# CLINICAL STUDY REPORT

A Prospective, Single-Center, Open Clinical Study to Evaluate Blood Collection Efficacy and Safety of Laser Blood Collection Device LMT-5000 in Newborns and Neonates.

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| **Clinical Site** | **:** | Gachon Unviersity Gil Medical Center |
| **Principal Investigator** | **:** | Choi Chang-hyu, professor of Thoracic and Cardiovascular Surgery |
| **Sponser** | **:** | LAMEDITECH, Inc. |

## SUMMARY

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| Title of Study | A prospective, single-center, open clinical study to evaluate blood collection efficacy and safety of laser blood collection device LMT-5000 in newborns |
| Protocol No. | LMT-01 |
| Sponser | LAMEDITECH, Inc.<br>#1002, ACE HighEnd Tower6th, 234, Beotkkot-ro, Geumcheon-gu, Seoul, South Korea |
| Clinical Site | Gachon Unviersity Gil Medical Center<br>21, Namdong-daero 774 beon-gil, Namdong-gu, Incheon, 21565, South Korea |
| Investigator(s) | 1. Principal Investigator<br>Department of Thoracic and Cardiovascular Surgery at Gachon Unviersity Gil Medical Center<br>Associate Professor Choi Chang-hyu, M.D., Ph.D.<br>2. Coordinating Investigator<br>Department of Pediatrics at Gachon Unviersity Gil Medical Center<br>Associate professor Cho Hye-jung, M.D.<br>3. Clinical Research Coordinator<br>Medical Device convergence Center of Gachon Unviersity Gil Medical Center<br>Clinical Research Coordinator Seo Bo-mi, Park Bo-young<br>4. Independent Evaluator<br>Department of Pediatrics at Gachon Unviersity Gil Medical Center<br>Professor Son Dong-woo, M.D., Ph.D.<br>* The work of the medical device manager was delegated by the investigational product manager. |
| Indication studied | Subjects who were admitted to the neonatal intensive care unit and required blood collection at least four times |
| Study Period | August 27, 2019 to August 31, 2020 |
| Statistician | Ko Kwang-pil / Gachon University |
| Author(s) of the report | Cho Hye-jung / Pediatrics<br>Yoon Ji-won / Gachon Medical Device Convergence Center |

This study was conducted in compliance with related laws such as the Bioethics and Safety Act, the Pharmaceutical Affairs Act, and the standards for investigational devices and the protocol approved by the Institutional Review Board (IRB).

## · SYNOPSIS

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| Title of study | A prospective, single-center, open clinical study to evaluate blood collection efficacy and safety of laser blood collection device LMT-5000 in newborns |
| Type | Prospective study |
| Clinical site | Gachon Unviersity Gil Medical Center |
| Investigational Device | Product name: LMT-5000<br>Item name: Medical device for examination for blood collection or transfusion<br>Manufacturer: LAMEDITECH, Inc. |
| Objectives | The objective of this study was to verify the efficacy and safety of blood collection by comparing and evaluating the laser blood collection device LMT-5000 with the conventional manual needle lancet in newborns who require blood collection. |
| Design | A prospective, single-center, open study |
| Number of Subjects | Number of Subjects Planned: 20 subjects<br>- Basis of calculation<br>According to the results of pilot studies using the laser blood collection device, LMT-5000, (A single center, matched pairs, exploratory clinical trial study to verify effect of blood collecting in capillary vessel with the LMT-3000 and blood collection needles. A single center, matched pairs, KFDA approval post marketing clinical trial study to verify effect of NRS in capillary vessel with the LMT-3000 and blood collection needles) as the success rate of blood collection between the LMT-5000 and needle lancets was 100% with no difference, this study was intended to proceed explorative and descriptive. 40 cases per group, a total of 80 cases, conducted in the pilot study were recruited equally, and in this study, 20 subjects were recruited to make 4 groups per person. |
| Selection of Study Population | **1. Inclusion Criteria**<br>1) Subjects who were admitted to the neonatal intensive care unit and required blood collection at least four times<br>2) Subjects who could collect blood from the heel<br>3) In the case that guardians voluntarily decided to participate and agreed in writing with hearing sufficient explanation of the purpose, method, and effect of this clinical study<br><br>**2. Exclusion Criteria**<br>1) Subjects with hemostatic disorder |

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| | 2) Subjects who had received painkillers or administration within 48 hours prior to blood collection<br>3) Patients who had undergone surgery within a week or had other diseases that cause pain enough to interfere with this clinical study, such as intraventricular hemorrhage, pneumothorax, and necrotizing enterocolitis in the judgment of the researcher<br>4) If it is deemed inappropriate to participate in this clinical trial according to the judgment of other researchers |
| Methodology | **1. Screening (on days -14 to 1)**<br>*1)* Obtain parental consent<br>*2)* Check inclusion or exclusion criteria<br>*3)* Confirmation of drug use history<br><br>**2. Application of Investigational Device for Clinical Study (on days 1 to 10)**<br>*1)* Blood collection (use LMT-5000, lancet twice each)<br>*2)* Video recording during blood collection<br>*3)* Check whether blood collection is successful after each blood collection<br>*4)* Neonatal Infant Pain Scale (NIPS) measurement before and after each blood collection<br>*5)* Record the number of blood collection attempts for each blood collection<br>*6)* Check for adverse events<br>*7)* Confirmation of concomitant drugs<br><br>* The period of application of the investigational device can be up to 10 days. If blood collection is completed all four times before this, follow-up was conducted one day after completion date.<br><br>**<u>NIPS (Neonatal Infant Pain Scale)</u>**<br>It is a method to score the pain that a newborn feels by observing behavioral responses such as facial expressions, crying, and breathing patterns. Scores were given for a total of seven items and summed to calculate the total score, which ranged from 0 to 9. The total score of 0-2 was considered as painless, 3-4 as mild to moderate pain, and 5 or higher as severe pain. The NIPS evaluation was conducted before and after each blood collection. Before the blood collection, the NIPS scores were evaluated without any irritation to the subject, and immediately after the blood collection, the NIPS scores were evaluated for the facial expressions, etc. of the subject changed by the blood collection. |

| Variable | 0 | 1 |
|---|---|---|
| Facial expression | Relaxed facial muscles<br>Netural expression | Tight facial muscles<br>Furrowed braw, chin, jaw |
| Cry | Quiet<br>Not crying | Mild moaning<br>Intermittent |
| Breathing pattern | Relaxed | Change in breathing:<br>irregular, faster than usual,<br>gagging, breath holding |
| Arms and Legs | Relaxed<br>No muscle rigidity<br>Occasional random<br>movements of arms and legs | Flexed/Extended<br>Tense<br>Straight arms and legs<br>Rigid or rapid extension,<br>flexion |
| State of Arousal | Sleeping/Awake<br>Quiet/peaceful | Fussy<br>Alert<br>thrashing |
| Heart Rate | Within 10% of baseline | 11-20% of baseline |
| $O_2$ Saturation | No additional $O_2$ needed to<br>maintain $O_2$ saturation | Additional $O_2$ required to<br>maintain $O_2$ saturation |

*Modified from: Lawrence J, Alcock D, McGrath P, Kay J, MacMurray SB, Dulberg C. The development of a tool to assess neonatal pain. Neonatal Netw. 1993;12(6):59-66*

**Video Recording During Blood Collection**

During blood collection using the investigational device, video recording was taken for evaluation of an independent evaluator. Video recording was started at the time of sterilizing the blood collection spot immediately before blood collection, the blood collection was carried out using the investigational device, and recording was finished at the time of fixing the tourniquet.

For smooth NIPS evaluation, it was necessary to take a full-body recording. Thus, the camera was fixed in a position where the facial expression and arm and leg movements of the subject were clearly visible. The video recording time per blood collection was about three minutes, and the recording was done with

Gopro Hero 5 black.

**Blood Collection Officer and Independent Evaluator**

1) Blood collection officer

For consistent blood collection, one of the participating researchers was designated as the person in charge of blood collection, and the blood collection had to be conducted only by the blood collection officer. In this study, the blood collection officer was Cho Hye-jung, an associate professor of pediatrics. The blood collection officer conducted blood collection using the investigational device and evaluated heart rate and oxygen saturation among NIPS evaluation items before and after blood collection.

2) Independent evaluator

The independent evaluator did not participate in this study and checked the video of blood collection and evaluated facial expressions, cry, breathing patterns, arm and leg movements, and arousal state among the NIPS evaluation items. The independent evaluator was Son Dong-woo, a professor of pediatrics.

**3. Follow-up (on day 11/1 day after blood collection was completed)**

*1)* Check for adverse events

**4. Methods**

Prior to screening, among patients who were admitted to the neonatal intensive care unit and needed blood collection at least four times, voluntary written consent was obtained after fully explaining the study to the guardians of the patients suitable for this study. Through screening, subjects who met the selection/exclusion criteria were enrolled in the study. Blood collection was carried out from the right or left heel and was applied in the order of investigational device-control device-investigational device-control device.

The blood collection was performed when an ABGA (Arterial Blood gas assay) test is required, and if not, the blood collection was not carried out.

- Investigational device: LMT-5000, Control device: Lancet

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| | When using LMT-5000: After sterilizing the blood collection spot, put single-use cap on the main body of the device, and set the laser step in Level 3 to irradiate the blood collection spot to take a sample.<br>When using a lancet: After sterilizing the blood collection spot, use the sterilized lancet to puncture the blood collection spot and take a sample.<br><br>After participating in the study, the subjects conducted the study for a maximum of 11 days. |
| Criteria and method for evaluation | **1. Endpoints**<br>(1) Primary endpoint:<br>Difference in the success rate of blood collection by group<br><br>(2) Secondary endpoint:<br>- Difference in NIPS scores before and after blood collection by group<br>- Difference in the number of blood collection attempts by group<br><br>**2. Safety**<br>- Adverse events and serious adverse events |
| Statistical methods | **1. Endpoints Analysis**<br>For the difference in the success rate of blood collection by group, the primary endpoint, the number and ratio of patients were presented by group, and the statistical significance of the difference between groups was tested with the Chi-square test or Fisher's exact test.<br><br>For the difference in NIPS scores before and after blood collection by group, which was the secondary endpoint, the number of subjects and cases, the mean, the standard deviation, the median, the minimum value, and the maximum value were presented as descriptive statistics for each group. In addition, the statistical significance of the comparison of NIPS difference values before and after the blood collection between groups was tested with Independent two-sample t-test or Wilcoxon Frank sum test.<br><br>For the difference in the number of blood collection attempts by group, which was the secondary endpoint, the number of subjects and cases, the mean, the standard deviation, the median, the minimum value, and the maximum value were presented as descriptive statistics for each group. |

**2. Safety Analysis**

Adverse events were classified according to the MedDRA and summarized in 'system organ class' and 'preferred term.' Adverse events, adverse device effects, and serious AE were presented as frequency (ratio) and number of subjects, summarized as severity and causal relationship. List of subjects who had been dropped out due to adverse events or serious adverse events is listed.

Efficacy Results

**Primary endpoint**

· Difference in success rate of blood collection by group

| | | Lancet | |
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| | | Success | Failure |
| LMT-5000 | Success | 40 | 0 |
| | Failure | 0 | 0 |

The blood collection conducted 40 times for each device showed 100% success rate for both devices, and it was found that there was no difference since both devices had the same success rate. Accordingly, it was confirmed that the investigational device is non-inferior to the control device, and this means that the newborn heel puncture method using the investigational device is as useful as the lancet puncture method, which is a conventional blood collection method.

**Secondary endpoint**

· Difference of NIPS score before and after blood collection by group

① NIPS (after) – NIPS (before)

② NIPS (immediately after_ independent evaluator) – NIPS (immediately before _ independent evaluator)

Full comparison between LMT-5000 and lancet, n=40 pairs

| | Mean | Minimum value | Maximum value | IQR |
|---|---|---|---|---|
| LMT-5000 NIPS difference | 0 | 0 | 3 | 0-0 |
| Lancet NIPS difference | 1 | 0 | 7 | 0-3 |

In comparison of the change in pain scale before and after blood collection in the total 40 cases, as the investigational device had a median value of 0 (IQR 0-0)

<table>
<tr><td></td><td>and the control device had a median value of 1 (IQR 0-3), the increase in pain scale of the investigational device was statistically and significantly small compared to the control device (P=0.0002). This means that the puncture using the investigational device causes less pain than the control device, which can be seen that the investigational device has the effect of alleviating pain compared to the control device.<br><br>· Difference in the number of blood collection attempts by group<br><br>Full comparison between LMT-5000 and lancet, n=40 pairs<br><br>
<table>
<tr><th></th><th>Median value</th><th>Minimum value</th><th>Maximum value</th><th>IQR</th></tr>
<tr><td>LMT-5000 blood collection attempts</td><td>1</td><td>1</td><td>3</td><td>1-2</td></tr>
<tr><td>Lancet NIPS blood collection attempts</td><td>1</td><td>1</td><td>2</td><td>1-1μ</td></tr>
</table>
<br>To sum up, comparing the total 40 cases, the median of the number of blood collections using the investigational device and the control device was the same as 1, but statistically, it was analyzed that the number of blood collections using the control device was low (P=0.001).</td></tr>
<tr><td>Safety Results</td><td>As an adverse event, one subject showed intermittent convulsions (clonus) after blood collection with an investigational device and a control device. However, it was confirmed that it was not convulsions through follow-up, and there was no causal relationship with the use of the device. Therefore, no action was taken against the investigational device, and no adverse events were reported after follow-up.</td></tr>
<tr><td>Conclusion</td><td>Blood collections using the investigational device and the control device were successful in all 80 cases. In order to exclude the effects of pain occurring in the skin sterilization step and repeated puncture attempts during the blood collection, the difference between the pain scales (NIPS) before and after the blood collection was analyzed only by the difference between the NIPS measured immediately before and after the first blood collection. As the result, the difference in NIPS before and after blood collection was significantly smaller in</td></tr>
</table>

blood collection using the LMT-5000 device compared to the lancet. This suggests that neonatal heel blood collection using LMT-5000 is as useful as a lancet, and the pain that occurs during blood collection is less than that of a lancet. In other words, the LMT-5000 can be regarded as a blood collection device useful for alleviating pain in newborns.

On the other hand, in the analysis of the number of blood collections, which is the secondary endpoint, the number of blood collections with the lancet was lower than that of LMT-5000. This is because the blood collection volume was set to 150μL for blood gas analysis in this study, and LMT-5000 device has less damage to skin tissues and blood vessels compared to lancet and has a good hemostasis characteristic. As a result, hemostasis may have occurred during blood collection, and it is thought that more additional puncture than lancet may have been required. In general, in the case of lancet puncture, as it causes a lot of damage to tissues and blood vessels, it is possible to collect a large amount of blood even with a single puncture. However, support must be applied for hemostasis, and there is a risk of bleeding if the tourniquet is released due to patient movement. In addition, considering that tests such as blood sugar and bilirubin analysis, which are mainly performed on newborns, can be performed with a much smaller amount of blood (10-30 μL), and that only 100-120 μL can be used for blood gas analysis depending on the device, the limitation of this study is that this study aimed to collect somewhat excessive blood volume. Even though not included in the evaluation criteria in this study, in the actual study, the first puncture in all 40 cases of blood collection with LMT-5000 could collect small amounts of blood and that the median of the number of blood collections with both devices was one. Although the number of blood collection with the two devices has shown a statistically significant difference, from these results, it is not appropriate to draw the conclusion that blood collection with LMT-5000 will increase the number of times of puncture in the general blood collection test in newborns compared to the lancet device.

As the results of this study, there were no significant pain differences between the two devices in the total NIPS differences analyzed, including heart rate and oxygen saturation evaluated at the start of the blood collection preparation and end of the blood collection. This may be due to the effect of interference, such as increased time taken for the entire blood collection and repeated preparations for skin sterilization, due to the additional puncture caused by the process of

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| | collecting large amounts of blood.<br><br>As previously suggested, since LMT-5000 does not use a needle, the skin and subcutaneous blood vessels and pain nerve fibers are less damaged, and the effect of automatic disinfection and hemostasis can be expected at the same time as perforation and hemostasis when collecting blood. Nevertheless, blood collectors should consider that additional blood collection may be required to collect large amounts of samples. Also, further studies will be needed on the amount of blood collected, the number of blood collections, and the time until blood collection is completed when punctured with LMT-5000 in newborns.<br><br>Newborns who require hospitalization, particularly premature infants, are required to collect frequent heel blood, which is known to cause continuous pain-evoked not only causes pain to the baby in itself, but also affects cranial nerve development in the long term. Therefore, consideration for pain during blood collection of newborns is necessary, and the introduction of examination devices that reduce stress in newborns with less pain can be considered very important. Moreover, as has already been identified in previous studies, the LMT-5000 can easily collect blood regardless of their proficiency and the risk of damage, infection, and injury to blood vessels is low despite frequent blood collection. Consequently, the LMT-5000 is considered a more suitable tool for newborns with immature skin and susceptible to infection.<br><br>Summing up the results of this study, the LMT 5000 is a safe and useful examination device not only for adults but also for newborns and can be expected to have an effect of alleviating pain compared to conventional lancet collection. |