ORIGINAL RESEARCH

Analgesic Effect and Safety of Lidocaine Liposome vs Oral Sucrose Water in Blood Collection and Intramuscular Injection in Neonates

Jing Liao, MD; Juan Fan, PhD; Mengni Li, MD

ABSTRACT

Objective • To compare the analgesic effect of oral sucrose water (Su) vs local application of lidocaine liposome (LC) in blood collection and intramuscular injection in neonates.

Methods • A total of 300 neonates admitted to Sichuan Provincial People's Hospital in China between June 2019 and December 2021 who were to receive intramuscular injection and heel blood collection were enrolled in the study. The neonates were assigned to one of the following groups (n = 30 in each): control, 30% Su, 25% Su, 24% Su, 12% Su, 8% Su, LC 15-min, LC 30-min, LC 45-min or the combination group. The groups received different concentrations of Su or the application of LC liposome at different timepoints and the control group was given no analgesia. Before and after puncture, the Neonatal Facial Coding System-Revised (NFCS-R) was used for pain evaluation in the neonates. The heart rate (HR), respiratory rate, blood oxygen saturation (SpO2) and blood pressure (BP) in each group were compared, and the starting and ending time of crying and latent crying time were recorded and analyzed. After the optimal concentration of Su and optimal application time of LC were understood, the combination group was used to evaluate the analgesic effect of Su combined with LC.

Results • Using various concentrations of Su, neonate pain was alleviated to varying degrees; 24%, 25%, and 30% Su did not reveal any difference in various investigation items, although their effect was superior to 8% and 12% Su. The LC 30-min and LC 45-min groups performed better than the LC 15-min group with regard to NFCS-R score, vital signs and BP. However, no notable difference was observed between the LC 15-min and LC 45-min groups in latent time. Moreover, the combination of 24% Su and application of LC 30 minutes before puncture provided a better analgesic effect than a single anesthesia intervention.

Conclusion • The combination of 24% Su and the application of LC 30 minutes before puncture delivered better analgesic effect than a single anesthesia intervention alone. (*Altern Ther Health Med.* 2023;29(1):156-162).

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INTRODUCTION

Neonates face a high risk of illness because of their poorly developed organs and tissues and low general resistance.[1] However, during the associated examination and treatment of neonatal illness, it is usually imperative to conduct puncture operations such as venous blood collection and intramuscular injection; thus, the management of neonatal pain requires attention. Neonates have more sensitive, diffuse, intense and lasting pain perception than adults, so pain has been defined as the fifth vital sign of neonates after breathing, heart rate (HR), blood pressure (BP) and body temperature.[2] As is well known, it is more difficult to perform a puncture in neonates than adults because of the narrow diameter of their veins.[3] Moreover, neonate's language ability has not yet developed, so they generally cry, are agitated and show resistance when they feel pain, which increases the difficulty of venipuncture and disrupts follow-up examination and treatment.[4]

According to studies, aggravation of neonate pain can give rise to changes in cerebral blood flow and oxygen content, triggering serious adverse events such as cerebral hypoxia, intracranial pressure increase, ventricular hemorrhage and leukomalacia.[5] In more severe cases, it can trigger permanent central nervous system damage, making

neonates prone to diseases including attention deficit-hyperactivity disorder (ADHD), depression and autism during the development process.[6] Puncture inevitably gives rise to pain, so finding ways to alleviate neonatal pain has become a vital and difficult focus of clinical research.

Analgesic drugs are usually used for pain relief in clinical practice, but in neonates with compromised metabolism ability, conventional analgesic drugs can be associated with serious toxic adverse events—even respiratory depression in severe cases—that are life-endangering.[7] Accordingly, in neonates, extremely safe oral sucrose solution (Su) with no notable analgesic effect is usually chosen for pain management.[8] Su is a sweetener that can activate the release of opioid peptides and thus suppress adenylate cyclase, regulate the flow of potassium and calcium ions and weaken the transmission of pain signals.[9]

However, oral administration of Su can hardly achieve the desired pain relief for invasive punctures. Lidocaine (LC) is an amide local anesthetic and also a membrane stabilizer that can block conduction of various nerve impulses by inhibiting the influx of sodium ions and blocking the generation of action potentials. Able to make local sensation and pain disappear during local application, it is an anesthetic with stable performance, quick effect and low toxicity that also has strong tissue permeability.[10]

Nevertheless, its rapid drug metabolism greatly hinders the clinical application of LC.[11] As medical technology advances, liposomes loaded with LC have been developed to address these delivery deficits. Liposome is a novel drug carrier similar to micro-capsules, which is considered an artificial cell membrane due to its similar structure to cells.[12] According to studies, liposome encapsulation can substantially prolong the drug metabolism cycle of LC and its anesthetic effect, and it has delivered excellent results in oral anesthesia.[13,14] Moreover, with stable drug safety, LC is of high potential application value for anesthesia and analgesia in neonates.[15]

Given the problems involved with clinical neonatal pain, this study aimed to evaluate pain in neonates due to receive heel blood collection and intramuscular injection by giving oral Su and pre-applying anesthetic drugs at the procedure site, with the goal of finding the best neonatal pain relief, improving neonate health and benefitting neonates and infants in society as a whole.

MATERIALS AND METHODS

Study Patients

A total of 300 neonates (gestational age 34 to 42 weeks) admitted to the Sichuan Provincial People's Hospital in China between June 2019 and December 2021 for hepatitis B vaccine intramuscular injection and heel blood draw to screen for hereditary metabolic diseases were enrolled in the study. This study was carried out with the approval of the hospital Ethics Committee of the hospital and informed consent forms were signed by the parents/guardians of all enrolled neonates. No notable difference was found among the patient groups in gestational age, weight or sex (all $P > .05$), suggesting comparability of all groups.

Inclusion criteria

Patients were (1) full-term infants with gestational age ≥37 weeks and <42 weeks, weight ≥2500 g and <4000 g and 5-minute Apgar score ≥8; (2) near-term infants with gestational age ≥34 weeks and <37 weeks, weight ≥2000 g but <2500 g and 5-minute Apgar score ≥7; (3) without nervous system or cardiovascular system disease; (4) neonates whose mothers did not use muscle relaxants, antidepressants, antiepileptic drugs or street drugs ≤1 week before delivery; (5) neonates whose mothers did not have gestational diabetes or hypertension; (6) neonates whose last breastfeeding was 1 to 1.5 hours before the procedure.

Exclusion criteria

Patients were neonates: (l) whose one-off heel blood collection was unsuccessful; (2) who had undergone surgery before blood collection; (3) who had received sedative or analgesic injections within 24 hours of pain stimulation; (4) with active diseases such as sepsis and respiratory distress syndrome; (5) who required antibiotic treatment; (6) whose mothers had an upper respiratory tract infection.

Preparation of LC Liposome

Vitamin E (30 mg), lecithin (2500 mg) and cholesterol (1000 mg) were accurately weighed and mixed with 200 mL dichloromethane, followed by rotary evaporation (45°C) to form a film. Subsequently, the film was added to 4 mg LC, 12 mg vitamin C, 40 mL phosphate buffer with pH 6.8 and 2 ml polysorbate-80, followed by 5 minutes of rotary evaporation (45°C) and 5-minute intermittent ultrasonic emulsification. The solvent was recovered by rotating the film and thus a gelatinous solid was formed, followed by the addition of PBS to adjust the total amount to 200 g to obtain the liposome. The indicated concentration of LC in the liposome was 20 mg/g.

Study Design

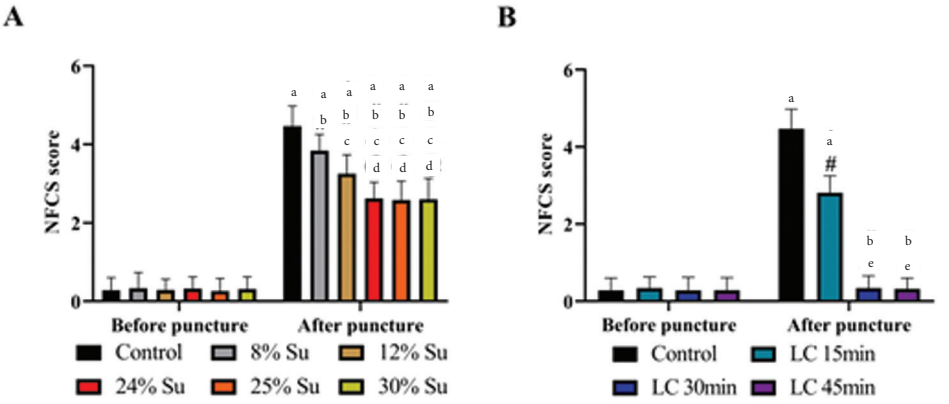
The neonates were numbered 1 to 300 based on their order of inclusion in the study. A third party (unrelated to the study) repeatedly selected 30 serial numbers as a group in a random manner, and labeled them as the control group, 30% Su group, 25% Su group, 24% Su group, 12% Su group, 8% Su group, LC 15-min group, LC 30-min group and LC 45-min group. The 9 groups (n = 30) were evaluated to find the optimal concentration of Su and the optimal use time of LC liposome for reducing pain levels in the neonates. Then, the remaining 30 neonates were identified as the combination group and treated with Su at the optimal concentration and LC liposome at the optimal use time.

Intervention

On the first day after delivery, the nurses took the neonates to the inoculation room for intramuscular injection,

and on the fourth day, the nurses facilitated heel blood collection in the neonates. Both intramuscular injection and heel blood collection were performed by blood collection doctors in the pediatric department under the same stimulation criteria. Different concentrations of Su water and LC liposome cream were prepared for the neonates after they were transferred to the inoculation room; the doors and windows were closed to keep indoor noise at a constant level. The power supply of the monitoring instrument was checked, and the connector of the monitor line was connected to the neonatal plantar artery pulse. The neonates in the groups were given different concentrations of Su water 2 minutes before intramuscular injection and heel blood collection; the LC liposome cream was applied at different times before the puncture in neonates in the LC groups. The control group was not given any analgesia. The whole process of injection and blood collection was recorded by video camera.

Figure 1. Comparison of NFCS-R scores. **1A**. The effect of Su on NFCS-R score. **1B**. The effect of LC on NFCS-R score.



[a]$P < .05$ NFCS-R score *vs* before puncture
[b]$P < .05$ NFCS-R score *vs* control group
[c]$P < .05$ NFCS-R score *vs* 8% Su group
[d]$P < .05$ NFCS-R score *vs* 12% Su group
[e]$P < .05$ NFCS-R score *vs* LC-15 min group

Evaluation Criteria

The Neonatal Facial Coding System-Revised (NFCS-R) was used for pain evaluation in the neonates. The NFCS covers 5 items including frowning, winking, deepening of nasolabial groove, horizontal extension of the mouth and cupped tongue. Each item is scored 1 (yes) or 0 (no) points, and the total score ranged from 0 to 5 points. A higher score indicated more severe pain.

Outcome Measures

The NFCS-R score, vital signs (including HR, respiratory rate, SpO2) and BP at 1 minute before puncture and 7 minutes after puncture were all recorded and evaluated. The duration of crying of each neonate (the time from the beginning to the end of crying during pain stimulation) was acquired by watching the video and recorded, and the latent time (from the time of receiving pain stimulation to the starting time of crying) was also acquired in the same manner and recorded.

Statistical Analyses

This study used IBM® SPSS 22.0 software for data processing. Counting data (n[%]) were compared between the groups via the chi-square test, and multigroup comparison of measurement data ($\bar{\chi} \pm s$) was carried out using the one-way ANOVA and least significant difference (LSD) post hoc test. $P < .05$ denoted a significant difference between groups.

RESULTS

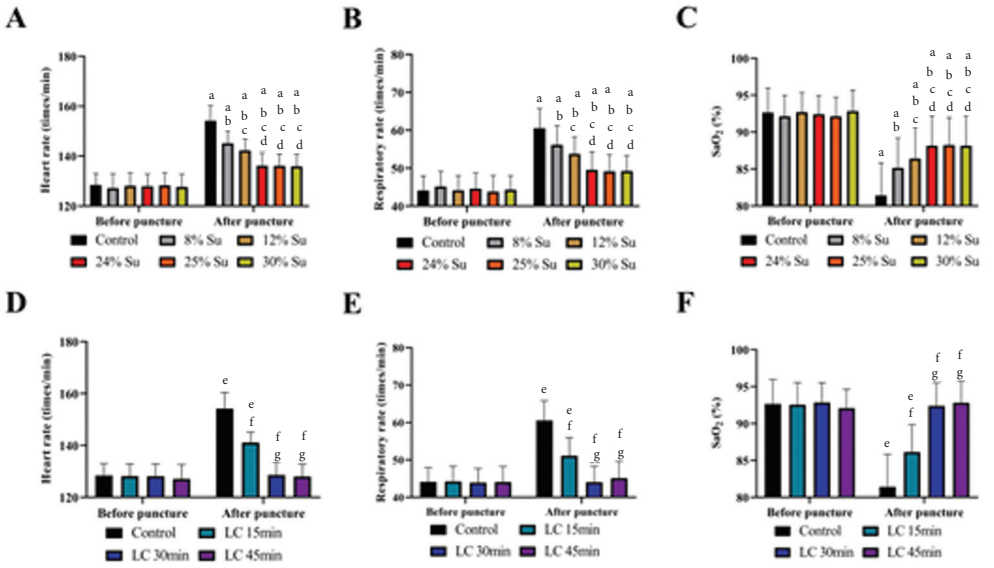
Comparison of NFCS-R Scores

Before puncture, no notable difference was observed among the 9 groups in NFCS-R scores (all $P > .05$). After puncture, scores in all groups except the LC 30-min group and LC 45-min group increased (all $P < .05$); the highest NFCS-R score were found in the control group ($P < .05$). Among the Su groups, the NFCS-R scores of the 25% Su, 24% Su and 30% Su groups showed no notable difference (all $P > .05$), and were lower than in the other Su groups (all $P < .05$); the NFCS-R scores in the 8% Su and 12% Su groups were similar (both $P > .05$) and higher (all $P < .05$). In the 3 groups treated with LC, the NFCS-R scores in the LC 30-min and LC 45-min groups were similar ($P > .05$), and were lower than in the LC 15-min group ($P < .05$; see Figure 1).

Comparison of Vital Signs

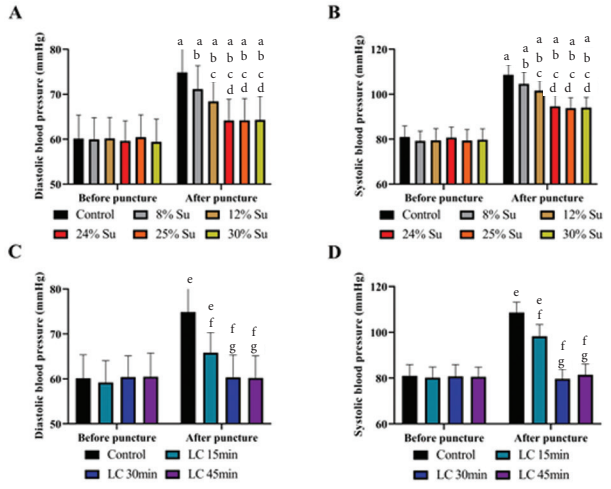
Before puncture, the vital signs in the 9 groups were similar (all $P > .05$). After puncture, the HR and respiratory rates in all groups except the LC 30-min and LC 45-min groups increased, with the highest rates being in the control group, while the SpO2 in each group except the LC 30-min and LC 45-min groups decreased, with the lowest rates in the control group ($P < .05$); vital signs in the 25% Su, 24% Su and 30% Su groups showed no notable difference (all $P > .05$), and the 12% Su group showed a higher HR and respiratory rate than the 25% Su, 24% Su and 30% Su groups and a lower HR and respiratory rate than the 8% Su group, as well as lower SpO2 than in the 25% Su, 24% Su and 30% Su groups and higher SpO2 than in the 8% Su group (see Figure 2A-2C). Among all groups treated with LC, the LC 30-min group and LC 45-min group presented similar HR, respiratory rate and SpO2 (all $P > .05$), and the HR and respiratory rate in the 2 groups were both lower than in the LC 15-min group; SpO2 in the 2 groups was higher than in the latter (all $P < .05$; see Figure 2D-2F).

Figure 2. Comparison of vital signs. **2A-2C.** The effect of Su on vital signs. **2D-2F.** The effect of LC on vital signs



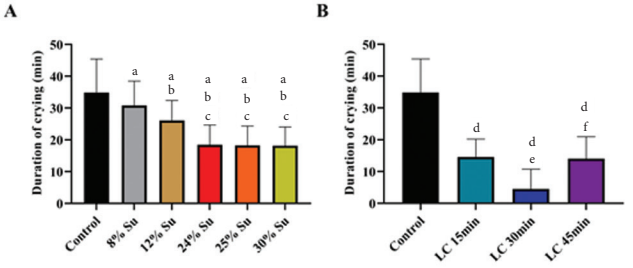
[a]$P < .05$ effect of Su on vital signs *vs* before puncture
[b]$P < .05$ effect of Su on vital signs *vs* control group
[c]$P < .05$ effect of Su on vital signs *vs* 8% Su group
[d]$P < .05$ effect of Su on vital signs *vs* 12% Su group
[e]$P < .05$ effect of LC on vital signs *vs* before puncture
[f]$P < .05$ effect of LC on vital signs *vs* control group
[g]$P < .05$ effect of LC on vital signs *vs* LC-15min group

Figure 3. Comparison of BP **3A**, **3B**. The effect of Su on BP. **3C**, **3D** The effect of LC on BP.



[a]$P < .05$ effect of Su on BP *vs* before puncture
[b]$P < .05$ effect of Su on BP *vs* control group
[c]$P < .05$ effect of Su on BP *vs* 8% Su group
[d]$P < .05$ effect of Su on BP *vs* 12% Su group
[e]$P < .05$ effect of LC on BP *vs* before puncture
[f]$P < .05$ effect of LC on BP *vs* control group
[g]$P < .05$ effect of LC on BP *vs* LC-15min group

Figure 4. Comparison of crying duration. **4A** The effect of Su on crying duration. **4B** The effect of LC on crying duration.



[a]$P < .05$ effect of Su on crying duration *vs* the control group
[b]$P < .05$ effect of Su on crying duration *vs* 8% Su group
[c]$P < .05$ effect of Su on crying duration *vs* 12% Su group
[d]$P < .05$ effect of LC on crying duration *vs* the control group
[e]$P < .05$ effect of LC on crying duration *vs* LC-15min group
[f]$P < .05$ effect of LC on crying duration *vs* LC-30min group

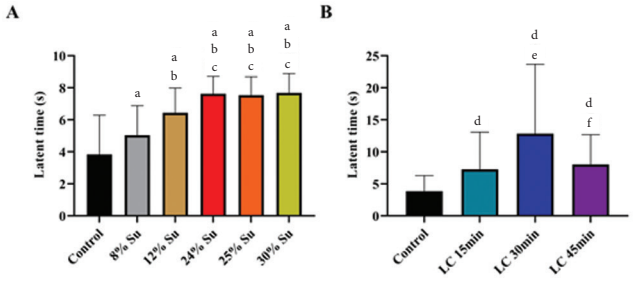
Comparison of BP

Before puncture, no notable difference was observed among the 9 groups (all $P > .05$). After puncture, the BP in each group except for the LC 30-min and LC 45-min groups increased, with the highest in the control group (all $P > .05$). Among the groups treated with Su, the BP in the 25% Su, 24% Su and 30% Su groups was similar (all $P > .05$), while the BP in the 12% Su group was higher than in the 8% Su group and lower than in the 25% Su, 24% Su and 30% Su groups (all $P < .05$; see Figure 3A, 3B). Among the groups treated with LC, BP in the LC 30-min and LC 45-min groups was similar ($P > .05$), and lower than in the LC 15-min group ($P < .05$; see Figure 3C, 3D).

Comparison of Crying Duration

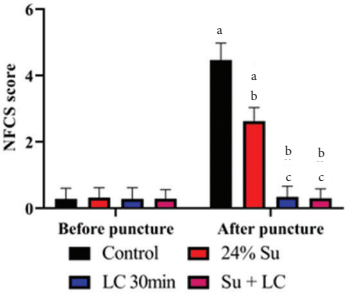
The longest crying duration was found in the control group ($P < .05$). Among the groups treated with Su, crying duration in the 25% Su, 24% Su and 30% Su groups was similar (all $P > .05$), while the crying duration in the 12% Su group was shorter than in the 8% Su group and longer than in the 25% Su, 24% Su and 30% Su groups (all $P < .05$; see Figure 4A). Among the groups treated with LC, the crying duration in the LC 15-min and LC 45-min groups was similar ($P > .05$), and longer than in the LC 30-min group ($P < .05$; see Figure 4B).

Figure 5. Comparison of latent time. **5A.** The effect of Su. **5B**. The effect of LC on latent time.



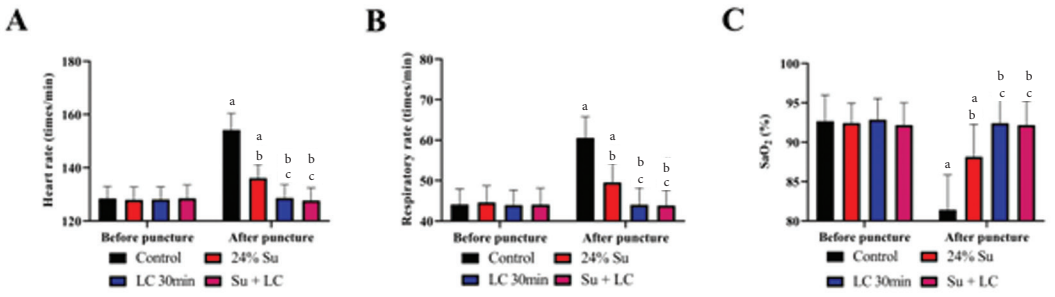
[a]$P < .05$ effect of Su on latent time *vs* the control group
[b]$P < .05$ effect of Su on latent time *vs* 8% Su group
[c]$P < .05$ effect of Su on latent time *vs* 12% Su group
#$P < .05$ effect of LC on latent time *vs* the control group
[e]$P < .05$ effect of LC on latent time *vs* LC-15min group
[f]$P < .05$ effect of LC on latent time *vs* LC-30min group

Figure 6. Influences of SU combined with LC on NFCS-R score.



[a]$P < .05$ NFCS-R score *vs* before puncture
[b]$P < .05$ NFCS-R score *vs* control group
[c]$P < .05$ NFCS-R score *vs* 24% Su group

Figure 7. Influences of Su combined with LC on vital signs.



[a]$P < .05$ before puncture
[b]$P < .05$ control group
[c]$P < .05$ Su group

Comparison of Latent Time

The shortest latent time was found in the control group ($P < .05$). Among the groups treated with Su, the latent time in the 25% Su, 24% Su and 30% Su groups was similar (all $P > .05$), while the latent time in the 12% Su group was longer than in the 8% Su group but shorter than in the 25% Su, 24% Su and 30% Su groups (all $P < .05$; see Figure 5A). Among the groups treated with LC, the latent time in the LC 15-min and LC 45-min groups was similar ($P > .05$), and shorter than in the LC 30-min group ($P < .05$; see Figure 5B).

SU Combined with LC: NFCS-R Score

The combination group was treated with 24% Su and application of LC at 30 minutes before puncture and compared with the control group, 24% Su and LC 30-min groups. No notable difference was observed among the 4 groups in NFCS-R score before puncture (all $P > .05$), while after puncture, the scores in the combination and LC 30-min groups were similar (both $P > .05$), which were lower than in the 24% Su and control groups (both $P < .05$) (see Figure 6).

Su Combined with LC: Vital Signs

Before puncture, no notable difference was observed among the 4 groups with regard to vital signs ($P > .05$). After puncture, both HR and respiratory rate in the combination and LC 30-min groups were similar (both $P > .05$), and lower than in the 24% Su and control groups (both $P < .05$); the SpO2 in the 2 groups was higher than in the 24% Su and control groups ($P < .05$; Figure 7).

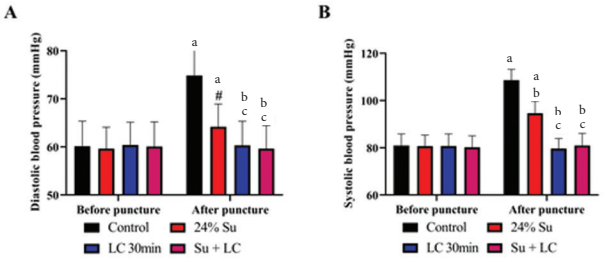
Su Combined with LC: BP

Before puncture, no notable difference was observed among the 4 groups in BP ($P > .05$). After puncture, BP in the combination and LC 30-min groups was similar (both $P > .05$), and lower than in the 24% Su and control groups (both $P < .05$) (see Figure 8).

Su Combined with LC: Crying Duration

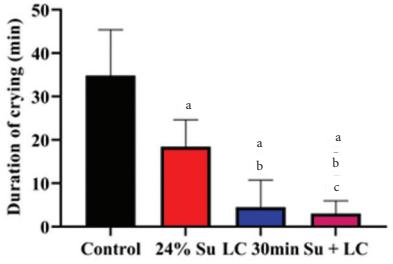
The shortest and longest crying duration was found in the combination and control groups, respectively. The LC 30-min group experienced shorter crying duration than the 24% Su group ($P < .05$; see Figure 9).

Figure 8. Influence of Su combined with LC on BP



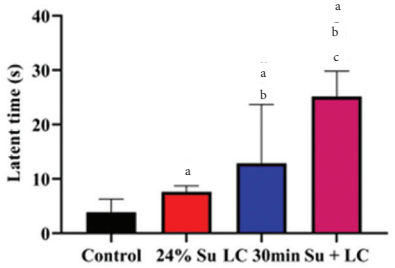
[a]$P < .05$ before puncture
[b]$P < .05$ control group
[c]$P < .05$ 24% Su group

Figure 9. Influence of Su combined with LC on crying duration.



[a]$P < .05$ control group
[b]$P < .05$ 24% Su group
[c]$P < .05$ LC 30min

Figure 10. Influence of Su combined with LC on latent time.



[a]$P < .05$ control group
[b]$P < .05$ 24% Su group
[c]$P < .05$ LC 30min

Su Combined with LC: Latent Time

The longest and shortest latent time were found in the combination and control groups, respectively, and the LC 30-min group experienced longer latent time than the 24% Su group ($P < .05$; see Figure 10).

DISCUSSION

Neonatal pain is a hot topic in modern clinical research, with crucial significance in the normal growth and development of neonates. In the short term, pain can shunt blood from the foramen ovale, resulting in changes in cerebral blood flow and oxygen content, which in turn give rise to intraventricular hemorrhage, prolong foramen ovale closure and aggravate foramen ovale shunt in what can result in a vicious cycle.[16]

Moreover, persistent brain hypoxia will trigger an increase in intracranial pressure, intraventricular hemorrhage and cerebral white matter softening, and repeated stimulation will make peripheral receptors sensitive and produce a pain response even with pain-free stimulation.[17] In the long term, pain can harm the developing neonate central nervous system, and make individuals less sensitive to pain in adolescence and more sensitive to pain in adulthood.[18] The pain experience in the neonatal period is likely to induce psychological and behavioral dysfunction such as emotional problems, hyperactivity disorder and social defects, compromising an individual's future growth and life and laying the groundwork for social instability.[19]

Accordingly, it is urgent that the best management of and intervention in neonatal pain be determined. As an inevitable issue in pediatric wards, pain is the most important of all topics, and disputes between doctors and patients caused by pain can be seen everywhere, especially with regard to neonatal pain.[20] Moreover, the number of neonates has increased sharply in China, an already populous country, following the implementation of the second and third child policies, which also pose a great burden on and challenge to medical resources.

Clinical analgesia for neonates mainly includes non-drug-induced and drug-induced analgesia. The former includes breastfeeding, non-nutritional suck, oral Su, and music therapy, which are safe, but not as effective as anesthesia, and the mechanism involved is primarily diverting the neonate's attention from the pain.[21] Drug-induced analgesia involves opioid drugs, non-steroidal analgesics and antidepressants, with the advantage that they can directly produce a stable anesthetic effect and completely block the transmission of pain. However, in neonates, due to immature glucuronidation function of the liver, the limited ability of th kidneys to remove metabolites, obvious competition with bilirubin for albumin and influence on platelet aggregation function, drug analgesia generally brings with it significant toxic adverse events, ranging from a series of complications to life-threatening functional failure.[22,23]

LC liposome is a relatively novel topical local anesthetic, which has been recognized I China and abroad for its anesthetic and analgesic efficacy,[24,25] but the advantages and disadvantages of using LC liposome alone and in combination with Su are rarely reported. Thus, this study sought provides a more realistic environment and objective and reliable basis for future clinical pain management, with investigation into the influence of LC and Su on neonatal pain.

At the present time, there is a lack of related research on the combined application of Su and LC, so we needed first to determine the optimum dosage and timing of the combined application of Su and LC. The common concentrations of Su in clinic practice include 8%, 12%, 24%, 25% and 30%, so we used

Su at those concentrations to intervene in neonates for assay. As a result, with the intervention of various concentrations of Su, neonatal pain was alleviated to varying degrees. Among these concentrations, 24%, 25%, and 30% Su did not result in any difference in various investigation items (all $P > .05$); however, their effect was better than with 8% and 12% Su (all $P < .05$). According to meta-analysis on the effective analgesic concentration of Su by Bradshaw, et al., the effective analgesic concentration of Su was approximately 24%.[26]

In a similar fashion, when the Su concentration reached 24%, inhibition of neonatal pain did not change significantly. However, given that frequent use of high-concentration sweeteners may trigger adverse diseases such as an increase in neonatal blood sugar and necrotizing colitis, and since most of the previous studies used 24% as the Su concentration,[27,28] we also used 24% as the optimal Su concentration.

As for LC liposome, we applied this on neonates 15, 30 or 45 minutes before puncture. Our findings showed that the LC 30-min and LC 45-min groups showed better results than the LC 15-min group in NFCS score, vital signs and BP. However, no notable difference was found between the LC 15-min and LC 45-min groups in latent time, which indicated the optimal action time of LC might be 30 min before puncture. When LC liposome was applied 15 minutes before puncture, it did not fully exert its anesthetic effect during puncture, and neonatal pain was obvious at that time. At the end of puncture, the anesthetic effect of LC began to take effect, so that neonatal pain gradually disappeared, and the crying time after puncture was significantly reduced.

However, in the LC 45-min group, due to the long anesthesia time, despite the excellent analgesic effect during puncture, neonates began to feel obvious pain with the gradual disappearance of the anesthetic effect. Therefore, crying duration and latent time showed a relatively consistent state. We found that 30 minutes before puncture is the optimal time to apply LC. Application of LC at that time was able to effectively relieve pain before and after puncture, so we used it as the optimal time for application.

Based on the above findings, we used 24% Su in combination with application of LC at 30 minutes before puncture in the combination group. As a result, the analgesic effect was better than that of a single anesthesia intervention, which suggested that LC liposome combined with Su could effectively achieve puncture analgesia in neonates, keep their vital signs stable and facilitating the implementation of invasive stimulation.

Study Limitations

This study had many limitations. For instance, the temperature, sound, needle penetration depth, strength, and duration of the procedure by the inoculation clinician may have an influence on neonatal pain, and the number of patients in this study is small, so the representativeness of the results needs to be improved. In addition, the enrolled neonates needed to be followed up for a longer period of time to more extensively evaluate the influence of the use of LC combined with Su on the lives of neonates after discharge from hospital.

Therefore, we will conduct more in-depth and comprehensive research to address the above limitations and explore the application of LC and Su in neonatal analgesia to obtain better results for clinical reference.

CONCLUSION

Oral administration of 24% Su and the application of lidocaine liposome 30 minutes before puncture can effectively relieve puncture pain and ensure the stability of vital signs in neonates, and has great prospects for clinical application.

AUTHOR CONTRIBUTIONS

Juan Fan and Jing Liao contributed equally to this work and are co-first authors.

REFERENCES

1. Yap V, Perlman JM. Mechanisms of brain injury in newborn infants associated with the fetal inflammatory response syndrome. *Semin Fetal Neonatal Med*. 2020;25(4):101110. doi:10.1016/j.siny.2020.101110
2. Maxwell LG, Fraga MV, Malavolta CP. Assessment of pain in the newborn: an update. *Clin Perinatol*. 2019;46(4):693-707. doi:10.1016/j.clp.2019.08.005
3. Field T. Preterm newborn pain research review. *Infant Behav Dev*. 2017;49:141-150. doi:10.1016/j.infbeh.2017.09.002
4. Perry M, Tan Z, Chen J, Weidig T, Xu W, Cong XS. Neonatal Pain: Perceptions and Current Practice. *Crit Care Nurs Clin North Am*. 2018;30(4):549-561. doi:10.1016/j.cnc.2018.07.013
5. Beltramini A, Milojevic K, Pateron D. Pain assessment in newborns, infants, and children. *Pediatr Ann*. 2017;46(10):e387-e395. doi:10.3928/19382359-20170921-03
6. Seixas Silva AM. [Pain in the newborn: a challenge for nursing practice]. *Servir*. 2013;58(1-2):40-46.
7. Montaldo P, Vakharia A, Ivain P, et al. Pre-emptive opioid sedation during therapeutic hypothermia. *Arch Dis Child Fetal Neonatal Ed*. 2020;105(1):108-109. doi:10.1136/archdischild-2019-317050
8. Stevens B, Yamada J, Ohlsson A, Haliburton S, Shorkey A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev*. 2016;7(2):CD001069. doi:10.1002/14651858.CD001069.pub5
9. Alberice RMC, Silva S, Leite ACC, Manzo BF, Simao D, Marcatto JO. Assessment of newborn pain during arterial puncture: an observational analytical study. Rev Bras Ter Intensiva. Sep 24 2021. S0103-507X2021005002206. [Online ahead of print] doi:10.5935/0103-507X.20210058
10. Berk T, Silberstein SD. The use and method of action of intravenous lidocaine and its metabolite in headache disorders. *Headache*. 2018;58(5):783-789. doi:10.1111/head.13298
11. Herminghaus A, Wachowiak M, Wilhelm W, Gottschalk A, Eggert K, Gottschalk A. [Intravenous administration of lidocaine for perioperative analgesia. Review and recommendations for practical usage]. *Anaesthesist*. 2011;60(2):152-160. doi:10.1007/s00101-010-1829-0
12. Kharitonov V. A review of the compatibility of liposome bupivacaine with other drug products and commonly used implant materials. *Postgrad Med*. 2014;126(1):129-138. doi:10.3810/pgm.2014.01.2733
13. Franz-Montan M, Baroni D, Brunetto G, et al. Liposomal lidocaine gel for topical use at the oral mucosa: characterization, in vitro assays and in vivo anesthetic efficacy in humans. *J Liposome Res*. 2015;25(1):11-19. doi:10.3109/08982104.201.911315
14. Omar MM, Hasan OA, El Sisi AM. Preparation and optimization of lidocaine transferosomal gel containing permeation enhancers: a promising approach for enhancement of skin permeation. *Int J Nanomedicine*. 2019;14:1551-1562. doi:10.2147/IJN.S201356
15. Duncan SM, Massicotte MP, Ray L, Kuhle S, Bauman ME. Topical lidocaine and the effect on enoxaparin absorption in children: a pilot study. *Thromb Res*. 2010;125(1):e1-e4. doi:10.1016/j.thromres.2009.08.003
16. Cignacco E. [Pain assessment in newborn infants--a review of the literature]. *Pflege*. 2001;14(3):171-181. doi:10.1024/1012-5302.14.3.171
17. Olsson E, Ahl H, Bengtsson K, et al. The use and reporting of neonatal pain scales: a systematic review of randomized trials. *Pain*. 2021;162(2):353-360. doi:10.1097/j.pain.0000000000002046
18. Cong X, McGrath JM, Cusson RM, Zhang D. Pain assessment and measurement in neonates: an updated review. *Adv Neonatal Care*. 2013;13(6):379-395. doi:10.1097/ANC.0b013e3182a41452
19. Chen H, da Palma Afonso E, Zhou J. Newborns' voice: we need pain management! *Intensive Crit Care Nurs*. 2021;62:102976. doi:10.1016/j.iccn.2020.102976
20. Bellieni CV, Stazzoni G, Tei M, et al. How painful is a heelprick or a venipuncture in a newborn? *J Matern Fetal Neonatal Med*. 2016;29(2):202-206. doi:10.3109/14767058.2014.992334
21. Craft RM. Sex differences in drug- and non-drug-induced analgesia. *Life Sci*. 2003;72(24):2675-2688. doi:10.1016/S0024-3205(03)00178-4
22. Romanowicz M, Vande Voort JL, Shekunov J, et al. The effects of parental opioid use on the parent-child relationship and children's developmental and behavioral outcomes: a systematic review of published reports. *Child Adolesc Psychiatry Ment Health*. 2019;13(1):5. doi:10.1186/s13034-019-0266-3
23. Van Eyken P, Nemolato S, Faa G, Ambu R. Hepatic injury to the newborn liver due to drugs. *Curr Pharm Des*. 2012;18(21):3050-3060. doi:10.2174/1381612811209023050
24. Taddio A, Soin HK, Schuh S, Koren G, Scolnik D. Liposomal lidocaine to improve procedural success rates and reduce procedural pain among children: a randomized controlled trial. *CMAJ*. 2005;172(13):1691-1695. doi:10.1503/cmaj.045316
25. Wang J, Zhang L, Chi H, Wang S. An alternative choice of lidocaine-loaded liposomes: lidocaine-loaded lipid-polymer hybrid nanoparticles for local anesthetic therapy. *Drug Deliv*. 2016;23(4):1254-1260. doi:10.3109/10717544.201.1141259
26. Bradshaw CM. Effects of sucrose concentration on choice in an adjusting-magnitude schedule. *Behav Processes*. 2018;157:562-569. doi:10.1016/j.beproc.2018.04.017
27. Stevens B, Yamada J, Lee GY, Ohlsson A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst Rev*. 2013;(1):CD001069.
28. Stevens B, Yamada J, Campbell-Yeo M, et al. The minimally effective dose of sucrose for procedural pain relief in neonates: a randomized controlled trial. *BMC Pediatr*. 2018;18(1):85. doi:10.1186/s12887-018-1026-x