Effects of dexmedetomidine addition to low concentration of lidocaine/ropivacaine mixtures for ultrasound-guided axillary brachial plexus block

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Research article

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Abstract

Background

Dexmedetomidine (DEX) has been used in combination with different local anesthetics (LAs) to improve the quality of peripheral nerve blocks. However, there is little evidence of the effects of DEX in a mixture of two LAs for brachial plexus block (BPB). The aim of this study was to investigate if DEX combined with low concentration of lidocaine/ropivacaine mixtures may further reduce the onset time and prolong block duration and analgesia time for performing ultrasound-guided axillary BPB.

Methods

Seventy-five ASA I or II patients, scheduled for forearm or hand surgery were randomly allocated into three groups: Group R (n = 25) received 30 mL of 0.25% ropivacaine + 3 mL of 0.9% NaCl; Group RL (n = 25) received 30 mL of 1:1 0.25% ropivacaine/0.5% lidocaine + 3 mL of 0.9% NaCl; Group RLD (n = 25) received 30 mL of 1:1 0.25% ropivacaine/0.5% lidocaine + 3 mL of 0.75 µg/kg DEX. The hemodynamic changes, BIS values, onset time and duration of sensory and motor blocks, the analgesic time and the times of rescue analgesics within 48 h were recorded.

Results

The onset times of sensory and motor blocks were significantly shorter in group RL and group RLD compared with group R (P < 0.0001), but no significant difference was detected between group RL and group RLD (P > 0.05). The analgesic time and the block durations in group RLD were significantly longer than that in group R and group RL (P < 0.0001). In group RLD, the times of flurbiprofen treatment were significantly reduced compared with group R and group RL (P < 0.0001). The BIS values in group RLD were significantly decreased than those of group R and group RL from 20 min till 60 min (P < 0.05).

Conclusions

Combination of ropivacaine and lidocaine produces shorter onset time than ropivacaine alone in axillary BPB. DEX added to ropivacaine/lidocaine mixtures prolongs the duration of sensory and motor blocks, extends analgesic time and exerts a considerable sedative effect.

Trial registration

The clinical trial was registered in “Chinese Clinical Trial Registry” (http://www.chictr.org.cn/index.aspx) and the registered number was “ChiCTR-IPR-16007742”, on 12th January 2016.

Background

Brachial plexus block (BPB) is an economical, effective and the most commonly used method with improved postoperative analgesia for hand and forearm surgeries, but a long time is necessary to achieve
complete block after local anesthetics (LAs) injection. The latter feature makes BPB infeasible for fast surgeries, especially not feasible for implement of enhanced recovery after surgery (ERAS) and may also cause anxiety to patients.

The safety and effectiveness of two LAs combination for peripheral nerve block were obscure and controversial for years. Some trials showed that combination of two LAs did not affect block onset or analgesia time in BPB[1, 2]. However, it was also published[3] that mixtures of two different LAs used for BPB provided satisfactory anesthesia and analgesia. What's more, application of combined LAs is proved to be prominent in providing a rapid onset time, concurrently contribute to shorter block duration than single long-acting LA[4–6].

The use of various additives such as clonidine[7, 8], dexmedetomidine[9, 10], dexamethasone[11, 12], tramadol[13, 14] and magnesium sulfate[15, 16] in peripheral nerve block, has been proven to shorten the onset of the block, prolong the duration of analgesia, lower the doses of LAs and to minimize the toxic effect. Dexmedetomidine (DEX) is a highly selective α2-adrenergic agonist. A number of trials have demonstrated the efficacy in the prolongation and intensification of anesthesia and safety of DEX administered by epidural[17, 18], intrathecal[19, 20], and peripheral injections[21, 22]. Besides its analgesic effect acting through receptors in the spinal cord, DEX also exerts sedation through interaction with receptors in the locus ceruleus[23]. In a previous study, perineurally administered DEX resulted in achieving a state of lucidity and anxiety relief of patients[24].

So far, studies have mostly focused on the effects of DEX in a mixture with one long-acting LA for BPB, such as bupivacaine[25], levobupivacaine[10, 26] or ropivacaine[27–29], but few studies have investigated the effects of mixtures with two LAs in upper extremity surgeries. Our study was designed to elucidate whether ropivacaine/lidocaine, compared with ropivacaine alone, shortens onset time, and if the addition of DEX to the solution of ropivacaine/lidocaine mixture would further shorten the onset time and lead to longer block durations and analgesic time in ultrasound-guided axillary BPB.

**Methods**

**Study design**

After approval by the Ethics Committee of the Second Affiliated Hospital, Harbin Medical University, China and obtaining informed consents, 75 ASA grade I and II patients were enrolled in this prospective, randomized, double-blind controlled trial. The participants, aged between 18 to 60 years old, were scheduled for forearm or hand surgery through the ultrasound-guided axillary BPB. The exclusion criteria included: patients with a history of allergy to the study medication, peripheral neuropathy, central nervous system disease, puncture site infection, a history of severe hepatic, renal, cardiac or pulmonary disease, coagulation disorder, alcohol or opioid abuse, chronic pain, severe/morbid obesity, pregnant or lactating women.
Patients were randomly allocated into three groups (n=25) using a sealed envelope technique and all patients were administered 33 mL of the investigated solutions:

Group R received 30 mL of 0.25% ropivacaine (75 mg) plus 3 mL 0.9% NaCl;

Group RL received 15 mL of 0.25% ropivacaine (37.5 mg) and 15 mL of 0.5% lidocaine (75 mg) plus 3 mL of 0.9% NaCl;

Group RLD received 15 mL of 0.25% ropivacaine (37.5 mg) and 15 mL of 0.5% lidocaine (75 mg) plus 3 mL of dexmedetomidine (0.75 µg/kg).

**Monitoring**

Insertion of 18-gauge intravenous catheter in a peripheral vein of the lower extremity was performed and 5 mL/kg/h infusion of lactated Ringer’s solution was started. Oxygen (3 L/min) was delivered to the patients through a face mask without any sedative medication. Standard monitoring was established for non-invasive systolic arterial pressure (SAP) and diastolic arterial pressure (DAP), heart rate (HR), the respiratory rate (RR), the peripheral oxygen saturation (SpO\textsubscript{2}) and the bispectral index (BIS) values. The axillary BPB was performed by an anesthesiologist unaware of which agents were being used. The patients were placed in the supine position with the upper arm in 90° abduction and the elbow in 110° flexion. After preparation and disinfection of the injection site, the axillary artery and axillary vein were visualized under the ultrasound-guidance (Terason 2000+, America, 14 MHz) and the median, ulnar and radial nerves were explicitly identified. A 22-gauge needle was advanced with real-time guidance closely approach to the nerve. After repeated aspiration to avoid intra-vascular injection, each nerve was observed surrounded by 11mL of the LA solutions tested.

**Assessment**

Blocks were assessed at 30-sintervals until a confirmation of fully block was achieved since the onset time was exceedingly short. After the surgery, we performed the block evaluation every 30 min until complete recovery of the sensation and motor function. The sensory block was assessed by a 3-scale pinprick test (0=normal sensation; 1=blunt sensation; 2=no sensation). The motor block was evaluated by a 3-scale system (0=normal motor ability; 1=capable of moving fingers only; 2=no motor ability).

The onset time of the sensory and motor block, the duration of the sensory and motor block, and the analgesic time were recorded. The onset time of sensory block was defined as the time from the end of injection to the disappearance of pain sensation in the three nerve territories (score 2). The interval from the sensory onset time to the normal sensation (score 0) was denoted as durations of the sensory block. The motor onset time was defined as the period from the end of the injection to achieving only movement of any finger (score 1). The motor block duration was determined as the time from the motor onset time to the complete motor recovery of the hand and forearm (score 0). The end of the administration of the solutions to the first analgesics request after the operation was considered as the analgesic time.
**Supplementary Protocol**

Flurbiprofen 50 mg was intravenously (IV) administered one time to the patients if they complained of pain and how many times of rescue analgesia for a period of 48h were recorded. The anesthesiologist who evaluated the block responses and the patients were blinded to the solution used. The patients who were not completely blocked 30 min after the injection were excluded from the study. If patients suffered pain during the operation, they received IV fentanyl 1 µg/kg plus midazolam 0.02 mg/kg and the block was considered failure. These patients were also excluded from the trial.

SAP, DAP, HR and SpO$_2$ were recorded at baseline and 5, 10, 15, 30, 45 and 60 min after the injection of LAs. The BIS values were registered at baseline, as well as 5, 10, 15, 20, 25, 30, 45 and 60 min post-injection. Bradycardia and hypotension were defined when the values decreased by 20% from their baseline levels. Hypertension was present when mean arterial pressure (MAP) increased by more than 20% over the baseline values. SpO$_2$ less than 90% was considered to indicate respiratory depression. The incidences of other side effects, such as nausea, vomiting, dizziness, dry mouth were also recorded.

**Statistical analysis**

The duration of analgesia was considered the primary outcome variable. To show a 30% increase in the value of the variable and to detect power of 0.9 and a level of the significance of 0.05, we calculated the respective values of at least 19 patients for each group.

Statistical analysis was conducted with SAS9.13(SAS Institute Inc., Cary, NC). Demographic and time data were analyzed by $t$ test. The hemodynamic data and the BIS values were subjected to repetitive measure analysis of variance (ANOVA), followed by single effect analysis. To identify gender heterogeneity between the groups, $x^2$ test was used. $P<0.05$ was considered statistically significant.

**Results**

An adequate block was achieved in all patients that participated in the study. No significant difference was detected among the patients regarding the demographic characteristics or the duration of surgery and anesthesia performance. ($P>0.05$; Table 1)

Onset times of the sensory and motor block were shorter in group RL (7.83 ± 3.00 min; 13.33 ± 5.38 min) compared with those in group R (12.84 ± 3.00 min; 20.52 ± 4.36 min). Though group RLD further shortens the onset times (7.10 ± 3.46 min; 10.90 ± 4.70 min), no significant difference was detected between group RL and group RLD. ($P>0.05$). Importantly, the durations of the sensory and motor block were significantly longer in group RLD (685.95 ± 209.25 min; 620.15 ± 134.72 min) than in group R (452.30 ± 81.20 min; 518.60 ± 99.80 min) and group RL (389.05 ± 114.28 min; 500.80 ± 137.26 min) ($P<0.05$). What’s more, the analgesia time in group RLD (812.4 ± 173.48 min) was significantly longer than that in group R (518.6 ± 99.8 min) and group RL (500.8 ± 137.26 min)($P<0.0001$). The times of flurbiprofen treatment
were significantly reduced in group RLD (2.15 ± 1.14) compared with those in group R (4.38 ± 1.20) and group RL (4.35 ± 2.28) (P < 0.0001; Table 2).

SAP, DAP and HR levels were represented as Fig. 1 and Fig. 2 respectively. SAP levels were significantly lower in group RLD compared with group R and Group RD form 15 min. DAP and HR of group RLD were significantly lower as early as 10 min than the other groups. The BIS values were significantly reduced in group RLD than the other two from 20 min till 60 min (Fig. 3).

No side effects were observed in the patients in either group. No patients received additional analgesics during the surgery.

**Discussion**

Our study showed that first, mixture of ropivacaine and lidocaine provided significantly more rapid sensory and motor onset time compared with ropivacaine alone in ultra-sound guided axillary brachial plexus block (BPB) without significantly decreased block durations. Perineural 0.75 µg/kg dexmedetomidine (DEX) did not further reduce the onset time, but substantially extended the sensory and motor block durations and prolonged the analgesia time compared with LAs alone (both group R and group RL). Proper sedation and improved postoperative analgesia were also accomplished with DEX without observed hypotension or bradycardia.

Inconversial to our study, several clinical investigations reported that DEX shortened the onset times compared with LA alone[29]. We speculate that, first, as stated above, the technique of anesthesia and LA were different, which may have led to different LA distribution in the plexus sheath, thus influencing the concentration and impact of additives[7]. Second, some trials[25, 26, 30, 31] used higher doses of DEX, which a stronger impact on the onset time may have been obtained. Third, in our study, the mixtures of lidocaine and ropivacaine have already achieved fast onset time (7.83 ± 3.00 min; 13.33 ± 5.38 min) compared with group R (12.84 ± 3.00 min; 20.52 ± 4.36 min). In that case, DEX did not further significantly reduce the onset time.

To the best of our knowledge, the sensory onset time (7.10 ± 3.46 min) of group RLD is the shortest one that has ever been published for BPB at the time of preparation of the manuscript. This data increased the rationality of combined administration of two LAs when performing BPB. The motor onset time of group RLD in our study was 10.90 ± 4.70 min, which is longer than that reported in a previous publication[32]. We assume this result is due to the use of a low concentration of ropivacaine (0.25%) and lidocaine (0.5%) in our study, which was sufficient to achieve adequate anesthesia but influenced the motor function to a lower extent. Lower concentration is adopted to avoid the complication of motor block prolongation. We also observed that some patients were able to move their fingers until the end of surgery. This in no doubt is beneficial to patients. That also accounts for the reason why the motor onset time in our study was defined as the end of the injection to the time of finger movement instead of the time point of total paralysis of the hand and forearm. The latter has been addressed by other articles[26, 27, 30]. We believe this is beneficial for patients to keep the motor function.
The BIS values dropped to 81.9 ± 8.11 at 20 min and remained at a stable low level until the 60-min time point. At 35 min, BIS achieved the minimum level of 73.05 ± 7.8, and patients be in a lucid, comfortable state and could be easily awakened. DEX produced sedation via $\alpha_2$-adrenoceptors rather than GABA receptors, and natural sleep without respiratory depression was induced[24, 33]. This suggests that the perineural route of DEX administration can provide a proper sedative effect, rather than the systemic one. We speculate that the decreased values of SAP, DAP, and HR after the administration of DEX could be ascribed to both the sedative effect and the $\alpha$-adrenoceptor cardiovascular effect. However, it is a shortcoming that we did not observe for longer duration for BIS values.

The mechanism by which DEX intensifies axillary BPB is not completely established. Basically two aspects may be hypothesized: DEX may exert an effect on nerve fibers independently of the $\alpha_2$-adrenergic receptor through the enhancement of the hyperpolarization-activated cation current[22, 31]. On the other hand, it may also be absorbed in the circulation, transported to the brain regions containing $\alpha_2$-adrenergic receptors and produce analgesia and sedation by activation of $\alpha_2$-adrenoceptors in the locus coeruleus[34, 35]. It remains a shortcoming that we did not have the group with intravenous infusion of DEX as comparison.

There are still several limitations in our study. First, we did not measure the plasma concentration of LA and DEX, thus were not able to clarify its relationship with the BIS values or analgesia effects. Second, we did not compare different doses of DEX. In accordance with the previous findings, we selected a low dose of DEX to avoid certain widely reported side effects, such as hypotension and bradycardia. Finally, we did not monitor the hemodynamic changes or BIS for longer follow-up period. Moreover, in the preliminary experiment, we evaluated the postoperative VAS within 48 h. However, patients were unavoidably interrupted during normal sleep at night and we finally abandoned the data collection of VAS.

Conclusions

In conclusion, low concentration of ropivacaine and lidocaine provided significantly more rapid sensory and motor onset time compared with ropivacaine alone, the addition of 0.75 µg/kg dexmedetomidine to combined lidocaine/ropivacaine in patients undergoing hand or forearm surgeries for ultrasound-guided brachial plexus block prolongs the duration of sensory and motor blocks and extends the analgesic time without significantly affecting the block onset time. Dexmedetomidine contributed to obtaining a BIS value of 70, inducing a sedative state without side effects observed. 0.25% ropivacaine and 0.5% lidocaine plus 0.75 µg/kg dexmedetomidine, serves as a rational and beneficial regimen to provide rapid onset time, better analgesia effect and proper sedative effect for brachial plexus block, without unwanted limb or finger paralysis and other side effects, and is worthy of clinical application.

Abbreviations

DEX
dexmedetomidine
LAs
local anesthetics
BPB
brachial plexus block
ERAS
Enhanced Recovery After Surgery
SAP
systolic arterial pressure
DAP
diastolic arterial pressure
MAP
mean arterial pressure
BP
blood pressure
RR
respiratory rate
BIS
bispectral index
HR
heart rate
ANOVA
repetitive measure analysis of variance

Declarations

Ethics approval and consent to participate

The clinical trial was approved by the Ethics Committee of the Second Affiliated Hospital, Harbin Medical University, China. The clinical trial was registered in “Chinese Clinical Trial Registry” (http://www.chictr.org.cn/index.aspx) and the registered number was “ChiCTR-IPR-16007742”, registered 12th January 2016.

Availability of data and materials

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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None

Authors' contributions

Qi Wang was responsible for study design, visiting patients before surgery, performed the axillary brachial plexus block and was a major contributor in writing the manuscript.

Wengang Ding was major in technique guidance in performing axillary brachial plexus block under guidance of ultrasound and assessing patients after injection, follow-up after operation.

Lu Feng prepared the medication for block and assess patients after injection and after operation.

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Tables
Table 1: Characteristics of patient, BPB performance and surgical parameters

|                  | Group         | R(n=25)       | RL(n=25)      | RLD(n=25)     |
|------------------|---------------|---------------|---------------|---------------|
| Age              |               | 41.9±12.26    | 44.2±15.20    | 45±13.56      |
| Height           |               | 166.15±9.1    | 168.72±7.48   | 169.85±7.72   |
| Weight           |               | 65.85±11.43   | 62.23±15.58   | 63.33±13.27   |
| Gender (F/M)     |               | 12/13         | 9/16          | 10/15         |
| Duration of Surgery (min) |   | 64.95±24.13   | 70.28±31.20   | 67.35±33.42   |
| Duration of BPB (min) |          | 6.47±1.83     | 5.58±2.93     | 7.60±2.61     |

There were no significant differences between the groups. (P>0.05) The values were expressed as mean±SD. F=Female; M=Male; SD=standard deviation. Group R: 30 mL of ropivacaine +3 mL of normal saline; Group RL: 30 mL of lidocaine/ropivacaine mixture+3 mL of normal saline; Group RLD: 30mL of lidocaine/ropivacaine mixture+3mL of DEX(0.75 µg/kg).

Table 2: Onset time and durations of the sensory and motor block, analgesic time

|                  | Group         | R(n=25)       | RL(n=25)      | RLD(n=25)     |
|------------------|---------------|---------------|---------------|---------------|
| Onset time of sensory block (min) |   | 12.84±3.00    | 7.83±3.00 *   | 7.10±3.46 *   |
| Onset time of motor block (min)  |             | 20.52±4.36    | 13.33±5.38 *  | 10.90±4.70 *  |
| Duration of the sensory block (min) |   | 566.34±96.23  | 474.35±106.41 | 685.95±209.25 ▲ *|
| Duration of the motor block (min) |             | 452.3±81.2    | 389.05±114.28 | 620.15±134.72 ▲ *|
| Analgesic time (min)             |             | 518.6±99.8    | 500.8±137.26  | 812.40±173.48 ▲ *|
| Times of flurbiprofen treatment in 48 h |   | 4.48±1.2      | 4.35±2.21     | 2.15±1.14 ▲ * |

Compared with group R, p<0.05 *; Compared with group RL, p<0.05 ▲

Values are expressed as means±SD. Flurbiprofen treatment was IV administered one time at a dose of 50 mg. Group R: 30 mL of ropivacaine +3 mL of normal saline; Group RL: 30 mL of lidocaine/ropivacaine mixture+3 mL of normal saline; Group RLD: 30 mL of lidocaine/ropivacaine mixture+3 mL of DEX(0.75 µg/kg).

Figures
Figure 1

Systolic arterial pressure and diastolic arterial pressure for the three groups. * means time points of statistically significant difference compared with group R (P<0.05). Δ means time points of statistically significant difference compared with group RL (P<0.05). SAP systolic arterial pressure; DAP diastolic arterial pressure; BP blood pressure. Group R: 30 mL of ropivacaine +3 mL of normal saline; Group RL: 30 mL of lidocaine/ropivacaine mixture+3 mL of normal saline; Group RLD: 30 mL of lidocaine/ropivacaine mixture+3 mL of DEX (0.75 µg/kg).
Heart rate for the three groups. * means time points of statistically significant difference compared with group R (P<0.05). Δ means time points of statistically significant difference compared with group RL (P<0.05). HR heart rate. Group R: 30 mL of ropivacaine + 3 mL of normal saline; Group RL: 30 mL of lidocaine/ropivacaine mixture + 3 mL of normal saline; Group RLD: 30 mL of lidocaine/ropivacaine mixture + 3 mL of DEX (0.75 µg/kg).
Figure 3

BIS values for the three groups. * means time points of statistically significant difference compared with group R (P<0.05). Δ means time points of statistically significant difference compared with group RL (P<0.05). BIS bispectral index. Group R: 30 mL of ropivacaine +3 mL of normal saline; Group RL: 30 mL of lidocaine/ropivacaine mixture+3 mL of normal saline; Group RLD: 30 mL of lidocaine/ropivacaine mixture+3 mL of DEX (0.75 µg/kg).