Review Article

Exploring the transversus abdominis plane block in cesarean sections and the subsequent toxicity risk to neonates via breast milk

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Abstract

The transversus abdominis plane (TAP) block with its wide application has shown to be an analgesic effective for use in abdominal surgeries, including for cesarean section. However, the bupivacaine delivered in the TAP block comes with the risk of toxicity, both central nerve system (CNS) and cardiovascular system, and has been shown in some instances to reach maximum serum concentrations in excess of the 2 μg/mL associated with the lower end of CNS toxicity. There is a specific concern with cesarean section TAP blocks of the anesthetic passage to the neonate via maternal breast milk and whether this poses a toxicity risk. Bupivacaine has been shown to pass into maternal milk at concentrations 0.34 times the maternal serum concentration. Preliminary statistical analyses suggest that the bupivacaine delivered in breast milk is not in concentrations high enough to cause neonatal toxicity, but further studies would be useful in identifying what the toxicity risk is, if any, to the neonates' breastfeeding after the delivery and TAP block.

Keywords: Breastfeeding, local anesthetic toxicity, neonates, transversus abdominis plane blocks

Introduction to the Transversus Abdominis Plane Block

The transversus abdominis plane (TAP) block was first described by Rafi in 2001.[1] The block is applied in the lumbar triangle of Petit—an easily identifiable and palpable landmark bounded by the latissimus dorsi posteriorly, the external oblique anteriorly, and the iliac crest at the base.[1,2] When the TAP block was applied following abdominal surgery, it was shown to reduce postoperative pain scores with rest and movement and postoperative opioid requirements.[2] The block has also been used in the context of cesarean section deliveries under general anesthesia with lower visual analog score (VAS) pain scores, less tramadol consumption, and a longer time to the first request for analgesic.[3] However, applying the TAP block to women in the course of an operative delivery raises the question of whether the local anesthetic delivered poses any risk to the neonate in the course of breastfeeding following the delivery. The goal of this literature review is to examine the past applications of TAP blocks during cesarean sections and the effect of the block on serum concentrations of local anesthetics and the passage of local anesthetics into breastmilk to provide comprehensive information about the safety of the TAP block used in cesarean sections.

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Effectiveness of the TAP Block

When the TAP block was applied following abdominal surgery, it was shown to reduce postoperative pain scores with rest and movement and postoperative opioid requirements.[2,4] With patients undergoing abdominal surgery and general anesthesia, the TAP block significantly reduced visual analog score (VAS) pain scores at multiple time points up to 24 hours, overall tramadol usage (in mg) in the first 24 hours (210.05 ± 20.5 vs. 320.05 ± 10.6; $P < 0.01$), and time (in minutes) to first tramadol pain request (178.5 ± 45.6 vs. 23.5 ± 3.8; $P < 0.001$). The block has also been used to control postoperative pain in the context of cesarean section deliveries under general anesthesia. In a randomized controlled trial exploring TAP block vs. placebo in patients undergoing cesarean section delivery under general anesthesia, patients in the TAP block group demonstrated lower VAS pain scores and consumed less total tramadol (50 mg vs. 250 mg, $P = 0.001$).[3] There was also a significantly longer time to the first request for analgesic in the TAP block group (210 min vs. 30 min, $P = 0.0001$). Additionally, a meta-analysis that explored 20 randomized control trials comparing TAP blocks to placebo (no block) and intrathecal morphine demonstrated that TAP blocks were effective in providing post-cesarean section analgesia, especially in the short term directly following block administration.[5] Compared with a placebo, the TAP block resulted in significantly reduced pain at rest and with motion and decreased morphine consumption postsurgery. There was also some indication of reduced pain at rest when TAP blocks were used in combination with intrathecal morphine compared with the intrathecal morphine alone. However, results were less favorable to TAP blocks when directly compared with intrathecal morphine, showing no improvement in pain control or postoperative opioid requirements. The important conclusion to draw is that the TAP block has been consistently demonstrated to be an effective analgesic method in the postcesarean section period.

The Effect of Bupivacaine TAP Blocks on Serum Concentration

Having established that TAP blocks with bupivacaine are effective, the concern is the potential toxicity of the anesthetic. Signs of toxicity associated with bupivacaine can be reached in the 2–4 μg/mL range of serum levels,[6] although there are many factors that affect the toxicity including the number of binding proteins in the serum and the percentage of free vs. bound molecules. Central nerve system (CNS) toxicity initially can present as dizziness and tingling, then progressing to unresponsiveness and coma with higher levels. Cardiovascular toxicity is reached at higher serum levels and can cause arrhythmias and hypotension.[7] In pregnancy, a decrease in alpha-1-binding globulin and albumin results in an increase in the percentage of free vs. bound bupivacaine, which increases toxicity risk.[8]

To understand the toxicity risk, both to mother and newborn, the first step is to explore serum concentrations of bupivacaine following TAP blocks. In a 2017 study, patients received 10 mg of bupivacaine as spinal anesthetic prior to the cesarean section and then 20 mL of 0.25% bupivacaine bilaterally in a TAP block postoperation.[9] Serum bupivacaine concentrations were measured regularly after the TAP block. The maximum serum concentration was reached at 30 min with a mean of 802.36 ng/mL and a range of 231.8–3504.5 ng/mL. Serum bupivacaine concentrations exceeded 2 μg/mL in three patients, one of whom described quickly resolving dizziness. In another study, patients undergoing cesarean sections under general anesthesia received 20 mL bilateral TAP blocks with 0.5% levobupivacaine (closely related enantiomer) with maximum serum concentrations of levobupivacaine peaking at a mean of 1.05 μg/mL at a time of 32.4 min following the TAP block.[10]

Bupivacaine Passage to Breast Milk

With the TAP block applied in the context of cesarean section delivery, there is a concern for maternal and fetal toxicity, which can occur in the context of breastfeeding following delivery. Bolat *et al*. report that after epidural administration, both levobupivacaine and bupivacaine pass from the serum into breast milk similarly, with levobupivacaine found in a milk-to-plasma ratio of 0.34 ± 0.13 and bupivacaine with a milk-to-plasma ratio of 0.37 ± 0.14.[11] Another similar study reports that the milk-to-serum ratio is 0.34 ± 0.24 based on areas under the curve calculation for bupivacaine following epidural anesthesia.[12]

Pharmacokinetics in Infants/Neonates

The pharmacokinetics of bupivacaine in infants and neonates differs from adults. For adults, the volume of distribution has been estimated between 0.85 and 1.3 L/kg.[13,14] For neonates, the volume of distribution is estimated between 2.56 and 4.7 L/kg.[14-16] The half-time of elimination for bupivacaine in adults has been estimated between 1.8 and 5.1 h.[13,14] The half-time of elimination for infants and neonates has been estimated between 132 min and 7.7 h.[14,15]

However, studies have demonstrated that despite the similarities in estimated half-time, bupivacaine when delivered

via modalities, such as epidural or caudal injections, persists in the serum for longer in infants and children than adults.[17,18] This is due in part to the fact that infants have lower levels of alpha-1-acid glycoprotein in their serum, which is the primary protein that binds to bupivacaine. This can result in a higher free concentration of bupivacaine, placing an infant at a higher risk for toxicity.[16,18] Additionally, infants have lower levels of P450 CYP3A4, which is the primary enzyme that metabolizes bupivacaine to its active metabolite, further contributing to higher levels of the drug.[18]

Toxicity in Neonates

Given the increasing use of neuraxial anesthesia, the concept of local anesthetic toxicity has remained an important one in the field of anesthesia. The American Society of Regional Anesthesia and Pain Medicine has now published its third practice advisory on local anesthetic systemic toxicity.[19] In it, there is specific mention that the risk of toxicity in infants under 6 months of age is sixfold higher than other children. An additional risk for toxicity is low muscle mass, which the infants also have. Thus, increased vigilance for toxicity in neonates/infants following maternal TAP blocks would be merited.

Because of the differences in metabolism described above, bupivacaine toxicity can be found for neonates and infants in lower levels than the 2.0 – 4.0 μg/mL range described for adults.[6,16-18] This may be attributed to the differences in metabolism described above, causing a higher serum concentration of free bupivacaine. Seizure-like activity has been reported for bupivacaine concentrations in the 2.0 μg/mL serum concentration range in infants.[20] However, most documented episodes of bupivacaine toxicity have involved serum concentrations significantly higher than this.[16] The two major types of toxicity to be aware of are neurological and cardiovascular. The neurological side effects can include jitteriness and irritability in the early phases and seizure-like activity at higher levels.[16,21] Cardiovascular issues to be aware of include bradycardia, hypotension, and cardiac arrhythmias. No episodes of neonatal bupivacaine toxicity have been described following TAP blocks, either because of the block itself or breastfeeding subsequent to delivery.

A Pharmacokinetic Application

We applied the pharmacokinetic parameters for bupivacaine to estimate the concentrations that would be expected to develop in the neonate assuming that breastfeeding began immediately after delivery. With a typical TAP block (as noted above, 20 mL of 0.25% bupivacaine bilaterally in a TAP block postoperation) in a relatively small woman (55 kg; this would encompass the vast majority of mothers), the resulting plasma concentration would equilibrate at a concentration of 2.02 μg/mL.[9] Assuming even low-birth-weight infant (1500 g), a breast milk to plasma concentration ratio of 0.37 (as noted above),[11] and a relatively small volume of distribution (2.56 L/kg),[14-16] the neonate's plasma concentration after consumption of 60 mL of milk immediately after delivery would only reach 0.012 μg/mL. With two subsequent feedings, each 2 h apart, the concentration would reach a maximum of 0.018 μg/mL and then decline with subsequent feedings because of the decline in the mother's plasma concentration [Figure 1]. Thus, using the most cautious estimates of body weight and pharmacokinetic parameters, chosen to be expected to mediate toward higher concentrations in the neonate's plasma, the concentrations only approach 1% of the mother's plasma concentration, and likely threshold toxic levels.

Discussion

TAP blocks have been demonstrated to be effective in providing analgesia during cesarean section deliveries, either as stand-alone analgesia or part of multimodal pain relief. However, relatively few studies have been performed to examine toxicity risks of the bupivacaine in TAP blocks, either for adults or children. We explore some of the existing studies measuring serum bupivacaine concentrations after TAP blocks and studies that measure bupivacaine passage to breast milk. The next step is a study that combines these two, measuring maternal serum bupivacaine concentrations following TAP blocks during cesarean section deliveries and also subsequent

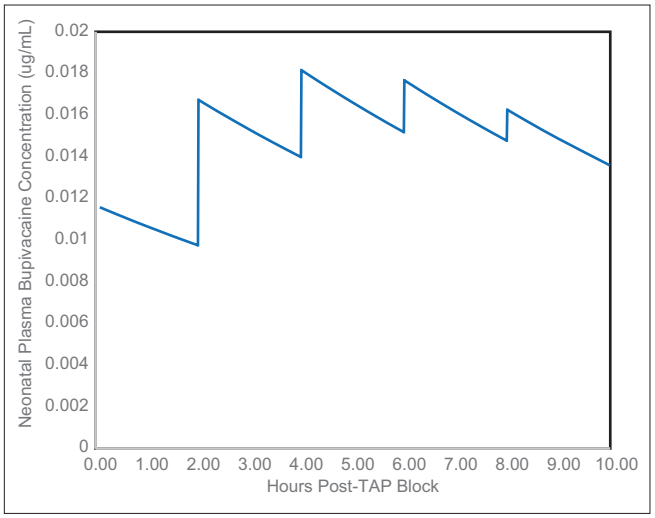

Figure 1: Plasma bupivacaine concentration of 1500 g neonate with 60 mL human milk feedings from 55 kg mother after TAP block. The plasma concentration reaches a level of 0.012 μg/mL after the initial feeding and a maximum value of 0.018 μg/mL after three feedings, declining after that point

maternal breast milk bupivacaine concentrations. This will help give a better sense of the toxicity risk, if any, to neonates breastfeeding after delivery. The predictions from our pharmacokinetic application would appear to indicate an extremely low risk of toxicity from breastfeeding in the neonate.

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Conflicts of interest

There are no conflicts of interest.

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