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Ropivacaine Decreases Tissue Oxygen Saturation Following Peripheral Nerve Block in Children

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Abstract

Background: Local anesthetics can cause vasoconstriction and disrupt neuronal impulses, reducing regional blood flow and increasing tissue oxygen consumption. This could alter regional oxygen supply and demand. Because microcirculation modifies during development and oxygen consumption kinetics differ between children and adults, we aimed to assess effects of ropivacaine Peripheral Nerve Block (PNB) on regional tissue saturation in children and young adults using Near-Infrared Spectroscopy (NIRS).

Methods: Following Institutional Review Board approval and informed consent, 20 patients undergoing PNB for various orthopedic surgeries were studied. NIRS sensors were placed on the operative limb, contralateral limb, and forehead. Tissue saturations (rSO_2) were recorded at baseline and every 5 minutes for 60 minutes following ropivacaine PNB. Mean rSO_2 was assessed with repeated measures ANOVA. Correlation of tissue rSO_2 with cerebral oximetry was calculated and significance determined with student's t-test.

Results: In all patients, blocked limb rSO_2 decreased significantly compared to control limb 20 minutes after injection and remained lower. Control limb rSO_2 and cerebral oximetry did not change over time. Non-blocked limb rSO_2 demonstrated weak but significant correlation with cerebral oximetry while blocked limb rSO_2 showed no correlation. Mean change in blocked limb rSO_2 from baseline was significantly negative compared to a net positive mean change in the non-blocked limb.

Conclusions: Decreased rSO_2 following PNB suggests reduced local blood flow due to vasoconstriction, increased tissue oxygen consumption, or both. Changes in rSO_2 provide an opportunity to develop NIRS as a non-invasive tool to identify successful PNB. Local anesthetic-induced decline in rSO_2 could have implications in operative settings with ischemia or low-flow.

Keywords: Local anesthetic ropivacaine; Peripheral nerve block; Tissue oxygenation; Spectroscopy; Near-infrared; Vasoconstriction

Introduction

Local anesthetics have intrinsic vasoactive properties and have been shown to cause dose-dependent vasodilation across a range of clinical concentrations [1]. However, by contrast, amide anesthetics can also cause dose-dependent vasoconstriction at lower concentrations [1]. Such vasoconstriction has been demonstrated following intradermal forearm injection of bupivacaine and levobupivacaine in humans and following direct tail artery application of ropivacaine in rats [1,2]. Furthermore, ropivacaine-induced vasoconstriction has been reported following peripheral and neuraxial nerve blockade [3]. Thus, it is possible that Peripheral Nerve Block (PNB) with amide local anesthetics could reduce regional blood flow or impair the microcirculation.

Nerve conduction and intact innervation are important for the regulation of muscle mitochondrial homeostasis [4,5]. Denervation affects tissue oxidative capacity differently over time. For example, chronic denervation results in progressive decline in mitochondrial electron transport chain enzyme function while acute denervation increases muscle oxygen consumption and resting metabolic rate [5-9]. In addition, post-ganglionic sympathectomy has been shown to increase oxidative phosphorylation in the affected tissue and organs [10]. It is possible, then, that local anesthetic-induced disruption of neuronal impulses following PNB could alter muscle and tissue bioenergetics.

Due to their potential direct and indirect effects on blood flow and tissue mitochondrial function, local anesthetics have the propensity to disrupt the balance of tissue oxygen supply and demand. The microcirculation and functional capillary density change during development and oxygen consumption kinetics differ between children and adults, yet the effect of local anesthetics on tissue oxygenation has never been assessed in the paediatric population [11,12]. Therefore, the aim of this study was to assess the effect of ropivacaine on tissue oxygen saturation *in vivo* in children and young adults. We tested the hypothesis that local anesthetics could affect tissue oxygenation by measuring changes in regional limb tissue saturation (rSO_2) using Near-Infrared Spectroscopy (NIRS) following PNB with ropivacaine.

Methods

This is a prospective observational study and was approved by the Institutional Review Board (IRB) of Children's National Medical Center. Written informed consent from each patient's parent or legal guardian and patient assent were obtained.

Patients

Twenty ASA status I and II patients aged between 8 and 18 years (weighing between 39 kg and 120 kg) undergoing orthopedic surgical

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procedures under general anesthesia with a PNB as part of their routine care were studied (Table 1). Each patient served as his/her own control. Exclusion criteria consisted of known allergy to the local anesthetic, ropivacaine, local infection in the area to be injected, coagulation disorder, or known neurologic, motor, or sensory deficits.

Study Protocol

Following induction of anesthesia with either inhalational sevoflurane (up to 8%) or intravenous propofol (up to 2 mg/kg) and placement of an appropriately sized endotracheal tube, three NIRS sensors (Somanetics Paediatric SomaSensor, Troy, MI) were placed. For femoral nerve block, a limb sensor was placed on the operative limb in the L2-3 dermatome on the upper thigh. For interscalene block, the limb sensor was placed in the C5-6 dermatome on the anterolateral aspect of the arm. For popliteal block, the sensor was placed in the L5-S1 dermatome on the lateral aspect of the lower leg. For axillary nerve block, the sensor was placed in the C8-T1 dermatome on the median surface of the upper arm. Sensors on the operative limb were placed a minimum of 15 cm from the injection site for PNB in order to avoid the possibility of measuring infiltrative effect of the local anesthetic. A second sensor was placed in the identical location on the contralateral non-operative limb as a control. A third sensor was placed across the forehead to measure cerebral oximetry to serve as a non-invasive indicator of global cardiac output [13,14]. The sensors were connected to an INVOS 5100C monitor (Somanetics Corp, Troy, MI) and baseline rSO_2 was recorded 20 minutes after induction. General endotracheal anesthesia was maintained with sevoflurane (up to 2.5%) or desflurane (up to 6%), based on anesthesiologists' preference, and 0.5 FiO_2 (air and oxygen).

The regional block was performed with ultrasound guidance (SonoSite, Bothell, WA). PNB was achieved with ropivacaine (0.5% without epinephrine, 0.3-0.4 mg/kg, with a maximum volume of 20-30 mL). Successful needle placement was further confirmed with use of a Stimuplex DIG nerve stimulator (Braun, Bethlehem, PA) at 0.4 m Amp or lower. Following injection of ropivacaine, bilateral limb and cerebral rSO_2 were recorded every 5 minutes for 60 minutes. At no time during the recording of data was a tourniquet used. Each subject was continuously monitored with pulse oximetry, non-invasive blood pressure, end-tidal CO_2 and temperature measurement.

Age (years)	
Mean ± SD	14.5 ± 2.8
Range	8-18
Weight (kg)	
Mean ± SD	67 ± 23.3
Range	41-120
	Number of patients
Sex	
Male	16
Female	4
Type of Surgery	
Repair of anterior cruciate ligament	10
Knee arthroscopy	6
Repair syndactyly	2
Shoulder arthroscopy	1
Open reduction/internal fixation ankle	1
Type of Peripheral Nerve Block	
Femoral	16
Interscalene	2
Popliteal	1
Axillary	1

Table 1: Demographic characteristics of patients undergoing peripheral nerve block.

Statistical Analysis

A sample size of 20 was chosen to provide at least 80% statistical power with a 2-tailed alpha level of 0.05 to detect a 15% difference in tissue oxygen saturation between the blocked and non-blocked limb. This estimate took into account 12 measurements per hour and assumed a 70% correlation between measurements on the same patient in the same limb. Data was assessed for normality by examining histograms and box plots.

Repeated measures ANOVA with post hoc Tukey's test were used to compare tissue oxygen saturation within and between groups. Correlation coefficients between time-matched tissue rSO_2 and cerebral oximetry were calculated and significance determined with student's t-test. The mean rSO_2 difference from baseline was calculated for the blocked and non-blocked limb and was compared by two-tailed Student's *t*-test. Statistical significance was set at $P<0.05$.

Results

All twenty patients had successful location of the peripheral nerve. All patients had verification of a successful block through clinical exam upon emergence from anesthesia at the end of the case. There was no difference in baseline tissue rSO_2 between limbs prior to placement of the nerve block. Tissue rSO_2 decreased significantly in the blocked limb compared to the non-blocked limb beginning 20 minutes after ropivacaine injection. Blocked limb rSO_2 remained significantly decreased compared to measurements at several different time points in the control limb beyond 20 minutes. Tissue rSO_2remained significantly lower in the blocked limb compared to control limb for the remainder of the study. Although rSO_2 in the non-blocked limb and cerebral oximetry fluctuated over time, these changes were not significant. Furthermore, rSO_2 in both limbs did not differ significantly from cerebral oximetry at any time point (Figure 1).

Mean rSO_2 difference across all time points from baseline was

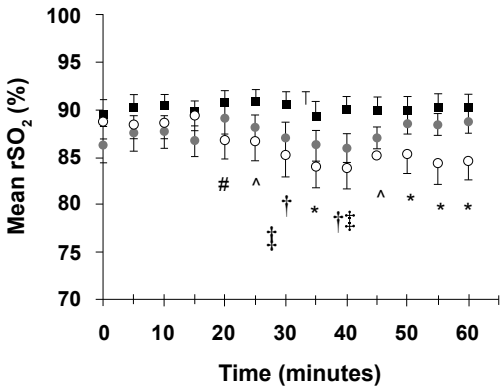

Figure 1: Tissue oxygen saturation (rSO_2) over time Mean rSO_2 values are depicted. Zero minutes represents baseline measurements. Values are means +/- standard deviation. Closed squares represent non-blocked limb rSO_2, open circles represent blocked limb rSO_2, and grey circles represent cerebral rSO_2. #P<0.0001 vs. time matched non-blocked limb values; *P<0.0001 vs. all time points in non-blocked limb; †P<0.0001 vs. 5, 15, 20, 25, and 35 minute values in non-blocked limb; ‡P<0.0001 vs. 60 minute time point values in non-blocked limb; ^P<0.0001 vs. 15, 20, 25, and 35 minute values in non-blocked limb.

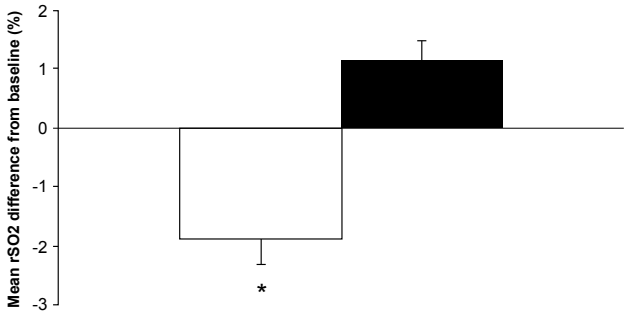

Figure 2: Mean change in tissue oxygen saturation (rSO_2) from baseline. Mean difference in limb rSO_2 values from baseline values for entire study period are depicted. Values are means +/- standard deviation. Closed bar represents non-blocked limb, open bar represents blocked limb. *P<0.0001 vs. non-blocked limb.

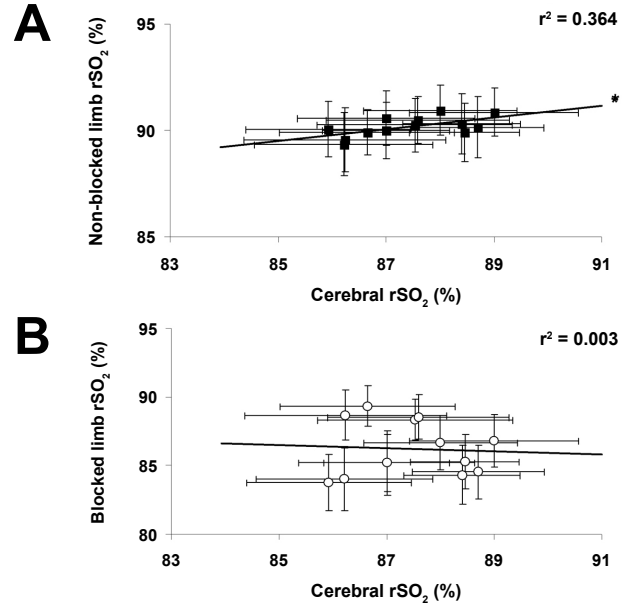

Figure 3: Time-matched correlation between limb tissue oxygen saturation (rSO_2) and cerebral oximetry. Linear regression analyses between time-matched mean (A) non-blocked limb rSO_2 or (B) blocked limb rSO_2 and cerebral rSO_2 with standard deviations are depicted. (A) For non-blocked limb rSO_2, r^2=0.364, *P<0.001. (B) For blocked limb rSO_2, r^2=0.003, P=NS.

calculated for both limbs. Mean tissue rSO_2 decreased significantly in the blocked limb by 1.9% (+/- 0.5%) from baseline compared to a 1.1% (+/- 0.3%) increase in tissue rSO_2 from baseline in the non-blocked limb (Figure 2).

Correlation coefficients were calculated between time-matched limb rSO_2 and cerebral oximetry. Tissue rSO_2 in the non-blocked limb demonstrated a weak but significant correlation with cerebral oximetry. Tissue rSO_2 in the blocked limb, however, showed no significant correlation with cerebral values (Figure 3).

Discussion

Here we demonstrate that tissue oxygenation decreased significantly following injection with ropivacaine. This decrease began 20 minutes post injection and persisted throughout the study period. There were no significant changes in tissue saturation in the control limb or cerebral oximetry over time and minor fluctuations likely reflected normal variation in cardiac output and oxygen delivery under general anesthesia following induction. Tissue rSO_2 in the non-blocked limb demonstrated a weak but significant correlation with cerebral oximetry. On the other hand, decreases in rSO_2 following ropivacaine injection had no correlation with cerebral oximetry. The significant net negative change in mean rSO_2 from baseline in the blocked limb compared to the net positive change in the control limb along with the lack of correlation of rSO_2 following ropivacaine injection with cerebral oximetry indicates that decreased tissue saturation in the blocked limb must have been due to ropivacaine and were independent of changes in global cardiac output.

Reduction in tissue saturation indicates a mismatch in oxygen supply and demand [15]. This can occur due to increased oxygen consumption in the setting of unchanged or reduced oxygen supply or due to decreased oxygen delivery with unchanged or increased oxygen consumption. Since there was no significant change in control limb saturation and no correlation between tissue saturation in the blocked limb with cerebral saturation, any change in the blocked limb must have been due to local effect. Thus, ropivacaine either caused a reduction in blood flow to the blocked limb or increased tissue oxygen consumption or both.

PNB has been shown to cause local vasodilation and increase regional blood flow in animal models and adult patients [16-18]. In recent work, NIRS technology demonstrated that tissue oxygen saturation increased in the ipsilateral blocked limb following PNB with ropivacaine compared to control, non-blocked, limb in adults [19]. Tighe and colleagues, in a method similar to ours, measured tissue oxygen saturation using NIRS in a limb that received a peripheral nerve block with ropivacaine and compared it to a control, non-blocked, limb. Contrary to our findings, they found that tissue oxygen saturation increased slightly in the blocked, but not the control, limb over time. They contribute this finding to sympathectomy, though no specific cause of their findings was further investigated. Consistent with our findings is the possibility that ropivacaine is acting as a local arterial vasoconstrictor [3,20]. Epidural ropivacaine (0.5%) has been shown to cause a 37% reduction in epidural blood flow 30 minutes following injection [20]. Furthermore, ischemia of the glans penis was reported in an 18 year old undergoing circumcision 40 minutes following injection of 0.75% ropivacaine [3]. In addition, direct application of ropivacaine caused tail artery vasoconstriction and significantly reduced blood flow in rats under isoflurane anesthesia [2]. Interestingly, tail artery blood flow began to decrease 10 minutes after ropivacaine application with maximal reduction at the 30 to 40 minute time point [2]. Moreover, ropivacaine-induced vasoconstriction was most profound with the 0.5% concentration (compared with 0.2% and 0.75%) [2]. In our study, the timing of onset and duration of decreases in rSO_2 following injection of 0.5% ropivacaine are reminiscent of the reductions in blood flow seen in these prior studies. Thus, it is quite possible that reduced tissue saturation following PNB with ropivacaine in children resulted in regional vasoconstriction. However, because we did not measure blood flow in this work, we cannot definitely state that vasoconstriction caused the decreased rSO_2 in this work. This represents a limitation of the study.

Reflectance NIRS measures tissue oxygen saturation by determining the difference between transmitted and received light delivered at specific wavelengths [21]. Within the near-infrared range, the primary light-absorbing molecules within tissue are hemoglobin, bilirubin, and cytochromes [21]. Depending on depth of photon penetration, average

tissue saturation determined by NIRS devices is usually distributed in a 70% venous to 30% arterial proportion [20,21]. Thus, our measurements likely reflect oxygen saturation within muscle and subcutaneous tissue. Although aromatic amine local anesthetics, such as ropivacaine, have been shown to disrupt mitochondrial function and uncouple oxidative phosphorylation, direct effect on tissue mitochondria due to local spread following subcutaneous infiltration is unlikely to explain our observations given that the sensors were placed at least 15 cm distal to the injection site [22-24].

Prior work suggests that intact innervation helps to regulate muscle mitochondrial enzyme function and homeostasis [4,5]. Disruption of neuronal input is known to affect tissue oxygen consumption. For example, acute denervation has been shown to increase resting metabolic rate in perfused rat skeletal muscle by 28% [8]. It is possible that local anesthetic-mediated inhibition of nerve conduction induces a state of reversible chemical denervation. Such functional denervation could disrupt neuronal regulation of mitochondria and result in increased muscle and tissue oxygen consumption. Increased metabolic demand could explain the reduced tissue saturation we observed following PNB with ropivacaine. However, our study design did not permit determination of the exact mechanism of ropirvacaine-induced reductions in tissue saturation. Furthermore, we only studied one specific local anesthetic. These represent important limitations of this work. Thus, future study will focus on identifying the mechanism of decreased tissue saturation following PNB and the effects of blockade using a variety of other local anesthetics.

Regardless of the mechanism of decreased tissue oxygen saturation following PNB with ropivacaine, our findings raise some points to consider. First, regional changes in tissue saturation provide a potential novel method to monitor for successful nerve block using NIRS technology. Because most nerve blocks in children and young adults are often placed under sedation or general anesthesia, immediate confirmation of successful block within a specific dermatome is challenging. Although use of a nerve stimulator permits immediate assessment of the effect of local injection on the targeted nerve, currently there is no technique to confirm local anesthetic effect in the dermatome of interest under general anesthesia. Thus, future efforts should focus on developing this potential tool as an adjunct to confirm onset and success of PNB.

Second, a fall in tissue saturation following local anesthetic injection, whether due to reduced blood flow or increased oxygen consumption, raises concerns. Oxygen supply and demand mismatch could potentially result in ischemia and tissue damage especially during low flow states such as with cross clamping of the aorta for surgical repair of thoracic aortic aneurysms and coarctation of the aorta or during periods when a tourniquet is used with various orthopedic surgical procedures. Because regional techniques are commonly used in these scenarios, further studies will need to assess the effect of local anesthetics on microvascular blood flow and tissue oxygen consumption in such settings.

In summary, PNB with ropivacaine decreased tissue oxygen saturation *in vivo* in children and young adults beginning 20 minutes following injection in the ipsilateral limb. Change in saturation suggests ropivacaine-induced local vasoconstriction or increased regional oxygen consumption due to uncoupling of oxidative phosphorylation. Future work will focus on defining the exact mechanisms and assessing the safety of local anesthetics in surgically induced low flow states.

Declaration of Interests

There are no conflicts of interest to report on behalf of any of the authors of this manuscript.

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