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New Application of Low-Molecular Weight Dextran as Local Anesthetic Adjuvant for Ultrasound-Guided Nerve Block

Masahiko Tsuchiya

Abstract

Advances in ultrasound technology and the increased risk of opioid overdose following surgery have expanded applications of nerve block for surgical cases, resulting in reevaluation of adjuvants used to potentiate local anesthetics. We have found that a mixture of local anesthetic with low-molecular weight dextran, one such local anesthetic adjuvant, greatly enhances analgesic duration and potency in patients receiving an interfascial compartment nerve block under ultrasound-guidance as well as those receiving a single peripheral nerve block. Notably, a compartment nerve block in the abdominal trunk with an extra-large amount of low-molecular weight dextran mixture, which results in a longer duration of the injected drugs at the injection site, provides good analgesia that is comparable to epidural anesthesia. Such a dextran mixture also suppresses systemic absorption of local anesthetics, thus reducing their systemic toxicity, which enhances regional anesthesia safety. Furthermore, it controls unintended spread of injected local anesthetics, thus increasing nerve block accuracy. In this chapter, recent findings regarding use of low-molecular weight dextran as a local anesthetic adjuvant obtained in our laboratory are presented.

Keywords: low-molecular weight dextran, ultrasound-guided nerve block, local anesthetics, adjuvant, regional anesthesia, anesthesia safety, toxicity

1. Introduction

Recent advances in ultrasound technology have improved the accuracy and reliability of nerve block procedures [1–3]. As a result, there has been a shift from general anesthesia alone to that in combination with a nerve block. In addition, important related issues are opioid abuse, which has become a matter of public concern [4], as well as possible reduction in the risk of cancer recurrence in patients undergoing surgery with regional anesthesia [5, 6]. Evidence suggesting that general anesthesia in combination with regional anesthesia is superior for intraoperative hemodynamic stability and postoperative recovery has been reported [7, 8] (**Figure 1**). Those findings further advanced the shift to application of nerve block with general anesthesia, thus techniques to modify the effects of local anesthetics including use of an adjuvant compound have also regained attention [9]. Dextran,

Figure 1.
Left panel: Comparison of intraoperative hemodynamic stability between patients with general anesthesia alone ($n = 35$) and general anesthesia with a transversus abdominis plane block (TAPB) ($n = 33$) [8]. General anesthesia was maintained in the same manner with sevoflurane and remifentanyl in both groups. The period during the operation when both systolic blood pressure and heart rate were within 70–110% of their pre-anesthesia value was defined as the hemodynamic stable time. The ratio of hemodynamic stable time to total operative time was used as an indicator of hemodynamic stability. The stability ratio was significantly higher in the group receiving general anesthesia with TAPB (91%, range 50–100%) as compared to general anesthesia alone (79%, range 40–91%), indicating greater hemodynamic stability with general anesthesia plus TAPB. Values are presented as the median and minimum–maximum range (mean value indicated by “+”). **Right panel:** Comparison of anesthesia emergence time between the same groups shown in left panel. Anesthesia emergence time was defined as the time from completion of surgery to extubation. That was significantly shorter in the group receiving general anesthesia plus TAPB (14 minutes, range 4–30 minutes) as compared to general anesthesia alone (18 minutes, range 9–52 minutes). Values are presented as the median and minimum–maximum range (mean value indicated by “+”).

which is composed of complex branched polysaccharides derived from sucrose with various lengths and weights, is such a local anesthetic adjuvant and investigated many decades ago, though nearly forgotten in recent times.

Accumulated attention and increased need of regional anesthesia have resulted in development of new nerve block procedures, with transversus abdominis plane and quadratus lumborum blocks typically employed [8, 10] (Figure 2). However, these new types of nerve blocks require accurate injection of a sufficient quantity of local anesthetic into the targeted interfascial compartment. A compartment nerve block performed in this manner has potential to serve as a substitute for epidural anesthesia, the current gold standard method for surgical pain control. On the other hand, there is a risk of systemic toxicity of local anesthetics associated with this procedure because the drug is given in a large amount [11]. Furthermore, another weak point to be solved is insufficient analgesic duration for controlling postoperative pain when the nerve block is performed with a single injection.

Figure 2.
Ultrasound image obtained during transversus abdominis plane block [8]. A local anesthetic solution was injected into the interfascial compartment between the internal oblique and transversus abdominis muscles.

Figure 3.
Molecular structure of low-molecular weight dextran.

We recently performed a reinvestigation of dextran effects under modern clinical environments and found that low-molecular weight dextran, with an average molecular weight of 40,000 (**Figure 3**), used as a local anesthetic adjuvant resolves the disadvantages of a trunk nerve block by improving the potency and safety of the local anesthetic [10, 12–15]. In this chapter, effects and clinical applications of low-molecular weight dextran as a local anesthetic adjuvant are discussed based on recent findings obtained by our research team.

2. Toxicity of adjuvant adrenaline and prevention by low-molecular weight dextran

Adrenaline (epinephrine) is the oldest adjuvant given with local anesthetics and continues to be used. When used as an adjuvant it is typically applied with lidocaine, and known to induce vasoconstriction for reducing systemic absorption of the administered local anesthetic and enhancing the analgesia effects, and seems to be an optimal application. However, the combination of adrenaline and lidocaine does not always lead to good results.

Lidocaine has potent vasodilation effects, thus it can enhance the absorption of adrenaline into systemic circulation when a lidocaine-adrenaline mixture is administered. Wasa Ueda, presently professor emeritus and executive advisor of our research team, validated this issue in a clinical study, in which application of a lidocaine-adrenaline mixture for infiltration anesthesia was shown to significantly increase the plasma concentration of adrenaline in comparison with an infiltration injection of the same amount of a pure adrenaline solution [16] (Figure 4). An increase in adrenaline concentration in the circulation can increase blood pressure and heart rate, sometimes leading to severe lethal cardiac dysrhythmia. Such toxic effects of a lidocaine-adrenaline mixture are a significant problem for patients under general anesthesia using halothane, which has a characteristic property to increase sensitivity to adrenaline, whereas aggravating effects on circulation, such as increase in blood pressure, can still develop when the more recently introduced anesthetics desflurane and sevoflurane are used as an inhalant (Figure 5).

Figure 4. Peak plasma concentration of adrenaline (epinephrine) following subcutaneous infiltrative injection of various adrenaline solutions in humans [16]. Each column indicates the following. (1) epinephrine: 1:200,000 adrenaline in normal saline solution. (2) lidocaine epinephrine: 1:200,000 adrenaline with 0.5% lidocaine in normal saline solution. (3) epinephrine dextran: 1:200,000 adrenaline with 10% low-molecular weight dextran in saline solution. (4) lidocaine epinephrine dextran: 1:200,000 adrenaline with 0.5% lidocaine and 10% low-molecular weight dextran in saline solution. The adrenaline concentration in the solutions was the same in all four groups. Values are expressed as the mean $\pm$ standard deviation. When adrenaline was subcutaneously injected with lidocaine (lidocaine epinephrine), the peak plasma adrenaline concentration showed an approximately 7-fold increase as compared with injection of the pure adrenaline solution (epinephrine). However, the presence of low-molecular weight dextran in the lidocaine adrenaline solution (lidocaine epinephrine dextran) suppressed the toxic increase in plasma adrenaline concentration.

Figure 5. Typical increases in blood pressure and heart rate with subcutaneous infiltration anesthesia using 20 ml of 0.5% lidocaine and 1:200,000 adrenaline in normal saline solution in patients receiving sevoflurane general anesthesia. Soon after injection of the lidocaine-adrenaline mixture, blood pressure was slightly decreased due to the β_2 -adrenergic effect of a small amount of absorbed adrenaline. Thereafter, blood pressure and heart rate were greatly increased due to the α - and β_1 -adrenergic effects of adrenaline.

Figure 6. Convulsion dose of plasma concentration of lidocaine in rat [17]. Male Wistar rats were divided into three groups and received continuous intravenous injections of 1.5% lidocaine, 1.5% lidocaine with 1:200,000 adrenaline (epinephrine), or 1.5% lidocaine with 1:100,000 adrenaline (epinephrine). Values are expressed as the mean $\pm$ standard deviation. The total lidocaine dose from the beginning of infusion of the lidocaine mixture to onset of generalized convulsions was analyzed. Addition of adrenaline to the lidocaine solutions significantly decreased the threshold of lidocaine-induced convulsions in a dose-dependent manner, indicating that adrenaline increased lidocaine systemic toxicity.

Furthermore, the presence of adrenaline decreases the threshold concentration of lidocaine to induce convulsions, leading to enhancement of the central nervous system toxicity of lidocaine [17] (**Figure 6**). Another study showed that concomitant administration of adrenaline with lidocaine increased the concentration of extracellular lidocaine in the brain [18], which may be another supporting mechanism by which adrenaline increases the toxicity of lidocaine for the central nervous system. Therefore, though this combination can be useful for regional anesthesia, a lidocaine-adrenaline mixture is not completely safe.

The Ueda research team found a solution to the hazardous risk of a lidocaine-adrenaline mixture, as addition of low-molecular dextran into the mixture was shown to suppress absorption of adrenalin into circulation [16]. The peak plasma adrenaline concentration with a lidocaine-adrenaline mixture with low-molecular weight dextran was $0.15 \pm 0.07 \text{ ng}\cdot\text{ml}^{-1}$, while that was $1.04 \pm 0.22 \text{ ng}\cdot\text{ml}^{-1}$ with the standard lidocaine-adrenaline mixture (**Figure 4**). Thus, it was concluded that a lidocaine-adrenaline-dextran mixture is safe for application as regional anesthesia, which is now considered to be a landmark finding indicating an adjuvant function of low-molecular weight dextran to improve the safety of local anesthetic usage.

3. Early history of dextran as local anesthetic adjuvant and possible action mechanism

Apart from the effects of dextran on lidocaine-adrenaline mixtures, the first description of the adjuvant effects of dextran with local anesthetics can be traced back to the 1960s [19]. Thereafter, prolongation and enhancement of analgesia by dextran were studied, and some favorable results reported [20–22], with possible mechanisms for those actions also investigated. Dextran may form a water-soluble complex with local anesthetics that is slowly absorbed and remains at the injection site for a longer period with increased viscosity [23, 24]. Moreover, addition of dextran was shown to change the pH of a local anesthetic solution and that may further contribute to prolongation of action [25]. Despite these positive results, several studies that failed to find potential effects for analgesia with dextran have also been reported [26, 27]. As a result, along with the expanding applicability of general anesthesia for surgery, dextran has gone largely unnoticed and its adjuvant effects remain inclusive.

4. Adjuvant effects of low-molecular weight dextran with current nerve block techniques

Assuming an interaction of dextran with local anesthetics, its effectiveness as a local anesthetic adjuvant may be dependent on the type of nerve block employed and procedure used. Such nerve block dependency may induce inconsistent adjuvant effects, as shown in several previous studies. Because an interfascial compartment nerve block, such as a transversus abdominis plane block, is required to perform accurate injection of a large amount of local anesthetic solution into the targeted interfascial compartment, that is difficult to perform with a conventional landmark method. Fortunately, advancements in ultrasound guidance techniques have made this possible at a clinically acceptable quality. Consequently, an interfascial compartment nerve block has become popular. Maintaining the amount of injected local anesthetics in the compartment for a longer period is essential to induce sufficient analgesia in cases with such a compartment block, thus it is quite reasonable to assume that the possible fluid retention properties of dextran have a favorable impact. Based on findings obtained in previous studies reported by the

Ueda research team concerning use of a lidocaine-adrenaline mixture, we consider that low-molecular weight dextran is the most suitable local anesthetic adjuvant among the various dextran compounds available for interfascial compartment nerve block procedures currently used.

4.1 Pharmacokinetics and analgesia: transversus abdominis plane block and rectus sheath block cases

First, we investigated the adjuvant effects of low-molecular weight dextran when used for a transversus abdominis plane block and rectus sheath block [12]. Patients scheduled for a laparoscopic colectomy [age 66 ± 9.8 years, body weight 59 ± 11.7 kg, anesthesia time 322 ± 69 minutes (values shown as mean $\pm$ standard deviation)] received a combination of two bilateral interfascial compartment blocks, a transversus abdominis plane block and rectus sheath block. Following anesthesia induction, they received this two-block combination with either 0.2% levobupivacaine in a saline solution (control group: 20 ml $\times$ 4 injections = total 160 mg of levobupivacaine in saline; $n = 27$), or 0.2% levobupivacaine and 8% low-molecular weight dextran (LMWD) in a saline solution (LMWD group: 20 ml $\times$ 4 injections = total 160 mg of levobupivacaine in LMWD; $n = 27$). General anesthesia was maintained with sevoflurane and remifentanyl, with 200 μ g of fentanyl given at the end of surgery. Continuous intravenous infusions of fentanyl at 25 μ g $\cdot$ hr $^{-1}$ and droperidol at 63 μ g $\cdot$ hr $^{-1}$ were postoperatively given for 24 hours as analgesia and antiemetic treatments.

There were no significant differences in regard to patient age, body weight, amount of intraoperative blood loss, or anesthesia time between the groups. Furthermore, no typical adverse effects, such as wound infection, delayed wound healing, tissue necrosis, or prolonged abnormal sensory disorder over the area of injection, or other systemic abnormalities were observed in either group. In the control group, the plasma concentration of levobupivacaine rose quickly just after performing the nerve block and reached a maximum at 51 ± 30 minutes (T_{max}), while in the LMWD group, that rose in a more gradual manner with a significantly longer T_{max} value (73 ± 25 minutes, $P < 0.05$ vs. control group) (**Figure 7**). The maximum concentration of levobupivacaine (C_{max}) in the control group was 1410 ± 322 ng $\cdot$ ml $^{-1}$, whereas that in the LMWD group was significantly lower at 1141 ± 287 ng $\cdot$ ml $^{-1}$ ($P < 0.05$). Also, the area under the plasma concentration-time curve (AUC) from 0 to 240 minutes was significantly lower in the LMWD as compared to the control group ($172,484 \pm 50,502$ vs. $229,124 \pm 87,254$ ng $\cdot$ min $\cdot$ ml $^{-1}$, $P < 0.05$). In contrast, the plasma levobupivacaine concentration in the LMWD group was higher than that seen in the control group after 1200 minutes. These results demonstrated that use of a low-molecular weight dextran mixture results in reduced systemic absorption of the local anesthetic from the injection compartment along with its longer retention in that compartment for more than 20 hours. Such a reduction in systemic absorption lowers the risk of local anesthetic systemic toxicity. In addition, the postoperative 24-hour numerical rating scale (NRS) for pain (0-no pain, 10-worst pain) demonstrated significantly better analgesia in patients with the local anesthetic mixture with low-molecular weight dextran as compared to those in the control group who received a standard local anesthetic solution (**Figure 7**). That result was considered to be due to extended presence of the injected local anesthetic in the injection compartment.

Together, our findings indicated that low-molecular weight dextran as a local anesthetic adjuvant provides great clinical advantages for enhancement of analgesia effect as well as reduction in systemic toxicity of a local anesthetic.

Figure 7.

Left panel: Changes in levobupivacaine plasma concentration in patients receiving bilateral transversus abdominis plane blocks plus rectus sheath blocks with 160 mg of levobupivacaine [12]. For nerve blocks, the control group ($n = 27$) received nerve blocks using 80 ml of 0.2% levobupivacaine in a saline solution, while the +LMWD group ($n = 27$) received 80 ml of 0.2% levobupivacaine and 8% low-molecular weight dextran in a saline solution just before starting a laparoscopic colectomy. Values are expressed as the mean $\pm$ standard deviation. Addition of low-molecular weight dextran to the levobupivacaine solution was shown to lower the peak level of levobupivacaine plasma concentration, indicating that dextran suppresses systemic absorption of levobupivacaine from the injection site, which may prolong analgesic effects and decrease the systemic toxicity of levobupivacaine. After 1200 minutes, plasma levobupivacaine concentration in the +LMWD group was significantly higher than that in the control group, indicating longer retention of levobupivacaine at the injection site following its slow release. **Right panel:** Numerical rating scale (NRS) scores for postoperative pain in the same patients. Values are expressed as the mean $\pm$ standard deviation. NRS: 0, no pain, to 10, worst pain. NRS scores in the +LMWD group were significantly lower at each time point after surgery as compared to the control group ($P < 0.01$ at 2, 8, 16 hours; $P = 0.035$ at 24 hours).

4.2 Extended retention time in injected area: quadratus lumborum block cases

To confirm the longer retention time of the local anesthetic and low-molecular weight dextran mixture at the injection site, a different group of cases that underwent a quadratus lumborum block, another type of interfascial compartment nerve block, were investigated [10]. A quadratus lumborum block using a low-molecular weight dextran mixture with ropivacaine was applied in 18 patients undergoing open abdominal surgery (age 67 ± 8.4 years, body weight 72.6 ± 4.6 kg, anesthesia time 429 ± 123 minutes) following anesthesia induction (**Figure 8**). One hundred ml of 0.1% ropivacaine and 8% low-molecular weight dextran in saline solution with 2 mg of morphine was injected into interfascial space posterior of the quadratus lumborum muscle (so-called QLB2 nerve block) on each side (total 200 ml in both sides). Anesthesia was maintained with desflurane and remifentanyl. Postoperatively, intravenous flurbiprofen (50 mg) was given every 8 hours, with acetaminophen ($15 \text{ mg} \cdot \text{kg}^{-1}$) used as rescue treatment for pain.

No rescue drug was given to any of the patients on the first night after surgery and the NRS for pain (0-no pain, 10-worst pain) during that period was 2.2 ± 1.7 .

Figure 8.
Upper panel: Transverse ultrasound image obtained just when nerve block needle reached target site in posterior quadratus lumborum block (so-called QLB2 nerve block) and related anatomical schema [10]. **Middle panel:** Transverse and sagittal ultrasound images obtained just after completion of posterior quadratus lumborum block with 100 ml of 0.1% ropivacaine with 8% low-molecular weight dextran in a saline solution in the same patient shown in the upper panel. The injected local anesthetic mixture (LA-LMWD) was correctly and widely spread over the interfascial space posterior to the quadratus lumborum muscle. **Lower panel:** Sagittal ultrasound image obtained from the same injection site at 24 hours after completion of quadratus lumborum block in the same patient shown in the upper panel. Some of the local anesthetic mixture (LA-LMWD) remained. PM: psoas major muscle; QL: quadratus lumborum muscle; TP: transverse process.

Each successfully walked more than 20 meters with less pain the next day. No local or systemic adverse effects from use of low-molecular weight dextran including tissue necrosis over the area of injection were observed. Ultrasound examinations performed after 24 hours indicated that some amount of local anesthetic mixture remained at the injected site (**Figure 8**). These findings well support the proposed mechanism of low-molecular weight dextran as an adjuvant that maintains the analgesic mixture at the injection site for an extended time, thus enabling longer lasting effects. The analgesia effect obtained with this method seems to be comparable with that with epidural anesthesia during the initial 24 hours follow surgery, thus is adequate for early postoperative pain control.

4.3 Guidance effect: erector spinae plane block cases

Findings obtained in transversus abdominis plane block, rectus sheath block, and quadratus lumborum block cases suggested that use of a mixture of local anesthetics and low-molecular weight dextran can provide good analgesia as part of an erector spinae plane (ESP) block in the same manner [14]. Thus, we applied such a block with a dextran mixture in patients undergoing video-assisted thoracic surgery (VATS) to confirm clinical feasibility and investigate the technical benefits of performing a nerve block with adjuvant dextran.

Five patients scheduled for video-assisted thoracic surgery for lung cancer (age 63 ± 7 years, body weight 59 ± 7 kg, anesthesia time 295 ± 94 minutes) received a unilateral erector spinae plane block just prior to starting surgery (**Figure 9**). Targeting the transverse process at the level of the thoracotomy incision, 40 ml of 0.3% ropivacaine and 7% low-molecular weight dextran in a saline solution were injected under ultrasound guidance. General anesthesia was maintained with

Figure 9. *Upper panel:* Anatomical scheme for erector spinae plane (ESP) block at T8 level of spine. **Lower left panel:** Positions of ultrasound linear probe and nerve block needle (BN) for ESP block targeting of the transverse process of T8 level of spine in patient positioned in a lateral decubitus position just prior to starting video-assisted thoracic surgery (VATS) for lung cancer [14]. **Lower right panel:** Corresponding ultrasound image obtained during ESP block with use of linear ultrasound probe (8–13 MHz). A mixture of local anesthetic and low-molecular weight dextran (LA-LMWD) was shown spread on the compartment just above the transverse process. ESM: erector spinae muscles; TM: trapezius muscle; TP: transverse process.

desflurane and remifentanyl. Acetaminophen ($15 \text{ mg} \cdot \text{kg}^{-1}$) was also administrated at the end of surgery. For postoperative rescue analgesia, intravenous flurbiprofen (50 mg) was prepared.

During the first night after surgery, no additional rescue analgesic was given to any of the patients and the NRS pain score (0-no pain, 10-worst pain) was uniformly very low at 2.2 ± 1.1 . No adverse effects were observed with use of the low-molecular weight dextran mixture, the same as seen in cases examined in our other nerve block studies that received a dextran mixture. As a control, we enrolled five patients who underwent our usual protocol for video-assisted thoracic surgery, general anesthesia combined with epidural anesthesia and $15 \text{ mg} \cdot \text{kg}^{-1}$ of acetaminophen, with postoperative continuous epidural anesthesia performed with $3 \text{ ml} \cdot \text{hr}^{-1}$ of 0.25% ropivacaine. The first night, NRS pain score (0-no pain, 10-worst pain) for those patients was 2.1 ± 1.2 , indicating that an ESP block with a mixture of ropivacaine and low-molecular weight dextran has nearly the same analgesia effect as epidural anesthesia.

It should be noted that use of low-molecular weight dextran significantly increases the viscosity of the injection preparation. Should such a high-viscosity mixture be injected into the wrong portion of parenchymal tissue or an area outside of the target compartment, extra high pressure will likely develop. A large increase in injection pressure related to the site of injection can be a great help to avoid miss-injection, resulting in accurate compartment injection. This guidance effect may be related, at least in part, to the adjuvant effect of low-molecular weight dextran. In addition, the impact of injection pressure could be especially beneficial for novice practitioners learning nerve block procedures.

4.4 Inhibition of unintended spread: mandibular nerve block cases

Based on the above results obtained in our study of compartment nerve block cases, we also examined use of low-molecular weight dextran for cases with a single nerve block [15]. Patients undergoing a mandibular nerve block performed at a site close to the oval foramen from which the mandibular nerve appears were enrolled. In this target site, various nerves and vessels are closely assembled, thus accuracy is essential. However, a correct nerve block needle tip position alone is not sufficient for an accurate injection. In addition to that, spreading of the injected local anesthetic into the unintended surrounding area must be avoided for precision as well as safety, thus the high viscosity characteristic of a dextran solution may be best for such a procedure. Based on this speculation, we performed a study.

A mandibular nerve block was performed using a lateral extraoral approach with guidance using ultrasound imaging in 10 patients undergoing a parotidectomy under general anesthesia (age 60 ± 12 years, body weight 69.5 ± 14.6 kg, anesthesia time 227 ± 92 minutes). Following anesthesia induction, the head of the patient was turned according to the surgical site with the mouth open, then a convex ultrasound transducer was placed just below and parallel to the zygomatic bone (**Figure 10**). Next, a 23-gauge nerve block needle was inserted towards the dorsal edge of the plate, close to the mandibular nerve. When the needle touched the plate edge, 3 ml of a mixture of 0.3% ropivacaine and 7% low-molecular weight dextran in a saline solution was injected. The maxillary artery frequently appears in this section and should not be traumatized. Eighteen hours after surgery, the NRS pain score (0-no pain, 10-worst pain) was 1.2 ± 0.4 without use of a rescue drug, as compared to 2.7 ± 0.7 in our previous non-nerve block cases ($P < 0.01$). No side effects related to unintended spread of the injected ropivacaine were noted.

Performance of a mandibular nerve block using a mixture of ropivacaine and low-molecular weight dextran provided good postoperative analgesia, as well as

Anatomy and ultrasound probe position for mandibular nerve block

Color doppler ultrasound image obtained by ultrasound probe at the above position

Ultrasound image just after the injection of LA-LMWD

Figure 10.
Upper panel: Anatomical relationships of mandibular nerve, lateral pterygoid plate, and maxillary artery. For a mandibular nerve block, the ultrasound probe is placed just below and parallel to the zygomatic bone [15]. **Lower left panel:** Typical color Doppler ultrasound image obtained at 4.5 MHz with curvilinear ultrasound probe placed as shown in the upper panel. The maxillary artery is frequently visualized in such cases. The mandibular nerve could not be seen with this view due to acoustic shadows from surrounding bone. **Lower right panel:** Ultrasound image obtained at the moment when 3 ml of a mixture of ropivacaine and low-molecular weight dextran (LA-LMWD) was injected to the site close to the mandibular nerve emerging from the oval foramen.

safety. These findings validated our speculation that such a dextran mixture enables an accurate single nerve block for enhancing analgesic potency of an injected local anesthetic without unintended spreading of the injectant.

Figure 11. Ultrasound probe positioning and block needle orientation during caudal block (left panel), and ultrasound longitudinal images obtained at the same moment (right panel) [2]. An ultrasound-guided caudal block procedure in adult patients is performed as follows. After prone positioning, the location and structure of the sacral hiatus are confirmed in ultrasound transverse and longitudinal images. Then, a 23-gauge nerve block needle is inserted in the direction of the sacral canal through the sacral hiatus while monitoring real-time ultrasound images. Next, the tip of the nerve block needle is inserted into the sacral canal approximately 0.5–1 cm ahead. After negative aspiration, a local anesthetic mixture is injected.

4.5 Advanced application of low-molecular weight dextran mixture

A local anesthetic and low-molecular weight dextran mixture can be used for a caudal block. Based on their experience, most anesthesiologists consider that a caudal block procedure in adults is generally not feasible and unreliable. However, an ultrasound-guidance technique makes such a procedure possible in adults and is rather easy to perform [2] (**Figure 11**). We consider that use of a block with a mixture that includes dextran can lead to a longer analgesia duration, thus is well applicable for gynecological, urological, and lower abdominal surgery procedures.

5. New local anesthetics with extended activities

Liposomal bupivacaine has recently become commercially available for use in cases with local infiltration anesthesia or a brachial plexus nerve block [28, 29]. Although this agent has shown excellent potential, it is quite expensive, and systemic or local toxicity occurring long after administration has yet to be determined. Low-molecular weight dextran was first used as an adjuvant more than half a century ago and its long history of clinical use, though recently limited in application, provides evidence of its therapeutic safety. Furthermore, it is inexpensive and approaches with it are easy to perform. Therefore, we consider that use of low-molecular weight dextran as a local anesthetic adjuvant remains beneficial even when compared with newer local anesthetics such as liposomal bupivacaine, with clinical condition a key factor for choosing the best method.

6. Conclusion

Findings obtained in our studies have demonstrated that low-molecular weight dextran functions as an effective adjuvant for potentiation of local anesthetic analgesia in patients undergoing an interfascial compartment nerve block, such as

a transversus abdominis plane block, under ultrasound guidance. Notably, use of an abdominal trunk block with a large amount of a mixture of local anesthetic and low-molecular weight dextran, which allows the injected mixture to remain for a longer period at the injection site, provides good analgesia comparable to epidural anesthesia. The high viscosity of dextran can cause extra-high injection pressure when injected into the improper area or portion, alerting the practitioner regarding improper injection, a guidance effect and another practical advantage. Also, use of a dextran mixture may inhibit unintended spread of the injected solution and increase the accuracy of the intended nerve block. As a pharmacological safety aspect, use of a dextran mixture reduces the risk of systemic toxicity related to local anesthetics by suppressing their systemic absorption. All of these factors are significant clinical advantages gained by use of low-molecular weight dextran as a local anesthetic adjuvant when performing various nerve block procedures.

Abbreviations

ESP block	erector spinae plane block
LA-LMWD	local anesthetic and low-molecular weight dextran
LMWD	low-molecular weight dextran
NRS	numerical rating scale

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