Adjuvants in Regional and Neuraxial Anesthesia: An Update

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Purpose of Handout:
Discuss the role of several local anesthetic adjuvants and their limitations in clinical practice.

Recent Findings:
Clonidine acts in the periphery to hyperpolarize sensory neurons.

Keywords:
Adjuvants; local anesthesia; epinephrine; clonidine; alpha-2 agonist; opioid; caudal; epidural; ketamine; pain; dexmedetomidine

Introduction

The treatment of acute pain and prevention of chronic pain remains one of the major challenges in anesthesiology. Side effects associated with the use of opioid analgesia, the most commonly administered form for pain control includes nausea and vomiting, delayed recovery of bowel function, sedation, respiratory depression, hyperalgesia and occasionally, prolonged hospital stay. Paradoxically, the administration of opioids to treat pain can be the catalyst that sensitizes patients to painful stimuli. Opioids cause changes in the central and peripheral nervous system that can ultimately trigger sensitization of pronociceptive neural pathways. Avoiding or minimizing the use of opioids with alternative treatments such as the administration of local anesthetics has become part of a multi-modal approach to quality pain management. The beneficial properties of local anesthetics have been well outlined by Dr. Berde in the first lecture and can be examined in a number of review papers. These drugs however, have the potential to produce very serious, deleterious side effects, including, but not limited to: cardiac arrhythmias, central nervous system (CNS) depression, seizures, hypotension, allergic reactions, and respiratory depression. Please see the following articles for more information about the topics[1, 2, 3, 4]. The coadministration of local anesthetic adjuvants, which at a variety of central and peripheral nervous system sites, may improve the side-effect profile of a LA by lessening the amount the LA required by a patient. See figure 1. Adjuvants can contribute in their own special manner to the overall benefit of the patient. Several important and more commonly used adjuvants in the pediatric population will be discussed. Unfortunately a review of newer modes of delivery of LAs is beyond the scope of this piece.

Background
Local anesthetic agents have been in daily use for thousands of years. The Spanish noted in writings from the 1500 that South American native peoples chewed the leaves of the coca plant for medicinal and recreational purposes. Dr. Koller in 1884 famously applied cocaine to his eye and anesthetized the organ[5]. The ability of these agents to modulate the stress response induced by trauma during surgery, to treat cardiac dysrhythmias, to limit the side-effects of both the inhaled anesthetics and systemic opioids and to potentially preempt the debilitating consequences of chronic pain, have been the main reasons for the administering LAs. Efforts to make LAs safer and more

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selective continue. Even though major advances have been made in local anesthetic chemistry, synthesis of an ideal agent remains illusive. An agent with a longer duration of action, shorter onset time, and a more selective sight of action is sought. In lieu of finding such an ideal agent, a number of adjuvants have been combined with LAs to improve the effectiveness of LAs.

Opioids

First given to human subjects in the neuroaxial spaces in the late 1970s, opioids are one of the most frequently used classes of adjuvants[6]. Given the ubiquity of opioid receptors in the CNS it is understandable that they display a wide variety of physiological and psychological effects. Opioid antinociceptive (pain relieving) properties is well documented, so consequently their addition to a LA solution as a means of extending the duration of pain relief and as a way of decreasing the dosage of LA required for pain treatment, is apparent. The mechanism by which opioids affect LA action is through a G-protein-coupled-receptor system. Opioids competitively bind to specific receptors to induce pain relief by hyperpolarizing the afferent sensory neurons in which the receptors are imbedded. Hyperpolarization of the cell membrane by an opiate decreases the propagation of neuronal action potentials thereby inhibiting afferent pain signals. Eventually this produces a decrease in the perception of pain[7]. Besides being located in the CNS, opioid receptors have been identified on a number of cells in the periphery of the body[8, 9]. Evidence demonstrating the benefits of administering opioids into peripheral tissues is inconclusive[10, 11]. This may be due to poor experimental design, or other confounding factors not the least of which is the complexity of opioid pharmacokinetics[12]. Factors such as dose, lipophilicity, site of injection and condition of the milieu into which the injection is made, play an important role on the eventual effect produced[13, 14]. Some of the opioids currently being administered along with LAs are discussed below.

Morphine is the prototypical opioid used in our clinical setting. It has multiple formulations but only the preservative free form is recommended for regional anesthesiology. Intrathecal and epidural administration of this morphine has been shown to improve post surgical pain in both children and adults[15, 16]. When administered into the intrathecal space the morphine with its hydrophilic properties, is not as easily absorbed into the surrounding tissues. Influenced by the hydrophilic nature of morphine, concomitant cephalad spread increases the area of analgesia. This spread also potentiates the risk of respiratory depression. Intrathecal morphine can cause respiratory depression within the first 6 hours after its neuraxial administration and it may also cause respiratory problems many hours later. However, with proper dosing, cardiorespiratory monitoring, and vigilance, respiratory depression can be avoided or identified and treated early. Other side effects of morphine include nausea, vomiting, itching, and urine retention. Remember this last symptom is also a side effect of inadequate pain relief. Anticipation and preemptive treatment of these potential side effects with the appropriate counter measures, can improve the patient's hospital experience. It should be noted that prolonged intrathecal infusion of morphine is associated with granuloma formation in adults so this practice is to be avoided if possible. The mechanism of this process is speculative[17].

Fentanyl is one of the more widely used opiates in conduction anesthesia. This agent is combined with a local anesthetic to act additively, if not synergistically, with LA to improve a variety of characteristics of the block. Fentanyl is a short acting opiate that is

more potent (70 to 100 time stronger) than morphine. In normal, children, fentanyl has limited untoward effects on the cardiovascular system. Since this drug has a short duration of action, to prolong its effects, it is often administered as a continuous infusion into the intrathecal space or into the epidural space. The short duration of fentanyl stems from fentanyl being rapidly taken up into blood vessels and redistributed into well-perfused tissues—such as muscle, heart, brain—and into fat. This is in contrast to drugs that disappear quickly due to rapid metabolism. It should be noted that a continuous infusion of fentanyl or with the administration of multiple large doses of the drug, fentanyl will accumulate in fatty tissues that act as a depot out of which the drug will later leach. Tissue saturation can result in either prolonged sedation or respiratory depression or both conditions. Be aware that there is increased risk of respiratory compromise if other depressant agents, such as lorazepam, are administered concomitantly. The site of action of neuraxially applied, highly lipophilic agents such as fentanyl and sufentanil is controversial. Bernards et al., have performed several elegant experiments countering the thesis that neuraxially administered, highly lipophilic agents, like fentanyl, work "via a spinal mechanism" [18]. This group believes that the mechanism of action of the lipophilic drug is produced via systemic mechanisms.

Hydromorphone is another drug that is used in regional anesthesia. It is 3 to 7 times stronger than morphine. Hydromorphone is metabolized by the liver and excreted by the kidneys. The metabolites of hydromorphone do not linger to the same degree as morphine metabolites and thus hydromorphone is preferred for patients with renal insufficiency. Even though hydromorphone appears to have a better overall side effect profile than morphine, i.e., less itching and less gastrointestinal problems, data research does not support these conclusions[19]. Hydromorphone may, however, have some advantage over morphine when administered into the epidural space due to its greater narrow pattern of spread. Hydromorphone can also be administered in the epidural space as a continuous infusion, alone or as a patient controlled epidural analgesic (PCEA) infusion. No granuloma formation similar to that seen with continuous intrathecal morphine infusion has been noted with hydromorphone infusions. As with all of the adjuvants, proper patient monitoring is essential.

Alpha-1 Adrenergic agents such as demonstrate a variety of effects on pain perception. Epinephrine is the prototypical drug agent administered as a local anesthetic adjuvant[20]. This neurotransmitter when administered exogenously with LAs prolongs the effect of the local anesthetics through its vasoconstrictive actions. Epinephrine increases the duration of caudal epidural bupivacaine in children and is used to prevent local anesthetic systemic toxicity (LAST) by testing for the presence of an intravascular injection[21, 22]. Jöhr and Berger recommend an epinephrine dosing of 0.5-1 mcg/kg and using 0.1-0.2 ml/kg[23]. Besides the vasoconstriction seen with epinephrine it may have intrinsic antinociceptive properties mediated by alpha-2 adrenoreceptor activation[24]. A recent report siting four cases of severe neurologic damage in children associated with epidural analgesia. Speculations by the authors that the epidural complications might be due to prolonged epinephrine exposure in the epidural space. They suggest that beyond the test dose, epinephrine should not be using in the continuous infusion or subsequent redosing of the catheter[25]. How reasonable this assertion is will need further investigation. Epinephrine may have intrinsic neurotoxic properties[26]. The vaso-active properties to the LA in the mixture should be accounted for when making the decision to use an adjuvant. Some of the LAs like ropivacaine have intrinsic vasoconstrictive

actions. There may be additive results when administered in conjunction with alpha-1-adrenergic agents.

Alpha-2 Adrenoreceptor Agonists (A2AA) are another large class of agents that are given in combination with LAs for regional anesthesia including central and peripheral blocks. It is generally held that centrally applied A2AA, "work in the locus coeruleus (LC)", however, work by Brown et al., despite this assertion[27]. These researchers point out that A2AA bind to presynaptic alpha-2 adrenoreceptors (A2A) in the CNS, specifically the basal forebrain, preoptic area, thalamus and cortex. In their model, the neurons projecting from the LC into the aforementioned areas of the brain, house at their ends, the binding sites for the A2AA.

In the PNS the actual A2AA pain-relieving sites of action are unknown and thus the mechanism remains speculative. Blockade by A2AA of the hyperpolarization-activated cation channels on peripheral sensory neurons inhibits repolarization of the sensory neurons in which the alph-2 adrenergic receptors are embedded. This is thought to produce the observed antinociceptive action. There is only a slight amount of inhibition of the compound action potential (CAP) i.e., local anesthetic activity, associated with A2AAs[28].

Clonidine is the most widely used representative of this class of drugs in regional anesthesiology. It prolongs the action of LAs when they are given intrathecally, epidurally and in some cases when it is administered through a peripheral nerve catheter[29, 30, 31, 32]. Although speculative, clonidine appears to decrease pain in the peripheral nervous system by hyperpolarizing the activity-dependent, I_h cation channels on sensory neurons[33]. Several studies suggesting that clonidine does not improve the quality of a peripheral nerve block can be cited[34, 35]. In a prospective, randomized, double-blind control study of sixty children receiving an axillary block, no benefit was found by the authors, except for an increase in the time to the first analgesia request, when clonidine was combined with ropivacaine for the block[36]. In another study Whiting et al., demonstrate the efficacy of clonidine and buprenorphine as sole analgesics[37]. If confirmed by further research this technique would be a very welcomed addition to our field Goodarzi et al., and Beschan et al., have used preservative-free clonidine to enhance caudal blockade[38, 39]. Goodarzi's group found that the addition of 1 mcg/kg of clonidine significantly increased the duration of caudal blockade when compared with plain ropivacaine. Their blinded, randomized study of 30 ASA I children com- pared plain ropivacaine with ropivacaine plus clonidine. The duration of the regional blockade in the plain group was 3.3±1.5 hours. The duration for the clonidine group was 7.2 ± 1.4 hours (P < .003). Also, the clonidine group needed significantly less supplemental analgesia. They had no reported cases of respiratory or cardiovascular problems. Breschan's group reported a single case of a full-term child who had multiple episodes of respiratory depression with bradycardia after receiving caudal 0.2% ropivacaine (2.7 mL) with 2 mcg/kg of clonidine. The 3-kg healthy infant had an inguinal herniorrhaphy and orchiopexy under general anesthesia with supplemental ropivacaine and clonidine. Postoperative monitoring indicated multiple episodes of desaturation. There was 1 episode of the patient having a saturation of 76%. The infant also had bradycardia. Oxygen and manual ventilation were necessary in the recovery room. The infant was started on aminophylline and was discharged 7 days after the dis- continued use of the aminophylline. The investigators recommend further study to determine the optimal dose of caudal clonidine. A word of caution, clonidine should not be administered to

premature infants or those at risk for apnea especially in an outpatient setting and without proper monitoring.

Dexmedetomidine is another more selective, A2AA imidazole compound than clonidine. It exhibits a high ratio of specificity for the alpha-2 versus alpha-1 adrenergic receptor. This agent causes sedation, anxiolysis, and analgesia. Dexmedetomidine had been approved for sedation in adults during mechanical ventilation in intensive care unit settings. There are few data addressing the use of this drug for regional anesthesia. Further clinical trials are needed to fully determine the potential clinical application of both clonidine and dexmedetomidine in children[40].

N-methyl D-Aspartate (NMDA) receptor agonists like ketamine and magnesium are used as adjuvants for intrathecal block, epidural blocks and peripheral nerve blocks. These adjuvants block the activation of the central NMDA associated glutaminergic system. This is important because activation of this system appears to play a role in the development of both central sensitization i.e., wind-up and opioid-induced hyperalgesia. A rise in glutamate concentration, an excitatory neurotransmitter, increases its availability for N-methyl d-aspartate (NMDA) receptors. Activation of these receptors induces an influx of intracellular calcium that stimulates protein kinase C and nitric oxide synthesis. This induces gene transcription that is associated with changes in CNS that are ultimately responsible for the development of sensitization and possibly hyperalgesia. Several adult studies have demonstrated efficacy of these agents in peripheral blocks to treat wind-up[41]. McCartney et al. extensively review the topic of NMDA agonists in humans and their role in preventative analgesia in the Anesthesia and Analgesia article, "*A Qualitative Systematic Review of the Role of N-Methyl-D-Aspartate Receptor Antagonists in Preventive Analgesia*"[42]

Ketamine was approved for clinical practice for humans in 1970[43]. This drug is usually used as an intravenous anesthetic however, recently it has been explored as an antagonist to wind-up and opioid induced hyperalgesia (OIH)[44]. Its anesthetic and analgesic properties possibly result from the activity within the limbic and thalamic systems, providing "dissociative anesthesia." Additionally, another site of action appears to be the NMDA receptors. After nerve damage, NMDA receptors play a key role in the induction and maintenance of spinal nociceptive events that incite a state of central sensitization.

It is likely that aberrant peripheral nervous system activity is amplified and enhanced by NMDA receptor-mediated mechanisms in several neuropathic pain states. Ketamine inhibits NMDA receptors. Bell et al., in a Cochrane analysis concluded from 55 randomized controlled trials from 1996-2004 that ketamine in sub-anesthetic dose decrease perioperative analgesic requirements and improved postoperative nausea and vomiting[45]. A meta-analysis performed by Dahmani et al., involving caudal ketamine, both the racemic and S (+) form of the drug, found prolonged caudal block times and lowered the pain medication requirement compared to patients who did not receive ketamine. Oddly, the average pain scores in the PACU were not lower in the ketamine group[46].

Lee and Saunders reported on the successful use of preservative-free ketamine (0.25 mg/kg) in conjunction with 0.2% ropivacaine at 1 mL/kg for a circumcision[47]. In a blinded, randomized study, 32 ASA I and II children were given a caudal block with or

without ketamine. The ketamine group had a significantly longer duration of analgesia (12 hours) compared with the plain ropivacaine group (3 hours). When side effects were examined, there were no differences between the groups.

De Negri et al., conducted a study of studied 58 male between 1 and 5 years of age who were scheduled to have hernia or orchiopexy surgery; the researchers. They determined that S (+) ketamine was a better analgesia than clonidine for pain relief when given into the caudal epidural space. The researchers compared three groups of children. Group R received 2mg/kg caudal ropivacaine (0.2%) plus saline. Group C received 2mg/kg caudal ropivacaine (0.2%) plus clonidine 2 mcg/kg and group K received 0.2% ropivacaine, 2mg/kg plus preservative free S (+) ketamine 0.5 mg/kg. The ketamine group needed less supplemental analgesia and had a longer period of time until their first rescue analgesic dose, 291 ± 30 min in group R, 492 ± 23 min in group C, 701± 33 min in group K (P < 0.05)[48].

Magnesium is another agent that works at the NMDA receptor. It has received much attention lately because of the positive risk benefit ration associated with its administration. Untoward effects like hallucinations, hyper-salivation and the associate laryngospasm and central sympathetic stimulation associated cardiac changes are side effects of ketamine that are avoided with the treatment of magnesium for pain relief. The intravenous route has been the main way magnesium has been administered[49]. However, at least one study investigating its utility in the epidural or intrathecal space has been reported[50]. More studies are needed to determine the safety and efficacy of magnesium being used in peripheral nerve blocks or the epidural or intrathecal spaces of children.

Alkalization of LA raises the pH of the solution and has been shown to increase the speed of onset of nerve blocks[51]. This process changes the ratio of nonionized to ionized species in solution, increasing the proportion of drug able to cross the lipid membrane of nerve cells. Ropivacaine can readily be alkalinized; however, when the volume of bicarbonate (8.4%) added to the ropivacaine is greater than 0.1 mL per every 20 mL of ropivacaine, precipitation occurs[52]. The alkalinized solution should be prepared just before it is to be used because it precipitates with time at room temperature. They also suggest that solutions used for long-term infusion should not be alkalinized.

Other agents such as dexamethasone, adenosine, neostigmine, dextran, and neuromuscular blocking drugs have been administered with LA to patients with varying results. The use of bicarbonate, which raises the pH of the LA solution with the goal of decreasing onset time of the LA, was in vogue in the 1980s and 90s. A nonsteroidal anti-inflammatory drug (NSAID), ketorolac, in combination with lidocaine was administered as an intravenous regional anesthesia IVRA) in two children for treatment of complex-regional pain syndrome with excellent results[53]. A fuller discussion of the other adjuvants can be found in excellent reviews authored by Wiles et al., or by Mazoit et al.[54, 55].

Neurotoxicity of agents administered along with LAs remains an important concern. Many of the adjuvants have not been fully scrutinized with rigorous research demonstrating their safety in children at various stages of development[56]. Williams et al., compared clonidine, buprenorphine, dexamethasone and midazolam and found that

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at clinically relevant concentrations these agents were by themselves less neurotoxic to rat neurons than ropivacaine[57].

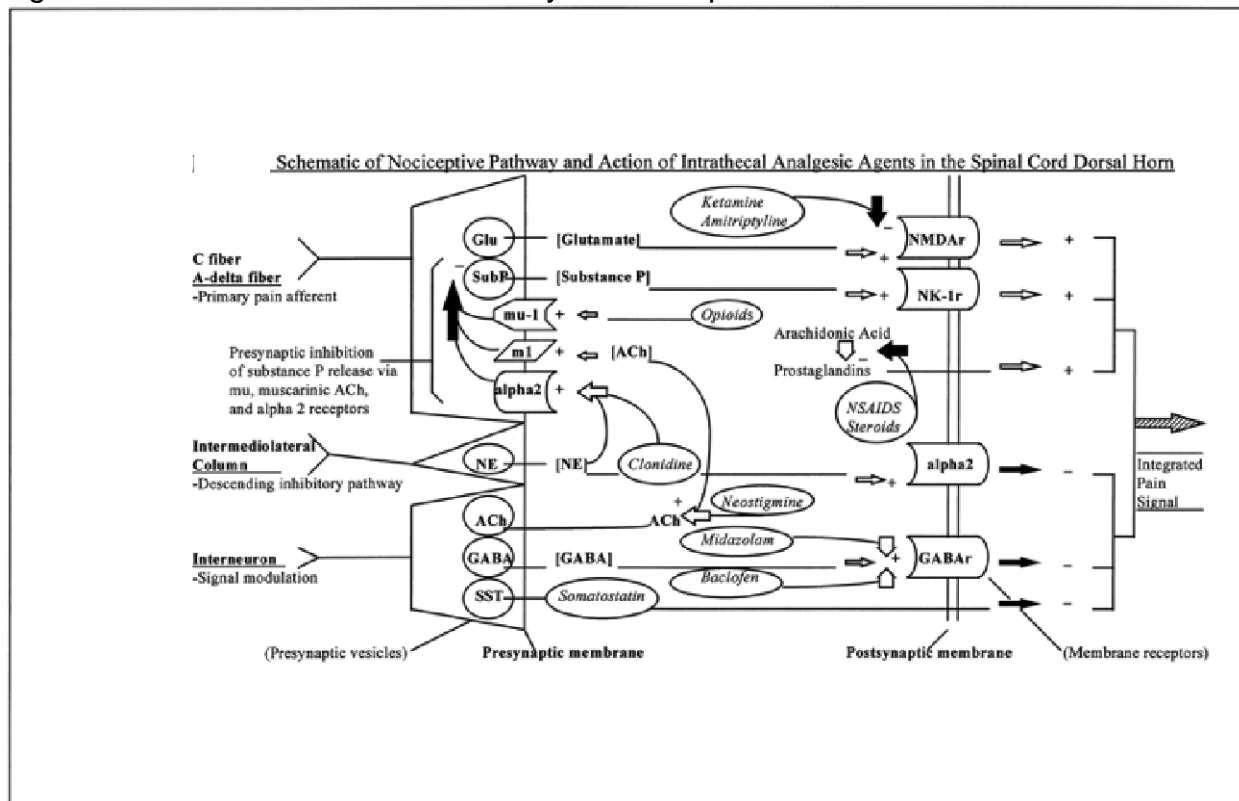See table1 and 2 for suggested epidural and spinal dosing recommendations respectively.

Summary
There is a dearth of published literature on the role of adjuvants in pediatric regional anesthesiology. The articles tend to be small series or case reports. Extreme caution should be exercised before administering an agent in combination with a local anesthetic. Pharmacokinetic and pharmacodynamic factors play crucial roles in drug safety. Know and prepare for the untoward pharmacological side effects of each agent. More research investigating issues of molecular mechanism, safety and efficacy with the administration of newer adjuvants in a setting of the ever-changing anatomy and physiology of pediatric patients is needed.

Select portions of this product were taken from Anderson, C. T. Ropivacaine for pediatric use. *Techniques in Regional Anesthesia and Pain Management* **5**, 70–79 (2001).

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Figure 1 Scheme of CNS Pain Pathway and Receptors

Schematic of Nociceptive Pathway and Action of Intrathecal Analgesic Agents in the Spinal Cord Dorsal Horn

Adapted from: Hodgson, P. S., Neal, J. M., Pollock, J. E. & Liu, S. S. The Neurotoxicity of Drugs Given Intrathecally (Spinal). *Anesthesia & Analgesia* (1999).

Table1 Epidural Dosing Guidelines for Local Anesthetic Adjuncts

Drug	Bolus Dose (mcg/kg)	Infusion (mcg/kg/hr)
Morphine	10-30 (> 50 leads to excessive side effects)	3-8
Hydromorphone	3 -4	2-4
Fentanyl	0.2-1.0 (max. 50 mcg/hr)	0.5-1.0
Clonidine	0.5-2	0.1-0.2
Ketamine	500 – 1000 (max: 100 **mg)**	NA
Butophanol	20 - 40 (lessens opioid side effects)	
Sodium Bicarbonate	1 mg/ml of lidocaine 0.1 mg/ml of bupivacaine, ropivacaine or levobupivacaine	NA

Adapted from: Deshpande and Tobias *The Pediatric Pain Handbook* Mosby Chicago 1996, Mazoit, J. -X. Local anesthetics and their adjuncts. *Pediatric Anesthesia* **22**, 31–38 (2011) and Schechter NL, et al. Pain in Infants, Children and Adolescents, 2nd ed, Philadelphia: Lippincott, Williams and Wilkins, 2003.

Table 2 Subarachnoid Block Local Anesthetic Adjuvants

Drug	Bolus Dose mcg/kg
Morphine	3-10
Fentanyl	0.25-0.5 (max. 25-50 mcg)
Hydromorphone	1-4
Clonidine	0.25-0.5 (max. 50 mcg)

The local anesthetics are combined with an equal volume of 10% dextrose and an epinephrine wash Modified from Suresh, S. and M. Wheeler (2002). "Practical pediatric regional anesthesia." Anesthesiol Clin North America 20(1): 83-113 and Lonnqvist, P. A. and N. S. Morton (2005). "Postoperative analgesia in infants and children." Br J Anaesth 95(1): 59-68. *Deshpande and Tobias *The Pediatric Pain Handbook*

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