Ultrasound-guided deep nerve block may increase the rate of local anesthetics toxicity in HBV carriers: A Randomized clinical trial

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Abstract

**Background:** Ultrasound-guidance might decrease the incidence of local anesthetics systemic toxicity (LAST) for many peripheral nerve blocks compared to nerve stimulation. However, it remained uncertain whether ultrasound-guidance would be superior to the nerve stimulation for deep nerve block in the lower extremity. This study was designed to investigate that deep nerve block with ultrasound-guidance would result in a lower rate of LAST comparing to that with nerve stimulator-guidance.

**Methods:** Three hundred patients who were 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 LPB and SNB with ultrasound-guidance (Group U), nerve stimulator-guidance (Group N) and dual-guidance (Group M). The primary outcome was the incidence of the LAST. The secondary outcomes were number of needle redirections, motor and sensory block onset and restoration times in the nerve distributions, and associated risk factors.

**Results:** There were 18 patients with the LAST, including 12 in group U, 4 in group N and 2 in group M. For multiple comparisons among the tree 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 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.

**Conclusions:** For patients undergoing LPBs and SNBs, use of ultrasound may increase the incidence of the LAST. HBV infection and female gender were risk factors for deep nerve block.

**Trial registration:** 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.

**Keywords:** Ultrasound; nerve stimulation; nerve block; female; HBV; LAST

Background

Although peripheral nerve block had 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 0.04/1000 to 1.8/1000[1]. LAST is a life-threatening and sometimes fatal condition. It 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 were more and more popular. Because of the depth of lumbar plexus and sciatic nerve, it was difficult to block and maybe more susceptible to the LAST[2]. LPBs and SNBs were traditionally performed using surface anatomical landmarks and nerve stimulation. Ultrasound could offer a direct visualisation 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 had been published suggesting higher efficacy and safety with ultrasound-guidance (US) for nerve block[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 nerve blocks. Due to the deep location of lumbar plexus and sciatic nerves, whether use of ultrasound in LPBs and SNBs would be beneficial for efficacy and safety was argued. Most of the published study 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 investigate that deep nerve blocks with ultrasound-guidance would result in a lower rate of the LAST comparing to that with nerve stimulator-guidance (NS) and associated risk factors.

Methods
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. The principal investigator was Bin Yi. The study took place at the Department of Anesthesia, Southwest Hospital, the Third Military 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 the blockade was strictly blinded to patients’ group assignment before the procedure. Only when the anesthesiologist commenced with the blockade, a prepared sealed opaque envelope containing the patient’s group assignment was opened. Then the anesthesiologist completed the blockade with the indicated technique. The 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 after completion of the nerve blockade. Finally, a statistician blinded to the blockade procedure or data collection did statistic analysis, with group data labeled only as numbers until all analyses were completed.

**Block preparation**
All nerve block procedures 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 were 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 performing the block only after preparation of both systems was completed and just before the block procedure. Patients were pretreated with 0.05mg/kg midazolam and 50 to 200 ug of 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 0.4% ropivacaine and 0.4% lidocaine. The total volume of the mixture was 50ml. The total amount of LAs used was determined by the dosage of ropivacaine needed, namely 3mg/kg. Patient and researcher assessing the block were kept away from seeing both the block procedure itself and the sonographic display by an opaque screen. According to group allocation, patients received their nerve blocks under one of the following two 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 intercristal 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. LAs were given half the amount according to the weight of patients for LPB and SNB respectively. 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 using 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 the blockade. 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 the LAST. LAST can present with both central nervous system (CNS) and cardiovascular system (CVS) clinical manifestations. The CNS symptoms were including 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 $c^2$ test or Fisher exact test when appropriate ($n<5$ in any field). In the $c^2$ 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 Dunett’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.

In the current study, there were 319 patients randomly allocated into the three groups. Finally, data from 100 patients for each group was 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 to 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 the ASA III status. Most of the operations were performed in knee and ankle. There was statistically significant difference in the time of surgical duration in group U (41.0±24.21minutes) compared to 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%. And there was statistically significant in the incidence of LAST among three groups. For multiple comparisons among the tree 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 were no statistically significant 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 from group U (66.7%), 4 from group N (22.2%) and 2 from group M (11.1%) during the procedure. 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 were ranged from 19 to 81. The shortest occurrence time was one minutes after the blockade, the longest time 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]. There were 52 HBV infectious patients in this study 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 of incidence of LAST in the current study. In a word, use of ultrasound, HBV infection and female gender may be related to the increase risk of LAST in the current study.

Discussion
There were three main findings in the current study. Firstly, use of ultrasound increased the incidence of the LAST. 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 the NS in the onset and restoration time. Spencer S. Liu et al[19] summarized that 8 of 10 RCTs reported use of ultrasound would shorter 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. Different admission passage for the nerve block may result in different outcome.

The lumbar plexus nerve was more difficult to block completely than other lower extremity blockade. Arnuntasupakul et al[12] reported that ultrasound with nerve stimulator for LPBs resulted a shorter total anaesthesia time comparing with US alone. Furthermore, some of the patients in this study were with comorbidity which may already have pathological changes in the targeted nerve which may influence the onset and restoration time. Our results were not in contradiction to other existing RCTs.

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 to the 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 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 nerve 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
near extremely vascular area resulting in the LAST. The PNS had advantages on determining the relative position of tip and nerve over the US. So the likelihood of injecting LAs near 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 the LAST[23]. Factors affected the systemic absorption of LAs, its peak plasma concentration and the time to reach that peak were all related to the LAST. Bupivacaine and ropivacaine were degraded in the liver by α1-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 doses 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 the LAST. The vascular endothelial growth factor(VEGF) and bone morphogenetic protein 9 (BMP-9) were 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]. Here some patients with LAST were positive carries. The increase of risk of LAST in female may be related to he 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-estrodiol to alleviate of relevant complications were diminished[33]. It indicated that HBV women carriers may have a lower level of ER/ER α that made them more susceptible to the LAST. It need further efforts to investigate the underlying mechanism. 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. What’s more 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. We attempted to minimize this bias by only involving staff anesthesiologists experienced in peripheral nerve blockades using both guidance modalities. 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
Use of ultrasound alone may increase the incidence of LAST in LPBs and SNBs. Meanwhile, LPBs and SNBs with US was neither inferior nor superior to that with NS. HBV infection and female gender may be related to the incidence of LAST in the deep nerve block. The probable mechanisms were as follows: 1) Angiogenesis and slower blood flow in deeply located small vessels; 2) It was difficult for ultrasound probe to detect the deeply located small vessels with the pressure near the injection site.

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 15\textsuperscript{th} 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.

References

1. Neal JMB, Michael J., Fettiplace MR, et al.: \textit{The Third American Society of Regional Anesthesia and Pain Medicine Practice Advisory on Local Anesthetic Systemic Toxicity}. \textit{Regional Anesthesia and Pain Medicine} 2018, \textbf{43}(2):113-123.

2. Auroy YB, D. Bargues, L. Ecoffey, C. Falissard, B. Mercier, F. J., Bouaziz HS, K.:: \textit{Major complications of regional anesthesia in France: The SOS Regional Anesthesia Hotline Service}. \textit{Anesthesiology} 2002, \textbf{97}(5):1274-1280.

3. Salinas FV, Hanson NA: \textit{Evidence-based medicine for ultrasound-guided regional anesthesia}. \textit{Anesthesiology clinics} 2014, \textbf{32}(4):771-787.

4. Gelfand HJO, J. P. Lesley, M. R. Ko, P. S.Murphy, J. D.Sumida, S. M.Isaac, G. R.Kumar, K.Wu, C. L.: \textit{Analgescic efficacy of ultrasound-guided regional anesthesia: a meta-analysis}. \textit{Journal of clinical anesthesia} 2011, \textbf{23}(2):90-96.

5. Liu SSZ, V. M. Gordon, M. A. Beathe, J. C.Maalouf, D. B.Paroli, L., Liguori GAO, J.Buschiazzo, V., Ngeow JS, T.Ya Deau, J. T.: \textit{A prospective, randomized, controlled trial comparing ultrasound versus nerve stimulator guidance for interscalene block for ambulatory shoulder surgery for postoperative neurological symptoms}. \textit{Anesthesia and analgesia} 2009, \textbf{109}(1):265-271.

6. Williams SRC, P. Arcand, G., Harris PR, M.Boudreault, D.Girard, F.: \textit{Ultrasound
guidance speeds execution and improves the quality of supraclavicular block. *Anesthesia and analgesia* 2003, 97(5):1518-1523.

7. Sauter ARD, M. S.Stubhaug, A.Halstensen, A. M.Klaastad, O.: **Electrical nerve stimulation or ultrasound guidance for lateral sagittal infraclavicular blocks: a randomized, controlled, observer-blinded, comparative study.** *Anesthesia and analgesia* 2008, 106(6):1910-1915.

8. Chan VWP, A. McCartney, C. J. Brull, R. Xu, D. Abbas, S.: **Ultrasound guidance improves success rate of axillary brachial plexus block.** *Canadian journal of anaesthesia = Journal canadien d'anesthesie* 2007, 54(3):176-182.

9. Barrington MJ KR: **Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade.** *Reg Anesth Pain Med* 2013, 38(4):289-299.

10. Amin WA SM, Elkersh MM, Mathai A, Medekova S, Husain T.: **Comparative study between ultrasound and nerve stimulator guided sciatic nerve block through the anterior approach.** *Middle East J Anaesthesiol* 2015, 23(2):185-191.

11. Danelli GF, A.Ghisi, D.Moschini, E.Rossi, M.Ortu, A.Baciarello, M. Fanelli, G.: **Ultrasound vs nerve stimulation multiple injection technique for posterior popliteal sciatic nerve block.** *Anaesthesia* 2009, 64(6):638-642.

12. Vanlapa Arnuntasupakul TC, Prangmalee Leurcharusmee, Worakamol Tiyaprasertkul, et al: **Ultrasound with neurostimulation compared with ultrasound guidance alone for lumbar plexus block: A randomised single blinded equivalence trial.** *Eur J Anaesthesiol* 2018, 35(3):224-230.

13. Mannion S: **Psoas compartment block.** *Continuing Education in Anaesthesia, Critical Care & Pain* 2007, 7:162-166.

14. Chayen D, Nathan H, Chayen M: **The psoas compartment block.** *Anesthesiology*
1976, 45(1):95-99.

15. Horlocker TT: Regional anesthesia and analgesia in the patient receiving thromboprophylaxis. Regional anesthesia 1996, 21(6):503-507.

16. Sauter AR UK, Bendtsen TF, Børglum J. Br J Anaesth 2013: e-letter, Published 26 February 2013, Online ISSN 1471-6771-Print ISSN 0007-0912 (http://bja.oxfordjournals.org/forum/topic/brjana_el%3b9814).

17. Yamamoto HS, S.Wada, M. Shido, A.: A prospective, randomized comparison between single- and multiple-injection techniques for ultrasound-guided subgluteal sciatic nerve block. Anesthesia and analgesia 2014, 119(6):1442-1448.

18. Fencl JL: Local anesthetic systemic toxicity: perioperative implications. AORN journal 2015, 101(6):697-700.

19. Liu SS: Evidence Basis for Ultrasound-Guided Block Characteristics Onset, Quality, and Duration. Regional Anesthesia and Pain Medicine 2016, 41(2):205-220.

20. Orebaugh SL KM, Williams BA.: Adverse outcomes associated with nerve stimulator-guided and ultrasound-guided peripheral nerve blocks by supervised trainees: update of a single-site database. Reg Anesth Pain Med 2012, 37(6):577-582.

21. Christie LE, Picard, John Weinberg, Guy L.: Local anaesthetic systemic toxicity. BJA Education 2015, 15(3):136-142.

22. Nevbahar A. Degirmenci AHO, Sahinde Atlanoglu, Esra Akcan, Salim Susuz: Increased incidence of abnormal reflux flow in lower extremity veins of cirrhotic patients by Doppler ultrasonography. Saudi medical journal 2013, 34(3):276-281.

23. Wadlund DL: Local Anesthetic Systemic Toxicity. AORN journal 2017, 106(5):367-
24. El-Boghdady K, Chin KJ: **Local anesthetic systemic toxicity: Continuing Professional Development.** *Canadian journal of anaesthesia = Journal canadien d'anesthesie* 2016, **63**(3):330-349.

25. Rosenberg PHV, B. T. Urmey, W. F.: **Maximum recommended doses of local anesthetics: a multifactorial concept.** *Reg Anesth Pain Med* 2004, **29**(6):564-575; discussion 524.

26. Davies TW, S.O'Beirne, J.Martin, D.Gilbert-Kawai, E.: **Review article: the role of the microcirculation in liver cirrhosis.** *Alimentary pharmacology & therapeutics* 2017, **46**(9):825-835.

27. Li CPL, F. Y. Hwang, S. J. Lu, R. H., Lee WPC, Y.Wang, S. S.Chang, F. Y.Whang-Peng, J.Lee, S. D.: **Spider angiomas in patients with liver cirrhosis: role of vascular endothelial growth factor and basic fibroblast growth factor.** *World journal of gastroenterology* 2003, **9**(12):2832-2835.

28. Peeters G DC, Friebel A, Cornillie P, De Vos WH, Favere K, Vander Elst I, Vandecasteele T, Johann T, Van Hoorebeke L, Monbaliu D, Drasdo D, Hoehme S, Laleman W, Segers P: **Quantitative analysis of hepatic macro- and microvascular alterations during cirrhogenesis in the rat.** *Journal of anatomy* 2018, **232**(3):485-496.

29. McAvoy NCS, S.Richards, J. M.Robson, A. J.Patel, D. Jardine, A. G.Leyland, K.Cooper, A. S.Newby, D. E.Hayes, P. C.: **Differential visceral blood flow in the hyperdynamic circulation of patients with liver cirrhosis.** *Alimentary pharmacology & therapeutics* 2016, **43**(9):947-954.

30. Jin Y, Kaluza, D.Jakobsson, L.: **VEGF, Notch and TGFbeta/BMPs in regulation of sprouting angiogenesis and vascular patterning.** *Biochemical Society*
transactions 2014, 42(6):1576-1583.

31. Li P LY, Zhu L, et al: **Targeting secreted cytokine BMP9 gates the attenuation of hepatic fibrosis.** Biochimica et biophysica acta 2018, 1864(3):709-720.

32. Wang SH, Chen, P. J,Yeh, S. H.: **Gender disparity in chronic hepatitis B:** Mechanisms of sex hormones. Journal of gastroenterology and hepatology 2015, 30(8):1237-1245.

33. Ho HL LF, Hsu SJ, Wang SS, Hsin IF, Huang HC, Lee JY, Lin HC, Lee SD.: **The ability of 17 β-estradiol to attenuate intrahepatic vasoconstriction to endothelin-1 in female rats is lost in cirrhosis.** Annals of Hepatology 2015, 14(3):404-413.

Tables

**Table 1: Patients characteristics**

|                      | Group U | Group N | Group M | 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   |        |       |
| **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 ± 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 | Group N | Group M | 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) | 0.000329 |
| 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 ± SD. 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) | Signs 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        | 80†                 |
| U     | F   | 46     | 54          | 158         | Tongue numbness,Tinnitus | 8               | /         | 9                   |
| U     | F   | 53     | 54          | 160         | Tongue numbness,Left hand and leg twitch | 13/17          | M2,P200   | 8                   |
| U     | F   | 26     | 70          | 161         | Tongue numbness     | 18              | /         | 4                   |
| U     | F   | 41     | 50          | 156         | Unconsciousness,Tachycardia,Hyper tension | 8              | M2,P200   | 63†                 |
| U     | F   | 61     | 60          | 155         | Agitation           | 9               | /         | 3                   |
| U     | F   | 46     | 60          | 159         | Scream,Unconsciousness | 1              | M2        | 100†                |
| U     | F   | 32     | 51          | 160         | Tachycardia         | 7               | M2        | 25                  |
| U     | M   | 81     | 63          | 152         | Right hand twitch,Unconsciousness | 4/9            | D0.5,M2   | 15                  |
| U     | F   | 62     | 58          | 150         | Transient numbness of right hand and leg Twitch | 20              | /         | 4                   |
| U     | F   | 26     | 46          | 161         | Hypertension,Tachycardia,Agitation | 12             | M2        | 5                   |
| U     | F   | 47     | 60          | 145         | Tinnitus,Whole body numbness | 10             | M2        | 25                  |
| M     | F   | 37     | 48          | 153         | anxiety,Confusion   | 11              | M2        | 15                  |
| M     | M   | 21     | 64          | 163         | Tinnitus,Whole body numbness | 8              | M2        | 10                  |

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 0.5µg.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                     | 4(4)             |        |                 | 0.037(N vs U) |
| U                     | 12(12)           |        |                 | 0.006 (U vs M) |
| M                     | 2(2)             |        |                 | 0.407 (M vs N) |
| Needle passes (times) |                  |        |                 |          |
| 2-5                   | 11(5.1)          | 0.58   | 0.217-1.550     | 0.272    |
| 6-                    | 7(8.4)           | 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)          | 0.731  | 0.093-5.766     | 0.765    |

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

Figures
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.