide polymorphisms in the mu opioid receptor gene can affect the activity of the mu opioid receptor [8]. This may hypothetically be a mechanism for differences in opioid administration by geographic regions. If children from these regions have different genetic variants of the opioid receptors, the pharmacodynamics of fentanyl may be different between the groups, resulting in differences in drug requirements.

Ethnicity of adult patients has been found to influence perioperative opioid requirements in several studies conducted in the U.S.A. [10-12] and in Singapore [13]. However, many of these studies examined postoperative opioids self-administered by patient controlled analgesia. Fewer studies are available in children [1]. Jimenez et al conducted a retrospective study comparing perioperative opioid consumption by 47 Latino and 47 non-Latino Caucasians stratified by age and gender after outpatient tonsillectomy and adenoidectomy [2]. Significantly less opioid was administered to Latino children in the early postoperative period. No differences were found intraoperatively or during late recovery periods. Median early postoperative opioid use in morphine equivalents was 0.05 mg/kg in Latino and 0.07 mg/kg in non-Latino Caucasian children.

The finding in the present study of lower perioperative opioid administration to children from Central and South America as compared to African and Indian children is consistent with findings of Jimenez et al. However we found differences in intraoperative opioid use whereas they found differences in early postoperative use. Important differences in design between the two studies may invalidate their direct comparison. We compared African, Indian and Latino children who lived and underwent surgery in their original cultural and geographic environment. Jimenez compared Latino to non-Latino Caucasian children who may be diverse in background and who all lived in the U.S.A.

Studies examining factors affecting perioperative pain in children have focused on postoperative pain. Psychosocial factors including preoperative anxiety [3] and coping strategies [4, 5] have been shown to influence postoperative pain in children and may contribute to these group differences. Palermo et al showed prospectively that psychosocial variables modify postoperative pain experience in children. This may play a role in the interaction between ethnicity and postoperative analgesic consumption. They found global anxiety to be a significant predictor of children's pain on the day of surgery. Anticipatory anxiety of surgery and coping history variables were predictive of postoperative pain even after controlling for type of procedure and demographic factors.

Ethnic differences have been shown in responses to multiple experimental pain stimuli in adults [14-16]. Laboratory studies of healthy young adults in the U.S.A. found lower tolerance to acute experimental pain (heat, cold and ischemic pain) in Hispanics and African-Americans as compared to Caucasians [14-16]. Possible physiological mechanisms of altered acute pain tolerance may involve blood pressure, cortisol and norepinephrine responses [15]. African-Americans had lower cortisol concentrations and blunted norepinephrine and blood pressure responses to mental stress. They did not have the positive correlation between baseline blood pressure and pain tolerance which was observed in Caucasians. African-Americans also did not have the expected relationship between higher physiological responses to stress (blood pressure elevation and increases in cortisol and norepinephrine blood levels) and greater pain tolerance. Authors hypothesized that these differences in endogenous pain regulatory mechanisms may contribute to lower pain tolerance in African-Americans. Hypothetically, if hemodynamic responses to pain are different between the groups in our study, it could explain the differing intraoperative opioid administration with similar postoperative administration. However, if this were the only mechanism then one would expect greater postoperative administration to the Latino children who, we found, had received less intraoperative opioid.

In the present study, children in three different geographic areas underwent similar surgeries under standardized anesthesia by SMILE Network International providers. The similarity of these conditions suggests that these differences in opioid administration by geographic location may be due to differences in pain sensitivity or opioid sensitivity or due to other differences related to ethnicity. Further research is necessary to elucidate mechanisms underlying these group differences.

Limitations

The retrospective design of this study limited us to data in the medical records. No previous medical records were available. Pain scores were not consistently recorded and therefore, in the absence of documented treatment endpoint, we could only assess opioid use and not opioid requirements. Anesthetics were standardized to some degree by SNI; however dosing of medications was at the discretion of the individual anesthesia provider. Children from Central and South America encompass a diverse population of indigenous Indian, European and mixed Euro-Indian ancestry.

Conclusions

Children in Central and South America received less opioid perioperatively than African and Indian children for similar surgeries. Further research is necessary to elucidate mechanisms underlying these group differences and to be able to better understand and manage children's perioperative pain.

Acknowledgments

The authors would like to thank Smile Network International for participating in this study and to acknowledge the life changing charity service SNI and their volunteers and donors provide to children around the world http://www.smilenetwork.org.

This project was supported by NIH/NCRR CTSA Grant Number UL1 RR024150. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

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Table 1

Baseline data from Children in Africa, India and Central and South America

Clinically significant differences were present with African children being younger and of lower weight. Relatively more males underwent surgery in Africa. Oxygen saturation was similar between groups. Anesthetic duration was shorter in India.

	Africa	India	Central/South America	p
n	79	76	153	
Age (years)	2 ± 4	5 ± 5	4 ± 5	0.002
Male/female	1.7	1.1	1.0	0.3
Weight (kg)	12 ± 12	16 ± 12	18 ± 15	0.003
Oxygen saturation (%)	97 ± 2	97 ± 2	96 ± 2	0.004
Anesthetic duration (min)	98 ± 32	86 ± 32	103 ± 43	0.009

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Table 2

Surgical procedures in Africa, India and Central and South America

The majority of surgical procedures in children in Africa, India and Central and South America were cleft palate and cleft lip repairs. Other procedures included macrostomia repair, frenulectomy and facial scar revision.

	Africa n (%)	India n (%)	Central/South America n (%)
Cleft palate surgery	14 (18)	35 (47)	77 (50)
Cleft lip surgery	62 (79)	39 (53)	70 (46)
Other minor surgery	2 (3)	0 (0)	6 (4)

Table 3

Fentanyl administration during perioperative periods to children in Africa, India and Central and South America

Intraoperative fentanyl use was different between children of the three different geographic locations. Postoperative fentanyl use was similar between groups. *Initial intraoperative* fentanyl is the first dose given after induction of anesthesia. *Subsequent intraoperative* fentanyl is all intraoperative fentanyl excluding the initial dose. *Total intraoperative* fentanyl is the sum of initial and subsequent intraoperative fentanyl. *Recovery room* fentanyl is all fentanyl given in the recovery room. *Total perioperative* fentanyl is the sum of total intraoperative and recovery room fentanyl.

	Africa		**India**		**Central/South America**		**p-value***
	mcg	**mcg/kg**	**mcg**	**mcg/kg**	**mcg**	**mcg/kg**	
Initial intraoperative	26 ± 17	2.7 ± 1.2	34 ± 20	2.5 ± 1.3	23 ± 18	1.4 ± 0.7	< 0.001
Subsequent intraoperative	12 ± 17	1.3 ± 1.9	26 ± 28	1.8 ± 1.6	9 ± 17	0.6 ± 0.9	< 0.001
Total intraoperative	39 ± 24	4.1 ± 2.4	60 ± 41	4.3 ± 2.2	32 ± 28	2.0 ± 1.2	< 0.001
Recovery room	8 ± 15	0.9 ± 1.5	6 ± 11	0.6 ± 1.6	12 ± 18	0.7 ± 0.5	0.4
Total perioperative	47 ± 35	4.9 ± 3.5	67 ± 42	4.9 ± 2.9	44 ± 39	2.6 ± 1.4	< 0.0001

* Fentanyl use in mcg/kg used for analysis

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Table 4

Perioperative fentanyl use during individual mission trips to Africa, India and Central and South America

Total perioperative fentanyl use was lower in all Central and South American locations than African and Indian locations. *Total perioperative* fentanyl is the sum of total intraoperative and recovery room fentanyl.

	Date of mission trip	Patients (n)	Fentanyl (mcg/kg)
Africa			
Mbale, Uganda	6/2010	27	6.2 ± 5.2
Mbale, Uganda	4/2011	25	3.7 ± 1.7
Kijabe, Kenya	4/2011	27	4.9 ± 1.8
India			
Calcutta	3/2010	50	5.5 ± 3.3
Bhuj	3/2010	26	4.0 ± 1.6
Central and South America			
Lima, Peru	4/2010	46	3.1 ± 1.7
Huanuco, Peru	4/2010	27	2.0 ± 0.8
Ambato, Ecuador	9/2010	31	2.0 ± 0.7
Puebla, Mexico	11/2010	49	3.0 ± 1.4

Table 5

Multivariable analysis of characteristics potentially associated with perioperative fentanyl administration (mcg/kg)*

Geographic location, age, procedure type and anesthetic duration were significantly associated with total perioperative fentanyl administration.

Characteristic	Parameter Estimate	Standard Error	P-value
Intercept	0.11	6.61	
Geographic location			
Central/South America	(reference)		
Africa	2.68	0.38	<0.001
India	3.03	0.41	<0.001
Age, years	−0.12	0.03	0.003
Gender			
Female	(reference)		
Male	−0.56	0.30	0.065
Oxygen saturation (%)	0.03	0.07	0.708
Procedure type			
Palate	(reference)		
Lip	−1.35	0.32	<0.001
Other	−1.42	0.90	0.115
Anesthesia duration (min)	0.015	0.004	<0.001

*Analysis was performed using a general linear model with total perioperative fentanyl administration (mcg/kg) as the dependent variable. Age, oxygen saturation and duration of anesthesia were modeled as continuous variables and other explanatory characteristics were modeled as nominal variables using the categories indicated.