

Combined Ultrasound and Nerve Stimulator-Guided deep nerve block may decrease the rate of local anesthetics systemic toxicity especially in HBV carriers: A Randomized clinical trial

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Research article

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Abstract

Background: Ultrasound-guidance might decrease the incidence of local anesthetics systemic toxicity(LAST) for many peripheral nerve blocks compared with nerve stimulator-guidance. However, it remained uncertain whether ultrasound-guidance would be superior to the nerve stimulator-guidance for deep nerve block in the lower extremity. This study was designed to investigate that whether ultrasound-guided deep nerve block would decrease the incidence of LAST comparing with those with nerve stimulator-guidance, and to find out associated risk factors for LAST. **Methods:** Three hundred patients for elective lower limb surgery and desiring lumbar plexus blocks(LPBs) and sciatic nerve blocks(SNBs) were enrolled in this study. Patients were randomly assigned to receive LPBs and SNBs with ultrasound-guidance (Group U), nerve stimulator-guidance (Group N) or dual-guidance (Group M). The primary outcome was the incidence of the LAST. The secondary outcomes were the number of needle redirection, motor and sensory block onset and restoration time in the nerve distributions, and associated risk factors. **Results:** There were 18 patients occurring with LAST, including 12 in group U, 4 in group N and 2 in group M. For multiple comparisons among the three groups, we found that the incidence of LAST in group U(12%) was significantly higher than that in group N(4%)($P=0.037$) and group M(2%)($P=0.006$). The OR of LAST with hepatitis B (HBV) infection and female gender were 3.352(95% CI,1.233-9.108, $P=0.013$) and 9.488(95% CI,2.142-42.093, $P=0.0004$), respectively. **Conclusions:** Ultrasound-guidance, HBV infection and female gender were risk factors for LAST in LPBs and SNBs. For patients with HBV infection or female gender undergoing LPBs and SNBs, we recommended that combined ultrasound and nerve stimulator-guidance should be used to improve the safety. **Trial registration:** This study was approved by the Ethical Committee from the first affiliated hospital of Army Medical University. The protocol was registered prospectively with Chinese Clinical Trial Registry (ChiCTR-IOR-16008099) on March 15th 2016. **Key words:** ultrasound; nerve stimulation; nerve block; female; HBV; LAST

Background

Although peripheral nerve blocks have been a safe and effective way to provide analgesia for procedures in a variety of settings, using this type of anesthesia did have risks that should not be overlooked. The incidence of the Local anesthetics systemic toxicity (LAST) was reported to be 0.04/1000 to 1.8/1000 in a latest summary[1]. LAST, life-threatening and sometimes fatal condition, was related to patient characteristics(such as aging, low muscle mass, liver disease, cardiac disease, renal disease or diabetes), local anesthetic characteristics and practice settings[1].

The lumbar plexus blocks (LPBs) combined with sciatic nerve blocks(SNBs) for lower extremity surgery are more and more popular nowadays. Because of the depth of lumbar plexus and sciatic nerve, LPBs and SNBs were advanced regional anesthesia techniques and may be more susceptible to the LAST[2]. LPBs and SNBs were traditionally performed by surface anatomical landmarks and nerve stimulator-guidance. Ultrasound could offer a direct visualization of nerve structures, needle pathway and local anesthetics(LAs) spread in real time so that it was widely used in peripheral nerve blocks. Accumulating data suggested higher efficacy and safety with ultrasound-guidance(US) for nerve blocks[3, 4], specifically for interscalene[5], supraclavicular[6], infraclavicular[7], axillary[8] blocks. Michael et al[9] reported that use of ultrasound reduced the risk of LAST throughout its continuum by 60%to 65% as compared with that not use. However, most of the studies were focused on upper extremity. Due to the deep location of lumbar plexus and sciatic nerve, whether use of ultrasound in LPBs and SNBs would be beneficial for efficacy and safety was argued. Most of the published studies suggested that ultrasound-guidance would shorten the performance time and onset time[10-12]. However, studies comparing the incidence of LAST between ultrasound-guidance and nerve stimulator-guidance specific to LPBs and SNBs were limited.

We designed this study to determine whether ultrasound-guided LPBs and SNBs would decrease the incidence of LAST comparing with those with nerve stimulator-guidance(NS), and to find out associated risk factors for LAST.

Methods

This study was approved by Committee from the hospital of Medical University the Ethical Committee from the First Affiliated Hospital of Army Medical University (previous name: Southwest Hospital of the Third Military Medical University). The protocol was registered prospectively with Chinese Clinical Trial Registry (ChiCTR-IOR-16008099) on March 15th 2016. The principal investigator was Bin Yi. The study took place at the Department of Anesthesia, the First Affiliated Hospital, Army Medical University, Chongqing, from 25 August 2016 to 14 August 2017. Patients scheduled for elective lower limbs surgery in the Southwest Hospital and desiring LPBs and SNBs were offered enrollment. Written informed consent was obtained from the participants for publication of this article and any accompanying tables. A copy of the written consent was available for review by the Editor of this journal. Inclusion criteria were as following: willingness to participate in the study (written informed consent), ASA classification of I to III, elder than 18 years old. Exclusion criteria were as following: refusal to participate, history of neurological diseases, coagulopathy and infection at the site of block, allergy to local anesthetics(LAs), and any contraindication to peripheral nerve blockade noted by the attending anesthesiologist. All patients were randomly allocated to Group U (ultrasound-guidance), Group N (nerve stimulator-guidance) or group M(combined-guidance) by random number table, respectively.

Blinding

The anesthesiologist performed LPBs and SNBs was strictly blinded to patients' group assignment before the procedure. Only when the anesthesiologist commenced with the block, was a prepared sealed opaque envelope containing the patient's group assignment opened. Then the anesthesiologist completed the block with the indicated technique. There were two investigators in the study. One investigator blinded to the technique used during the procedure was present in the block area to assess procedure-related outcomes. To ensure the blindness of the patient to the anesthesia method preferred, all procedures performed behind an opaque screen and investigators were required not to say anything about the technique in use. Another investigator assessing block quality was blinded to the group allocation and remained outside the block area until completion of the procedure. Finally, a statistician blinded to the whole process did statistic analysis, with group data labeled only as numbers until all analyses were completed.

Block preparation

LPBs and SNBs were performed preoperatively by 1 of 3 attending anesthesiologists who were skilled in peripheral nerve blockade with both US and NS guidance. Meanwhile all of them had been in clinical practice with an effort on regional anesthesia for at least 5 years. After arriving the operating room, patients were placed in the lateral decubitus position with the surgical limb uppermost and monitored continuously via electrocardiography, SpO₂ measurement, and noninvasive blood pressure monitoring during nerve blockade and surgery. Both the ultrasound and nerve stimulation systems were prepared and positioned conventionally in each group. The ultrasound machine and nerve stimulator were turned on, and a grounding lead was placed on the lateral aspect of the leg being blocked for each group. Patient's group allocation was given to the anesthesiologist only after preparation of both systems and just before the block procedure. Patients were pretreated with 0.05mg/kg midazolam and 1.5µg/kg fentanyl. The injection site was prepared with chlorhexidine gluconate. 5 ml of 0.5% lidocaine was injected subcutaneously at the site of needle insertion. The LA mixture was made up of 200mg ropivacaine, 200mg lidocaine and 20ml of 0.9% sodium chloride solution. The concentration of ropivacaine and lidocaine was 0.4%. The total amount of LAs used was determined by the dosage of ropivacaine needed, namely 3mg/kg. Patients and the investigator assessing the block quality were kept away from seeing both the block procedure itself and the sonographic displayed by an opaque screen. According to group allocation, patients received their nerve blocks under one of the following three techniques.

Nerve stimulation technique

In the operating room, LPB was performed using the Chayen's approach [13, 14]. The puncture site was located 4-5 cm lateral from posterior midline along the intercrystal line. A 110-mm, 22-G stimulating needle connected to a nerve stimulator (Stimuplex HNS 11, B. Braun) was advanced perpendicular to skin. The nerve stimulator was set to a pulse duration of 0.1 ms, current intensity of 1.0 mA, and frequency of 2 Hz. When the stimulating intensity was progressively reduced to 0.4 mA or less while maintaining the twitch in the quadriceps distribution. The total volume of LAs was determined by the amount of LA mixture according to patient's weight as we mentioned above. Each point was given half of the calculated total volume of LA mixture. When the correct needle position was achieved based on evoking the desired motor response, the amount of LAs described above was injected. SNB was performed with the classic Labat's approach [15]. The needle was inserted 5 cm below the midpoint of a line connecting the posterior superior iliac spine and the greater trochanter. After an appropriate stimulus was localized in the sciatic distribution, LAs described above was injected.

Ultrasound-guided technique

We chose "Shamrock Method" for LPBs [16]. A sterile cover was put on a 3MHz low-frequency ultrasound probe (LOGIQe 4C-RS, GE Inc, USA). The ultrasound transducer was positioned on the line connecting subcostal margin and iliac spine and adjusted until a clear view of psoas, erector muscle and quadratus lumborum appeared. The hyperechoic structure located in the posterior internal quadrant of psoas was lumbar plexus. The puncture site was beneath the probe and 4-5cm lateral from the vertebral body. We chose subgluteal approach for SNBs [17]. The ultrasound transducer was positioned perpendicular to the skin on the line connecting the ischial tuberosity and greater trochanter, and a clear transverse image of the hyperechoic sciatic nerve between the ischial tuberosity and greater trochanter was obtained. For LPBs and SNBs, the needle placement and spread of LAs were confirmed with ultrasound visualization. After the proper needle placement was confirmed, incremental injection of the same LA solution in the same volume occurred as described previously until circumferential spread around the nerve was obtained. The needle was redirected, when required, to achieve this goal. As for group M, initially, needle-to-nerve guidance was applied

according to group U. Maintaining the needle nerve position, the nerve stimulator was set as described for group N. When the correct needle position was achieved based on evoking the desired motor response, LAs described above was injected.

Block evaluation

Evaluation of nerve block was performed by an investigator blinded to those who administered LPBs and SNBs. The motor and sensory response in the nerve distribution area were assessed every 5 minutes until complete motor and sensory effects were achieved. If it took more than 30 minutes to achieve sensory loss in both distributions after the end of injection with LAs, we identified that it was failed block. The attending anesthesiologist had the right to perform general anesthesia, rescue blockade, or supplementation with a local field block when came

across with a failed block. The motor block was assessed with a modified Bromage Scale; 2, full motor strength, 1, decreased strength; and 0, no strength. Similarly, the sensory block was evaluated with ice: 2, full sensation (no change); 1, decreased sensation; and 0, no sensation.

Postoperative follow-ups were performed in the post-anesthesia care unit and by telephone within 72 hours after the procedure by clinical personnel in addition to study-related procedures.

Outcomes

The primary outcome was the incidence of LAST. LAST can present with both central nervous system (CNS) and cardiovascular system (CVS) clinical manifestations. The CNS symptoms included tongue numbness, tinnitus, light-headedness, metallic taste, nystagmus, confusion, tremors, agitation, seizures, coma, and respiratory arrest[18]. The CVS symptoms include tachycardia, arrhythmias, hypertension, and later toxic symptoms such as bradycardia, cardiac depression, cardiovascular collapse, and asystole[18]. The secondary outcomes were the quality of the nerve block and associated risk factors. The quality of the block included number of needle redirections, motor and sensory block onset and restoration times in the lumbar and sciatic nerve distributions. The associated factors included age, gender and comorbidities. Needle redirections were counted as the number of times in which the needle was withdrawn of at least 10mm with subsequent forward movement. The upper limit of redirections was 20, but if necessary the needle was allowed to redirect as many times as possible to achieve proper placement as described previously. The onset of motor and sensory block was assessed by the modified Bromage scale as mentioned above for the distributions of both the lumbar plexus and sciatic nerves. The onset time was measured between final LA injection and the first observation of a 0 score. During the phone follow-up, patient provided time of first return of sensation and block-related complications on post-operative day 1. The block duration time was defined as interval between block completion and first return of sensation. Any reported complications were recorded.

Statistical analysis

The statistical analyses were performed using Statistical Package for the Social Sciences (Windows Software, version 19.0; SPSS Inc, Chicago, IL) and Power Analysis and Sample Size (Windows Software, version 11.0; NCSS Inc, Utah).

Demographic and perioperative data were expressed as the means and standard deviations. Parametric and non-parametric Kolmogorov–Smirnov tests were applied to assess normality. The primary outcome (incidence of LAST) and potential risk factors were compared by 2 test or Fisher exact test when appropriate ($n < 5$ in any field). In the 2 test, we tested whether there were differences in the incidence of the LAST and the odds ratios of potential risk factors among different groups. The demographic and secondary outcomes were compared among the three groups by one-way ANOVA, following by multiple comparisons using LSD test or Welch and Dunnett's T3 test for unequal variances. In the one-way ANOVA, we tested whether there were differences in the patients' characteristics and block quality among the three groups. This analysis was followed by 95% CIs with Bonferroni correction to adjust for multiple comparisons (three different methods for nerve block for motor and sensory onset and restoration time data and demographic data) to minimize the chance of a type error I (0.05). For all comparisons, 2-tailed $P < 0.05$ was considered statistically significant.

The incidence of LAST was low according to published data. So we did a test for the power of test regarding the incidence of the LAST in three groups after the experiment. In the current study, there were 319 patients randomly allocated into the three groups. Finally, data from 100 patients for each group were analyzed. We did a test for the power of test regarding the primary outcome after experiment. We calculated the effect size (0.182) in the software PASS. Then we set the significant level as 0.05. Referring to the result, we found that when the total sample size was 300, the power($1-\beta$) of the test was 0.81.

Results

Study flow diagram was presented in Fig 1. A total of 319 patients were evaluated for eligibility and offered enrollment in this study. 18 were excluded, including 3 not meeting inclusion criteria, 13 declined to participate and 2 other reasons. There were no failed or aborted blocks in either group. One patient in group U was lost of follow-up.

Patient's characteristics were presented in Tab 1. There was no statistically significant difference in the age, gender, weight and height among the three groups. Only one patient in group M was with ASA ≥ 3 status. Most of the operations were performed in knee and ankle. There was statistically significant difference in surgical duration time in group U (41.0 ± 24.21 minutes) comparing with that in group M (51.5 ± 30.8 minutes).

The primary and secondary outcomes were shown in Tab 2. The incidence of LAST in all the three groups was 6%. What's more, there was statistically significant in the incidence of LAST among the three groups. For multiple comparisons among the three groups, we found that the incidence of LAST in group U (12%) was significantly higher than that in group N (4%) ($P=0.037$) and group M (2%) ($P=0.006$). (shown in Tab 4). As regard the LPBs: the motor onset time was statistically significantly shorter in group N (9.5 ± 3.55 seconds) compared with group U (11.30 ± 4.94 seconds) and group M (11.10 ± 4.38 seconds). (shown in Tab 2). There was no statistically significant difference in the sensory onset time, sensory and motor restoration time among the three groups. As regard the SNBs: patients in group N had a statistically significantly

shorter motor and sensory onset time comparing with that in group U and group M, respectively. Meanwhile, the sensory and motor restoration time in group N were statistically significantly longer than that in group U and group M, respectively.

The detailed information of the 18 patients occurring with the LAST was summarized in Tab 3. There were 12 patients from group U (66.7%), 4 from group N (22.2%) and 2 from group M (11.1%) occurring with LAST during the process. Most of the symptoms were CNS symptoms. None of the 18 patients had permanent complications after our correct and timely treatment. To our interest, 16 in 18 of the patients were female. The age of the 18 patients ranged from 19 to 81. The shortest occurrence time was one minute after finishing the block. The longest was 22 minutes. The shortest duration time was 3 minutes without any treatment. The longest duration time was 100 minutes due to the use of propofol. We analyzed risk factors such as age, gender, liver disease, diabetes according to *The Third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity*[1]. In the current study, 52 patients infected with HBV and 7 of them occurred with LAST. As shown in Tab 4, the OR of LAST with HBV infection and female gender was 3.352(95% CI, 1.233-9.108, $P=0.013$) and 9.488(95% CI, 2.142-42.093, $P=0.0004$), respectively. However, age, needle passes, renal disease and diabetes did not increase the risk for LAST in the current study. In a word, use of ultrasound, HBV infection and female gender may be related to increase risk of LAST in the current study.

Discussion

There were three main findings in the current study. Firstly, use of ultrasound did not improve the quality of deep nerve block. Secondly, use of ultrasound did not improve the quality of deep nerve block. Thirdly, use of ultrasound, HBV infection and female gender may be risk factors for LAST.

In the present study, we found that LPBs and SNBs with US were not superior to those with NS in the onset and restoration time. Spencer S. Liu et al[19] summarized that 8 of 10 RCTs reported use of ultrasound would shorten the onset time of the lower extremity block, 2 of 10 found no difference, and no RCT reported slower onset with ultrasound. However, most of the RCTs were about the femoral and peroneal nerve. Recently, Amuntasupakul et al[12] reported that ultrasound with nerve stimulator for LPBs resulted a shorter total anaesthesia time comparing with US alone. Due to the size and location of the lumbar plexus and sciatic nerve, LPBs and SNBs were advanced regional anesthesia techniques. Different admission passage for the nerve block may result in different outcome. Furthermore, due to the comorbidities, some of the enrolled patients may already have minor pathological changes in the targeted nerve which may affect the onset and restoration time.

The incidence of LAST was 6% which was much higher than previously reported[1]. LAST can occur as a result of the patient's risk factors and current medications, inadvertent injection of LAs directly into the vascular system, an exceeded maximum dose of the LAs, or immediate absorption of the LAs when it was injected into an extremely vascular area[18]. It had been widely reported that US was safer comparing with NS because US could provide direct visualization of the target nerve, surrounding tissues, and injectate spread[9, 20]. However, in our study, about two-thirds of the patients occurring with LAST were from the group U. There were two main reasons. Firstly, a fair amount of patients in our study were with HBV infection, renal diseases who may be more susceptible to LAST[21]. Secondly, the lumbar plexus and sciatic nerves were difficult to be visualized due to its depth. In order to get a better vision of tissues near the nerve, block needle and the deposition of LAs, ultrasonic probe was required a pressure near the injection site. The pressure would make the blood flow of the deeply located small vessels slower. It was difficult for the Doppler ultrasonography to exam the deeply placed small vessels especially with slow flow[22]. The continuous pressure caused by the ultrasonic probe made small deeply located vessels "invisible" thus it harder to avoid injecting into extremely vascular area resulting in the LAST. The nerve stimulator had advantages on determining the relative position of tip and nerve over the US. When the needle tip was near extremely vascular area, the electric current had an intensity loss result in failure of inducing twitch of muscles. In group M, after ultrasound-guidance, the rate of failure of inducing twitch of quadriceps distribution was 10% and that of gastrocnemius distribution was 12%. Under this circumstances the distance between the tip and the targeted nerve needed be adjusted. So the likelihood of injecting LAs into extremely vascular area was less than the US alone.

Patient's weight, comorbidities, use of other medications, genetics, allergies, and other physiologic limitations also affected the incidence of LAST[23]. Factors affected the systemic absorption of LAs, its peak plasma concentration and the time to reach that peak were all related to LAST. Bupivacaine and ropivacaine were degraded in the liver by α 1-acid glycoprotein(AAG)[21]. Patients with liver diseases would have a decreased clearance rate of LAs due to the low concentration of AAG, which may increase the incidence of the LAST. However, even patients with advanced liver dysfunction, synthesis of AAG was still maintained[21, 24]. In patients with hepatic dysfunction, single-dose blocks can usually be performed safely with normal dose of the LAs[25]. It indicated that decreased clearance of LAs caused by isolated hepatic dysfunction was not the main reason here. However, as shown in Tab 4, HBV infectious patients had a higher risk of LAST in this study. Patients who had been infected with HBV may result in chronic liver disease. Patients with chronic liver disease usually had vascular dysfunction, especially angiogenesis, microvascular derangements and microcirculatory dysfunction[26, 27]. Cirrhosis caused numerous microscopic vessel aberrations, may become entangled with each other, such as sharp bends, anomalous branching patterns, abnormal branching angles and tortuosity[28]. McAvoy et al[29] demonstrated that cirrhosis patients had selective regional increases in blood flow in the splanchnic and hepatic circulations, yet diminished flow in the peripheral limbs. Neovascularization and slower blood flow made it easier to inject with LAs into

extremely vascular area especially for the use of ultrasound, resulting in an increasing incidence of LAST. The vascular endothelial growth factor(VEGF) and bone morphogenetic protein 9 (BMP-9) had been widely reported to promote angiogenesis[30]. A higher BMP-9 levels in human serum accompanied with advanced stages of liver fibrosis, meanwhile overexpression BMP-9 accelerating the liver fibrosis and BMP-9 knockdown attenuated the liver fibrosis in a mouse model[31]. Plasma VEGF was elevated in cirrhosis patients, especially in those with spider angiomas[27]. A higher level of serum BMP-9 and VEGF in patients with HBV indicated a more advanced stage of liver dysfunction and more formation of new blood vessels. But it need our further efforts to determine the relationship of the VEGF and BMP9 between the HBV infection. VEGF and BMP9 may be promising prognostic indicators for the incidence of LAST for patients with HBV in deep nerve block.

Herein women were more likely to occur with the LAST, which was in consistence with the latest regional anesthesia and pain medicine practice advisory on LAST[1]. Some enrolled patients with LAST were HBV carries. The increase risk of LAST in female may be related to HBV infection. In physiological conditions estrogen/estrogen receptor α (ER/ER α) axis had a protective effect on HBV-associated liver damage and taking postmenopausal hormone replacement therapy resulted in a lower risk of hepatocellular carcinoma development for HBV positive women carriers[32].In a female cirrhosis rat model the mRNA expression of ER α was lower in that of a sham rats and the ability of 17β -estradiol to alleviate of relevant complications was diminished[33]. It indicated that HBV women carriers might have a lower level of ER/ER α that made them more susceptible to LAST. It need further efforts to investigate the underlying mechanism.

There are a number of limitations to this study. Firstly, it was not possible to blind the anesthesiologist performing the nerve block, we couldn't exclude the potential influence of a performance bias in this study. Secondly, although we made our efforts to maintain blinding among the investigators, patients, and statistician, it may be partial blinding due to muscle contractions elicited by nerve stimulation, collecting the needle redirections and so on. We attempted to minimize this bias by only involving staff anesthesiologists experienced in peripheral nerve blockades using both guidance modalities. Thirdly, part of the limitation was related to techniques and equipment used in this single-center study, so that it could not generalized to other techniques or peripheral nerve block locations. The degree of advantages and disadvantages provided by ultrasound-guided deep nerve block especially in HBV carriers was likely to vary by nerve block site as well. We only demonstrated some interesting phenomenon found in a single-center study. The underlying mechanisms were not illuminated in the present study. A multicenter and more detailed experiments were needed to certify our discovery and illuminate the mechanisms.

Conclusions

Our results suggested that ultrasound-guidance, HBV infection and female gender were risk factors for LAST in LPBs and SNBs. For patients with HBV infection or female gender undergoing LPBs and SNBs, combined ultrasound and nerve stimulation-guidance should be used to improve the safety. The probable mechanisms were as follows:1) Angiogenesis and slower blood flow in deeply located small vessels; 2) Use of nerve stimulator could avoid LAs injecting into extremely vascular area.

Abbreviations

LAST: Local Anesthetics Systemic Toxicity **LAs:** Local Anesthetics

LPBs: Lumbar Plexus Blocks **SNBs:** Sciatic Nerve Blocks

NS: Nerve Stimulator-guidance **US:** Ultrasound-guidance

VEGF: Vascular Endothelial Growth Factor **BMP9:** Bone Morphogenetic Protein 9

Declarations

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To our Families and colleagues.

Founding

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Availability of data and materials

The raw data and materials are available from the corresponding author upon reasonable request.

Authors' contributions

Xu-hao Zhang helped design and conduct the study; data collection and manuscript writing. Yu-jie Li helped with data analysis and interpretation; and drafting, revision, and final approval of the article. Wen-quan He helped conduct the study and collect data. Chun-yong Yang helped data analysis and revision. Jian-teng Gu helped with study design and data analysis. Kai-zhi Lu helped with study design and revision. Bin Yi helped design the study, write this manuscript and revision.

Ethics approval and consent to participate

This study was approved by the human research review committee at the southwest hospital of third military medical university. The protocol was registered prospectively with Chinese Clinical Trial Registry (ChiCTR-IOR-16008099) on March 15th 2016. Each participant was informed about the study protocol and the probability of publication of material relating to them in details and complete written informed consents were signed before enrollment in the study.

Consent for publication

Consent for publication was obtained from the participants' if appropriate.

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Tables

Table 1: Patients characteristics

	Group U(100)	Group N(100)	Group M(100)	F	P
Age (yr) (SD)	41.7(12.85)	39.9 (14.71)	42.0 (19.94)	0.6222	0.53745
Gender (F/M)	55/45	47/53	43/57		N vs U 0.51/M vs U 0.49
Weight (kg) (SD)	63.8 (11.92)	64.7(11.06)	64.7(11.20)	0.2185	0.8038
Height (cm) (SD)	163.0 (8.07)	165.0 (9.68)	164.9 (9.3)	1.5282	0.2186
Surgical duration (min)	41.0(24.21)	46.9 (32.26)	51.5(30.8)	3.1996	0.04219
Surgical site(knee/ankle/other)	89/10/1	78/21/1	84/16/0		
ASA I/II/III	53/47/0	48/52/0	49/50/1		

Data are expressed as mean \pm SD; Abbreviations: Group U, nerve block with ultrasound guidance; Group N, nerve block with nerve stimulation-guidance; group M, nerve block with combined guidance; F, female; M, male; ASA, American Society of Anesthesiologists

Table 2. Outcomes

Outcomes	Group U(100)	Group N(100)	Group M(100)	P
Incidence of LAST(%)	4%	12%	2%	0.007
Motor onset, Lumbar plexus, min (SD)	11.3(4.94)	9.5 (3.55)	11.1 (4.38)	0.00729
Motor onset, Sciatica, min (SD)	15.1 (4.04)	13.4 (3.03)	15.0 (3.20)	0.00041
Sensory onset, Lumbar plexus, min (SD)	8.5(3.64)	7.8 (2.52)	8.8 (2.88)	0.07676
Sensory onset, Sciatica, min (SD)	9.6 (2.62)	8.8 (1.59)	9.5 (1.79)	0.02399
Sensory restoration, Lumbar plexus, h (SD)	8.0 (1.90)	8.4 (1.71)	8.1 (1.63)	0.19313
Sensory restoration, Sciatica, h (SD)	7.1 (1.73)	7.7 (1.63)	7.0 (1.57)	0.00329
Motor restoration, Lumbar plexus, h (SD)	8.9 (2.11)	9.3 (1.78)	9.0 (1.59)	0.18912
Motor restoration, Sciatica, h (SD)	7.9(1.87)	8.5 (1.72)	7.8 (1.44)	0.00760

Data are expressed as mean \pm SD or number with %. Abbreviations: Group U, nerve block with ultrasound guidance; Group N, nerve block with nerve stimulation-guidance; group M, nerve block with combined guidance.

Table 3: Summary of Events of Local Anesthetic systemic Toxicity (LAST)

Group	Sex	Age(Y)	Weight(kg)	Height(cm)	Sings and symptoms	Occurrence time	Treatment	Duration time (min)
N	F	35	52.5	155	Lips numbness,Left hand twitch	17	M2	6
N	F	46	55	155	Lips numbness	11	/	5
N	F	65	62.5	163	Agitation,Chest tightness	9	/	3
N	F	19	35.5	149	Tachycardia,Seizures	12/22	M2 P200V	80+
U	F	46	54	158	Tongue numbness,Tinnitus	8	M2	9
U	F	53	54	160	Tongue numbness,Left hand and leg twitch	13/17	M2	8
U	F	26	70	161	Tongue numbness	18	/	4
U	F	41	50	156	Unconsciousness,Tachycardia,Hypertension	8	M2 P200	63+
U	F	61	60	155	Agitation	9	/	3
U	F	46	60	159	Scream,Unconsciousness	1	M2 P200	100+
U	F	32	51	160	Tachycardia	7	M2 D0.5	25
U	M	81	63	152	Right hand twitch,Unconsciousness	4/9	M2	15
U	F	62	58	150	Transient numbness of right hand and leg	20	/	4
U	F	26	46	161	Twitch	12	M2	5
U	F	47	60	145	Hypertension,Tachycardia,Agitation	10	M2	25
U	F	37	48	153	anxiety,Confusion	11	M2	15
M	F	35	64	163	Tinnitus,Whole bodynumbness	8	M2	10
M	M	21	60	170	Tongue numbness	11	/	6

Treatment: †M2 means venous injection of Midazolam 2mg; P200 means continuous intravenous infusion of Propofol 200mg with the rate of 3mg.kg-1.h-1; D0.5 means continuous intravenous infusion of Dexmedetomidine with the rate of 0.5ug.kg-1.h-1; V means mechanical ventilation. Dosage of local anesthetic: 0.4%Ropivacaine+0.4% Lidocaine, 3mg/kg)

†‡The main reason of long duration time was the use of propofol.

Table 4. Associated Risk Factors for Local Anesthetic Systemic Toxicity

Categorical Variables		No. LAST Events	OR	95% CI	P
Method of Block	N	44			0.037 (N vs U)
	U	1212			0.006 (U vs M)
	M	22			0.407 (M vs N)
Needle passes(times)	2-5	115.1	0.58	0.217-1.550	0.272
	6-	78.4	1		
Sex	Male	2(1.3)	1		
	Female	16(11.0)	9.488	2.142-42.093	0.0004
HBV infection	negative	11(4.4)	1		
	positive	7(13.5)	3.352	1.233-9.108	0.013
Renal disease	negative	17(6.1)	1		
	positive	1(4.5)	0.731	0.093-5.766	0.765
Diabetes	negative	18(6.3)			
	positive	0(0)			1.00

Data are expressed as number and %. Abbreviations: Group U, nerve block with ultrasound guidance; Group N, nerve block with nerve stimulation-guidance; group M, nerve block with combined guidance.

Figures

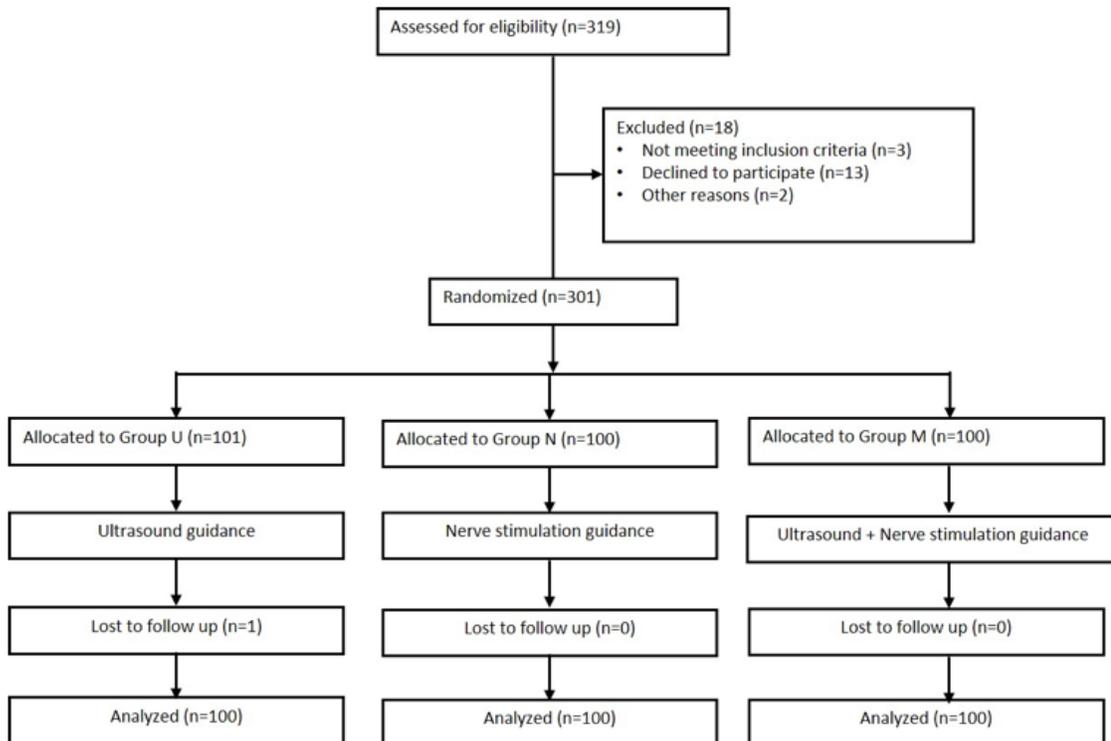


Figure 1

CONSORT flow diagram of the study. CONSORT indicates Consolidated Standards of Reporting Trials. Group U was short for nerve block with ultrasound guidance, Group N was short for nerve block with nerve stimulation guidance, group M was for nerve block with combined guidance.